

PEDIATRIC ADVISORY COMMITTEE MEETING

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WELCOME AND INTRODUCTIONS

DR. DRACKER: Good morning and thank you all for coming. Please be patient with me. My name is Bob Dracker and I'm filling in for Mark, who had difficulties getting here obviously. This is a very important meeting today, obviously, for the discussion of opioid use, codeine and hydrocodone in children. You're all well aware of the fact that this has really been a national problem with regards to opioid use and abuse that we've seen. Obviously, for me in my practice, it's a critical issue for the use in children.

Just to give you some of my background, and I'll go over some of the rules and regulations for the meeting. I am a pediatrician in the Syracuse area. My background is in pediatrics, hematology/oncology and in bloodbanking/transfusion medicine. I've been on this Committee for a number of years, and fortunately haven't had to have this responsibility before. So, again, please be patient with me.

I just want to mention to you that wireless internet connection is available. Just so you know, connect at HiltonMeeting, open the browser and enter access code 30926, if you need to do so.

During the speakers that we have today, there are a number of academic speakers and scientific speakers that will be going over the material. Some of them have already mentioned that they may be able to finish a little bit early. I'd like you to consider asking just one or two questions at that time. There will be additional time this afternoon, a half-hour period, to ask additional questions.

I think first, Marieann, would you like me to go around the table?

MS. BRILL: Yes, please.

DR. DRACKER: Okay. If we could start on the left-hand side and please introduce yourself. And again, remember to press the microphone red button. And when you're done, please shut it off. Thank you.

DR. KELLY STONE: I'm Kelly Stone. I'm the Deputy Chief, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases.

DR. PATRICK: Stephen Patrick, neonatologist at Vanderbilt Children's Hospital.

DR. NEVILLE: Kathleen Neville, hematologist-oncologist and clinical pharmacologist in pediatrics at Arkansas Children's Hospital.

DR. MEISEL: Steve Meisel, Director of Medication Safety, Fairview Health Services in Minneapolis.

DR. MCGOUGH: Jim McGough, child and adolescent psychiatrist at UCLA.

DR. LIEBELT: Erica Liebelt. I'm a pediatrician and pediatric medical toxicologist and Medical Director of the Washington Poison Center in Seattle.

DR. LASKY: Tammy Lasky. I'm a pharmacoepidemiologist. I work as a consultant at MIE Resources.

DR. FISCHER: Gwen Fischer. I'm a pediatric ICU physician at the University of Minnesota.

DR. DELOST: Kort Delost. I'm a community pharmacist, Bountiful Drug, Bountiful, Utah.

DR. CAMPBELL: Jeff Campbell. I'm a pediatric neurosurgeon at

Nemours.

DR. BRENT: Good morning. I'm Jeffrey Brent. I'm a medical toxicologist from the University of Colorado.

DR. WHITE: Michael White. I'm a pediatric cardiologist and IRB chair at the Ochsner Clinic in New Orleans.

DR. WADE: Kelly Wade. I'm a neonatologist for Children's Hospital of Philadelphia.

MS. BRILL: I'm Marieann Brill. I'm the DFO for this meeting.

DR. DRACKER: Bob Dracker again, acting chairman for the meeting.

DR. TURER: Christy Turer. I'm at UT Southwestern. I'm both an internist and a pediatrician with a specialty in obesity medicine.

DR. SAYEJ: Wael Sayej, pediatric gastroenterologist, Connecticut Children's Medical Center and University of Connecticut School of Medicine.

DR. JONES: I'm Bridgette Jones. I'm a pediatric allergist, asthma immunologist and clinical pharmacologist at Children's Mercy in Kansas City. And I'm the pediatric health care representative from the AAP.

DR. HOEHN: I'm Sarah Hoehn. I'm pediatric ICU and pediatric palliative care at the University of Chicago Children's Hospital.

DR. HAVENS: Peter Havens, pediatric infectious diseases at the Medical College of Wisconsin and Children's Hospital of Wisconsin in Milwaukee.

DR. CUNNINGHAM: Melody Cunningham. I'm a pediatric hematologist-oncologist and pediatric palliative care at University of Tennessee.

DR. CATALETTO: Mary Cataletto. I'm a pediatric pulmonologist from

NYU Winthrop in New York.

DR. CALLAHAN: David Callahan. I'm a child neurologist at Washington University in St. Louis.

DR. WAGENER: Jeff Wagener, pediatric pulmonologist and critical care at the University of Colorado and Children's Hospital in Denver.

DR. TYLER: I'm Linda Tyler. I'm the Chief Pharmacy Officer for University of Utah Health.

DR. NELSON: Skip Nelson. I'm the Deputy Director of the Office of Pediatric Therapeutics at FDA.

DR. ALEXANDER: John Alexander. I'm the Deputy Director of the Division of Pediatric and Maternal Health in the Center for Drug Evaluation and Research at FDA.

DR. SEYMOUR: Sally Seymour, Deputy Director for Safety in the Division of Pulmonary, Allergy and Rheumatology Products at FDA.

DR. STARKE: Peter Starke. I'm a Medical Officer and Associate Director for Labeling in the Division of Pulmonary, Allergy and Rheumatology Products at the FDA.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the Associate Director for Public Health Initiatives in the Office of Surveillance and Epidemiology, FDA.

DR. TAYLOR: Amy Taylor, Medical Officer with the Division of Pediatrics and Maternal Health.

DR. BUNTING: Good morning. Jason Bunting. I'm a Science Policy

Analyst in the Drug Safety Operations Team in CDER.

DR. DRACKER: Thank you.

MS. BRILL: We have Dr. Portman on the phone.

DR. DRACKER: Oh. Dr. Portman, are you there? Dr. Portman?

DR. PORTMAN: I'm Ron Portman. I'm a pediatric nephrologist and help lead the Pediatric Center of Excellence for Novartis Pharmaceuticals.

DR. DRACKER: Thank you very much. And thank the committee, for being here today. Marieann has a few opening statements.

OPENING STATEMENT

MS. BRILL: Thank you and good morning. The following announcement addresses the issues of conflict of interest with regards to today's discussion of reports by the Agency as mandated by the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

With the exception of the industry representative, all participants of the Committee are special government employees, or regular government employees from other agencies that are subject to the federal conflict of interest laws and regulations.

The following information on the status of the Advisory Committee's compliance with the federal conflict of interest laws, including but not limited to 18 USC Section 208 of the Federal Food, Drug and Cosmetic Act, is being provided to participants at this meeting and to the public. FDA has determined that members and temporary voting members of this Committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government 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, or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of their own, as well as those imputed to them, including those of their spouse or minor children, and for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of prescription opioid products containing hydrocodone or codeine for the treatment of cough in pediatric patients. 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, FDA has determined that members and temporary voting members of this advisory committee are in compliance with federal ethics and conflict of interest laws under 18 USC 208.

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

Dr. Bridgette Jones is participating in this meeting as the healthcare

representative, and that is a non-voting position.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Ron Portman is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Portman's role at this meeting is to represent industry in general and not any particular company. Dr. Portman is employed by Novartis.

Ms. Amy Celento is participating as the patient family representative, which is a voting position.

With regard to FDA's guest speakers, the Agency has determined that the information to be provided by these speakers is essential. The following interest is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. Oppenheimer has acknowledged that he has served as a consultant for Teva, GSK, DBV Technologies and AstraZeneca. He has also served as a chair of Adjudication for AstraZeneca Biologics and Teva Biologics.

We would like to remind members, and temporary voting members, that if the discussions involve any other products or firms 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. The exclusion will then be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that you may have with the firms that could be affected by the committee's discussions. Thank you.

DR. DRACKER: Thank you, Marieann. Next comments are from Dr. Alexander.

OPENING REMARKS

DR. ALEXANDER: Good morning. My name is John Alexander. I'm the Deputy Division Director for the Division of Pediatric and Maternal Health in CDER and I have a few brief opening remarks today. First, I'd like to welcome everybody to today's meeting, and I'd like to thank the members of the committee who came to attend the meeting and to provide us advice on today's topic.

The purpose of today's meeting is to discuss the benefit and risk of prescription opioid products for the treatment of cough in pediatric patients. Currently, as you'll hear, we have two products, hydrocodone and codeine, two active ingredients that are included in several products that are specifically labeled for use in pediatric patients for treatment of cough, usually cough associated with the common cold or allergies. And these products are also labeled with risks for the pediatric population with regards to respiratory depression.

Our purpose today in meeting is to discuss the overall risks and benefits of these treatments and to get an understanding from the committee about what the basis of the current views with regards to the risk/benefit of these products is.

Some people are asking why today, why are we meeting on these products? Part of the reason is because of the concerns currently in the US with regards to the opioid epidemic of misuse of abuse of the products. And so, the purpose of today's meeting is in part to get an understanding of how much the concerns about the public

health and the risks of the opioid misuse play a role in the decision about the risk/benefits of treatment of these products for an individual.

I will say also that this meeting is somewhat different because what we're asking you to do is to think more conceptually, with regards to the opioids, about what the overall risk/benefits are, how that affects the decision to treat an individual, and how much the public health concerns actually contribute to the decision that a product should or should not be used.

I'll also say that our meeting today is focused on the prescription products. Although we understand that there are OTC products that contain codeine that are available in the US, in some states, the focus on the prescription products is in part because we have now labeled the codeine products with regards to concerns about respiratory depression so that we contraindicated codeine specifically in children less than 12. For hydrocodone there are warnings with regards to respiratory depression; and part of our reason for meeting today is that now that those labeling changes have been accomplished, now that we've made those decisions on the basis of the safety information that we had, we want to understand further how much that concern contributes to the overall concern with regards to the use of these products in older pediatric patients.

So today's agenda I'll go over briefly. We have presentations from a couple of guest speakers. First there's a presentation by Dr. John Oppenheimer with regards to treatment of cough.

There's another presentation that's later in the morning by Dr. Sharon Levy, who's going to be talking about the concerns about opioid misuse in adolescents. But

her presentation is later on in the day to accommodate her time in being able to get here.

We have several FDA presentations providing some historical background information, information with regards to drug utilization and some safety concerns, as well as some view of the overall pediatric perspective on the use of these products. We do have a couple of manufacturer presentations today as well. I just want to note that these are two of several different product manufacturers that chose to make presentations today. We don't have presentations from all of the manufacturers. This afternoon we'll have an open public hearing, followed by a period that we've added into the afternoon session for questions from the Committee for clarifications from any of the speakers, and then the time for AC discussion.

I want to go over the questions briefly because I think it's helpful for the committee to have the list of questions and to try and keep them in mind as we go through the presentations that we're hearing today. The first question is a discussion question. We'd like you to discuss the benefit/risk of the use of prescription codeine and hydrocodone antitussives in pediatric patients. We also have five subquestions to this and we would like the committee to sort and try and go through each of the questions individually, spend some time sort of answering the individual topics, because that discussion is helpful to us as we try and take the advice of the committee and proceed with any actions on these products.

So first: What are the benefits and risks for the codeine and hydrocodone products intended for the treatment of cough associated with allergy and common cold? In your deliberations, include the benefits and risks of these products for the patients as well as the wider public health impacts of opioid-containing medications. So in

answering the overall question of risk and benefit, we want you to take into consideration not only what the individual's risks are but what the wider public health concerns are.

Next: Does the benefit/risk assessment change for the treatment of cough in other specific circumstances? So, outside of the question with regards to cough associated with allergy or the common cold. Are there important differences in the benefit/risk between hydrocodone and codeine that would affect your recommendations about use in pediatric patients? Are there differences in benefit/risk assessment for specific pediatric age groups? How do the wider public health impacts of opioid-containing medications affect your benefit/risk assessment of codeine and hydrocodone products intended for treatment of cough? And again, these questions are sort of intended to tease out what are the different aspects of the benefit and risk assessment that you're making.

So, following the discussion, then we have three voting questions. The first is a voting question: Is the benefit/risk favorable for use of prescription codeine cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients 12 to less than 18 years of age? Yes or no. And provide a rationale for your vote.

The next voting question is for hydrocodone. Is the benefit/risk favorable for use of hydrocodone cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients: A) Six to less than 12. Yes or no. And B) 12 to less than 18 years of age. Yes or no. And again, provide the rationale for your vote.

The last question is more of an overarching question, asking you to sort of consider the overall risks and benefits for opioid cough suppressants as a more general matter. So is the benefit favorable for use of prescription opioid cough suppressants for treatment of cough in pediatric patients? Yes or no, and provide the rationale for your vote.

And in ending my remarks, I just want to acknowledge the contributions of several different divisions and offices within CDER in preparing for today's presentation. Thank you.

DR. DRACKER: Thank you, Dr. Alexander.

Next speaker is Dr. Oppenheimer who's going to speak on Taming Chronic Cough in the Peds World. Personally, I'd like to rephrase your talk to "When to Treat or Not to Treat," because I'm plagued with chronic cough all the time in children. So I hope you can help personally. Thank you.

TAMING CHRONIC COUGH IN PEDIATRIC WORLD

DR. OPPENHEIMER: Thank you very much. I'd like to thank Dr. Alexander for inviting me. And you've just added more pressure, the chairman. I thought I had a difficult task already in 20 minutes to tame cough. I guess world peace will be my next goal.

So these are my potential conflict of interests, and I would add one more. I'm the token allergist on the American College of Chest Physicians Cough Panel -- writing panel. And we'll talk a bit about our research or our guidelines in a few

moments. I also want to mention that I'm going to have a few comments that are probably off-label, specifically regarding gabapentin, narcotics, PPIs, nasal corticosteroids, which really aren't FDA approved for cough itself.

Let's begin with: What's the reason we cough? It's a defense mechanism. It helps spread infection, keeps the infectious disease doctors going. And it's actually one of the most common causes for a patient to visit a physician. In the internal medicine world, it's the third most common cause. In the pediatric world, 10 to 20 percent of preschool and school-aged children presenting to a physician present with a cause of cough. So, a very common illness. And not a new problem. This is an ad I clipped from 1860, I believe it was -- 1840 rather -- Looking at a cough remedy. So this is a longstanding issue.

If you remember one thing from our discussion today, when you think about cough, think about the vagus nerve. Involuntary cough appears to entirely be mediated through the vagus nerve. So, if you think about stimulation of structures that are vagally mediated, things like the oropharynx, the trachea, the respiratory tract, tympanic membrane and external auditory meatus, you can think about the causes of cough. So we always say follow the vagus nerve, and in most cases you'll figure out why cough occurs. Now if you think about cough, the most sensitive sites to induce cough are the larynx, the tracheobronchial tree, especially the carina and branching points.

Now what's interesting is experimentally you can't induce cough in smaller airways and you can't induce cough in the alveoli. So there seems to not be a stimulus response when irritated in these portions of the body. The larynx and pharynx cough

receptors appear to belong to a group of rapidly-adapting irritant receptors. They're usually silent, but when stimulated result in a rapid adapting discharge with an irregular pattern, conducted by the fast velocity vagal myelinated fibers.

Now what are the triggers? Cigarette smoke. Irritants like ammonia, ether vapor, alkaline as well as acid solutions, and hypo and hypertonic saline solutions. In the old days, in England, one of the stimuli they used to use to study cough was to put people in fog, and you could actually measure cough response. So it shows you how irritant-related it may be. Other things include inflammatory mediators, namely histamine, bradykinin, prostaglandin; mechanical stimuli like mucus, dust, or foreign body like a catheter. And we'll talk more about these in a few moments.

The tracheobronchial tree also has similar rapidly-adapting irritant receptors. What's interesting is there is enhancement of response by pulmonary congestion, atelectasis and bronchoconstriction. Think about the various illnesses that that embodies and you can think about some of the triggers of cough. What about the central receptor? This has really been theoretical. It's never really been well established anatomically, but believed to be part of the medulla oblongata. It's also believed that most of our antitussive agents work centrally, but we're not really sure how. What happens with ineffective cough? Well, we can get atelectasis, with resultant pneumonia. If you remember, your zones of West's and V/Q mismatching, you can also get gas exchange abnormalities as a result of cough.

Let's talk a bit about time to resolution. In acute cough, recovery is seen in children in 50 percent of cases within ten days, and 90 percent of cases within 25 days. A good example is this study by Australia/New Zealand in which they looked at a

prospective community study, recorded respiratory episodes, and found that in children ten or less the duration of cough episodes resolved between 5.5 to 6.8 days.

Now why I keep showing you this data is, this is why most recommend that acute cough be defined as a cough lasting less than 14 days. When you look at guidelines for acute cough, there really are very few, largely because the data is surprisingly sparing. I think the best of the guidelines to approach this are the British Thoracic Society guidelines by Shield, et al. which appeared in Thorax several years ago.

And by the way, this is all strength C, so not all that robust. The majority of children with acute cough have viral respiratory tract infections. An attempt should be made to arrive to a specific clinical diagnosis when possible. Things to think about would be allergic rhinitis, a cold, something more severe or things as simple as possibly having a foreign body. And we'll talk more about that. They state that in the absence of fever, tachypnea and chest signs that might rule out further complications, simply relaxing, letting it pass is all that's needed. Specifically, most children with cough due to simple URIs will need no further investigation. Children in whom an inhaled foreign body is likely to be the cause should have emergent bronchoscopy. And finally, a chest x-ray should be considered in the presence of lower respiratory tract signs. Things like relentless progressive cough, hemoptysis or other features.

And that's really all we have in the form of guidelines. The ACCP did mention the following. And again, to be fair and transparent, I am on their guideline writing committee, so I'm biased, but for over-the-counter medications, systematic reviews have concluded that over-the-counter cough medications have little if any

benefit in the symptomatic control of acute cough in children. As a matter of fact, the AAP advised against the use of codeine and dextromethorphan for treating any type of cough. Furthermore, there are no effective medications for symptomatic relief of acute cough in children, and there was concern of serious adverse events and accidental poisoning because of reports that we're all going to talk about in a few moments.

What about a systematic review? Let's look at a study by Schroeder, et al. who actually looked at a systematic review and found that antihistamines and nasal decongestant combinations have shown that they really were no more effective than placebo at reducing the symptoms of acute cough. So again, the recommendations are most children with acute cough likely have a viral URI. You always want to think about key questions that might indicate a more serious illness; but if not, it's usually self-limited, and there really is a lack of data regarding symptomatic therapy.

Now I have ten minutes more to talk about chronic cough. Let's think about the vagus nerve again. We talk about something called the anatomic diagnostic protocol, which is simply a diagnostic evaluation in which we follow the vagus nerve in a systematic manner. In adults, and in some guidelines in children, eight weeks or more is considered a chronic cough. And when using this protocol, again following the vagus nerve, studies show that you can determine cause in 88 to 100 percent of the time. Resultant therapy has a success rate of 84 to 98 percent.

Now when you think about cause, this is where the complexity occurs. Only 73 to 82 percent of cases have a single cause. 26 percent have multiple causes. So unless you treat all of the potential triggers, cough will not resolve. And when looking at adults, 91 to 94 percent of cases, four different causes can be had: Postnasal drip,

now defined as upper airway cough syndrome, asthma, reflux, and chronic bronchitis.

Let's take a quick look at the common and the differential causes of cough.

The most common upper airway cough syndrome in adults -- and I'll show you data it's not true in children -- is stimulation of sensory nerves, inducing a cough reflex. The patient describes postnasal drip, has pharyngeal irritation, occasionally has a sense of globus or foreign body sensation within their throat. What do you want to consider? Allergic rhinitis, nonallergic rhinitis with eosinophilia syndrome, a post-infectious illness, environmental irritant, vasomotor rhinitis, and sinusitis.

On physical exam, posterior pharynx has mucoid secretions. There can be a cobblestoning appearance of the posterior pharynx. And frequently, I find helpful, throat clearing. You can actually see people clear their throat. Flow volume loops will actually show a variable extra-thoracic upper airway obstruction and cough transients. For those that don't think in terms of spirometry, let me share with you -- if I can make this pointer move. There we go. This is the inspiratory loop and it should be nice and open, and here you can see it's very truncated. This is because the upper airway is literally spasming. Thirty seconds you can have this answer.

Second most common cause, my biggest interest, is asthma. Again, inflammation inducing stimulation of sensory nerves. Symptoms include wheeze, dyspnea, think about triggers, season, around cats or dogs, having viral infections, cold air exercise. Spirometry shows obstructive patterns with reversibility following a beta agonist. Therapy is classic. Some sort of controller therapy like a leukotriene modifier in more mild disease; moving to an inhaled steroid in more mild to moderate disease; and finally, combination therapy.

Finally, what about reflux? It's the third most common cause in adults.

Again, stimulation of the pharynx limb of the cough reflex, here in the distal esophagus. Symptoms can include heartburn, sourbrash or regurgitation. What's interesting is if you look at the data, two thirds of patients with laryngeal pharyngeal reflux, as cause of cough, have no symptoms but to cough or clear their throat. This is where it becomes more subtle, and you might want to think about a pH probe and/or empiric therapy. Generally, an H2 blocker or proton pump inhibitor, as well as dietary manipulation.

Now here's the fun part. What about those less than six percent of cases?

What are the common causes? Well, they're all over the place. Things to think about are cancer, sarcoid, left ventricular failure, aspiration, irritation, tympanostomy tubes. It's not uncommon that you see somebody with a tube coming out and one of the results can be coughing. In older adults and older children, actually hair in the ear, helandric gene, if you recall, can actually stimulate the tympanic membrane to induce cough. For those that like trivia, that's called Arnold's Reflex. Tourette's syndrome, pertussis. And finally, unexplained cough, which we'll touch upon in the end and is very germane to the conversation about narcotics and cough. But I always argue that you only want to consider this diagnostic after you've really exhausted all other possibilities.

Let's go back to the pediatric guidelines. Currently the ACCP, American College of Chest Physicians, and the European Respiratory Society guidelines, define chronic cough in adults for the cough that lasts longer than eight weeks. But there's a divergence between these two organizations in pediatric cough. In the ACCP, we state it should be a four-week duration, while ERS is eight weeks. Again, we argue that four weeks is reasonable. I shared with you the data that in most cases cough will resolve in

one to three weeks in children. So we thought that four weeks was ample time to consider something more chronic.

I also touched upon the fact that the etiologies of chronic cough in children may be different than adults. This is an article that actually just appeared yesterday in CHEST. And our key question was the following: Among children with chronic cough -- again greater than four weeks duration -- are the common etiologies different from those of adults? So, hot off the press, I can tell you that they indeed are. We show that there's a moderate quality of evidence that common etiologies of chronic cough in children are different than that of adults. And what was interesting was also different by age, less than 14 might be something different than greater than 14.

Some of the themes that we saw -- and again, the data is not very robust -- is that asthma is a more common trigger of cough in children, as is something called protracted bacterial bronchitis; and I'll share with you what that is a moment. But what's surprising is that upper airway cough syndrome was not as common as that seen in adult, which was number one, as well as reflux not as common.

Let's touch upon protracted bacterial bronchitis. This is a fairly new entity. And it also speaks to a difference between adults and children. Matheson, et al., back in the '90s, showed that when you stratified cough, based upon dry or wet in adults, it was a useless stratifier; while in children it's actually quite helpful. Dry cough is more commonly seen in asthma, while wet cough is more commonly seen in protracted bacterial bronchitis. We're going to call that PBB.

What is PBB? Well, it's a persistent infection of the conducting airways by pathogenic bacteria, notably non-typable H flu, strep pneumonia and M. catarrhalis.

What's interesting is these bacteria appear to form a biofilm, which replicates slowly; and because of the biofilm it's very difficult to eradicate. The cough typically worsens with changing of posture and can be associated with dyspnea. And what's also interesting is that viral infections can exacerbate this PBB via release of planktonic forms of bacteria biofilms in response to the inflammation of the viral infection. When performing a chest x-ray it's usually normal, no hyperexpansion like in asthma. Bronchoscopy is actually the definitive diagnostic tool; and what you want to do is a BAL with culture. When looking at scoping, secretions are edematous and there's often collapsible bronchi with suctioning.

So here's the interesting part. There's tremendous controversy in treatment. So double-blind placebo controlled trials of 50 children demonstrated that with a greater than three-week wet cough, the use of a two-week course of amoxicillin clavulanate resulted in resolution in 48 percent of active versus 16 percent of placebo. But here's the tough love. If you follow these patients through, 70 percent treated for two weeks will relapse. Many experts in the field recommend a six to eight-week empiric course, but unfortunately there's lack of consensus. And it does bother me a bit to give a child eight weeks of antibiotics without a firm diagnosis. This is still a work in progress, but it's worth mentioning because studies do show this is a common cause of cough in children, and may explain why that ten days of antibiotics does not result in prolonged resolution of the cough. By the way, for those interested, pneumococcal vaccination doesn't seem to reduce incidence.

Finally, and my goal really is to stimulate, titillate, whatever you want, to begin your topic on understanding cough and where narcotics may fit. I thought we

would end my discussion by unexplained cough. This is the bane of all cough experts' existence. And I mentioned before that with using the anatomic diagnostic protocol, about 93 percent of patients could be improved, but there's still a percentage that continue to suffer from chronic cough with no obvious or treatable trigger. What's intriguing in adults, looking at SF-36, quality of life decrement is similar to those with severe COPD. This is a significant impactor of quality of life.

I didn't have time to show you, but studies clearly demonstrate that patients with chronic cough, this impedes their interaction with others. It could affect their work and pleasure life. I actually saw a patient, and it's been reported that people can have blackouts because of the cough. Think about the tremendous response that your body has when you cough. Some argue you can generate a force of 300 miles per hour. You can see how vehement this can be.

So people argue that we need to find some symptomatic reliever of cough, and I think that's how your conversation needs to be sort of couched. You need to think about something to help these people. What we did was a systematic review looking at the chronic cough literature, age 12 and above, in patients with unexplained or refractory, idiopathic or intractable cough, despite a very extensive evaluation. And what we found is the following: Over 1,000 articles, we were able to ultimately extract 16 articles. And what's sad is there really is no significant data in children.

With that said, we recommend the following -- and this is sort of hard to see. But obviously, you want to find cause, and in those that don't find cause, you want to consider speech therapy, you want to consider -- we suggest Gabapentin. You want to think about putting them in experimental protocols. There are new cough preparations

being developed. I was present by telephone during your last meeting and somebody was discussing some of the hopeful cures for the future.

But with that said, why did we pick Gabapentin? This is obviously a discussion in itself. But I'd like to share with you how great analysis can be so helpful because it's so transparent. So we vote on everything. Our initial panel vote was 75 percent in favor of a weak recommendation for the combination of either Gabapentin or morphine. But you need an 80 percent approval as per our guidelines to be included as a recommendation. Then what we had suggested was splitting these two agents, Gabapentin and morphine, into two separate categories. And with that, Gabapentin passed on first vote at 90 percent, but morphine again failed at 71 percent. And finally we changed the wording to say "close follow-up," and again it failed at 75 percent.

Now you're going to talk about this in more detail. But why did Gabapentin pass and morphine fail? We felt in looking at the literature, that Gabapentin's side effects were not profound, while morphine was. Patients dropped out, when looking at the studies, due to side effects like constipation in 40 percent and drowsiness in 25 percent. So, putting this together, we stated because of health-related quality of life, some patients can be so adversely impacted by their unexplained chronic cough; and because Gabapentin was associated with improvement of quality of life in a randomized controlled trial, our committee felt the potential benefits in some patients outweighed the risk. With respect to dosing, we had suggested beginning at 300 milligrams once a day, and then adding additional doses until cough is controlled and/or tolerated, to a maximal dose of 1800 milligrams a day in two divided doses.

So I've achieved my goal. This has been a whirlwind tour through acute

and chronic cough. I shared with you how we put together some of the guidelines. And I hope that I've shared with you the complexity of cough. It's not an easy "one medicine fits all." We have to think about multiple illnesses. And you're going to be charged with how to deal with those patients, despite very aggressive intervention, having continued cough with lack of control. I wish you well in your endeavor. Thank you.

DR. DRACKER: Thank you very much. I wish we could get CME out for this presentation. It was the best talk I've had on cough, personally.

We have time for one or two questions. And if I could take the liberty of asking one quick one. That's part of this job that I do like, that I get to ask a question first. So thank you. With your review of the literature regarding Gabapentin use, does it have any value when there's truly a pathogenic cause for the cough, or is it only when you cannot find a cause for the cough?

DR. OPPENHEIMER: We looked at literature only when you couldn't find cause. I think that would be different studies, and I can't really speak to that, because that wasn't specifically studied. But it makes sense. It's interesting. It does lower threshold, narcotics do also. So, one of the things we do is we actually can induce cough. And studies do show that these agents do raise the threshold to induce cough by irritant response. Please.

DR. TURER: I have two questions, if I may. The first is, do we know anything about the impact of unexplained chronic cough on quality of life in children?

DR. OPPENHEIMER: There are very little studies. They're small. But they do demonstrate impact. The way that they impact is that other people are fearful of letting their children next to the child that chronically coughs, number one. And number

two, they do miss school. Because obviously, after coughing enough, they'll be excused.

DR. TURER: The second question is with respect to the randomized trial of Gabapentin, was weight gain evaluated? We know from looking at micromedex and the drug label, Gabapentin increases the risk of weight gain in up to about four percent of patients who take it compared to placebo.

DR. OPPENHEIMER: That wasn't one of the signals I recall, but the data is included in your packet. So, I did include all the side effects.

DR. DRACKER: We can take one more question before we go to the next speaker.

DR. HOEHN: I just don't know if any of your studies reviewed anything about causes, other causes of cough, such as anxiety or psychogenic cough or anything like that.

DR. OPPENHEIMER: You know, we used to call it "habit coughing." And when I was a resident, I remember Waldo Nelson was my attending. And they used to wrap blankets around children and do horrible things.

You know, there is not a lot of data. It can be related to tic, it can be related to habit. It's very, very hard to prove these things. And again, I think the general tenet of unexplained cough really speaks to the fact that you want to make sure you've ruled everything else out before you call this. But often in the case of anxiety, you see other tip-offs also. It's not just cough, it's other things that children will do. A good tip-off I see is just before beginning school, cough begins. And then parents also will describe often stomach aches are also seen before school, and it sort of builds a model. But each one of these need to be individualized.

DR. DRACKER: I'm weak, so I'll take one more question, then we'll go on.

DR. CUNNINGHAM: I just wondered, you gave general guidelines on the doses, but are there any weight-related dosing guidelines?

DR. OPPENHEIMER: You know, no. The data was not robust enough for us to be able to make those calls. And again, I think that even that, as you saw, was a Level C. It's still a work in progress. And we do mention in the document that we hope further research will be ongoing. I thank you very much.

DR. DRACKER: Thank you, Dr. Oppenheimer. That was excellent. Next speaker is Dr. Starke, who will review Background on the Use of Opioids as Antitussives.

BACKGROUND ON THE USE OF OPIOIDS AS ANTITUSSIVES

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 at FDA. This morning I will provide some background for the use of opioids as antitussive agents.

This is an outline of what I will discuss, which will include some general background material, as well as a discussion of the regulatory history of both the prescription, though we will ask you to not focus on the over-the-counter products, the OTC monograph, and how it affects the prescription combination products. I'll then move on to more recent regulatory activities, leading up to this advisory committee meeting, followed by a brief discussion of the alternative non-opioid antitussive

products.

As you know, there are two opioids approved as prescription antitussive agents in the United States, hydrocodone and codeine. These are approved in combination with other medications, including but not limited to antihistamines, decongestants or expectorants. Note that codeine is also available as a non-prescription drug under the OTC monograph. And while I will explain the differences later, the over-the-counter cough products are really not the focus of today's discussion.

With regard to indications, except for one product, Hycodan, which is a combination of hydrocodone and homatropine, the indications for these combinations include relief of cough associated with allergies or the common cold. At today's advisory committee, we will ask you to primarily focus on this indication, namely the risk/benefit for relief of opioid antitussives in pediatric patients.

Now, a word about their mechanism of action. These drugs readily cross the blood-brain barrier and are thought to suppress cough by a centrally-mediated action in the respiratory center. They also produce a dose-dependent depression of respiratory function. However, a peripheral mode of action is also possible. Both hydrocodone and codeine act on the μ receptor, which is widely distributed in tissues throughout the body. Activation of the μ receptor leads simultaneously to both on and off-target effects; in other words, simultaneously to both intended therapeutic effects and adverse reactions.

This slide depicts the metabolic pathways for codeine and hydrocodone. Codeine has a very weak affinity for the μ receptor. It exerts its primary effect after conversion to the active metabolite morphine by CYP2D6 in the liver. And we'll come back to this later. By contrast, hydrocodone is active as a parent drug, although it's also

converted to an active metabolite, hydromorphone, by CYP2D6. Note that on the hydrocodone side, I've not shown the secondary metabolic pathways for simplicity on this slide.

As far as the regulatory history of these products is concerned, it's the same as many older drugs. The first Food and Drug Act was established in 1906, but at that time the focus was on adulteration of drugs. It wasn't until 1938, that the Food, Drug and Cosmetic Act, which established the basis of law that we know today, was enacted. Two things to be aware of: One, at that time it was all about safety. And two, the Act established the need for approval of a New Drug Application, or NDA, prior to marketing. But that application only needed to provide safety information, not efficacy information.

In 1962, things changed when President Kennedy signed into law the Kefauver-Harris amendments to the Food, Drug and Cosmetic Act. Now drugs had to be shown to be effective in addition to being safe. Not only did this apply to new applications, but it also applied, retrospectively, to all drugs approved as safe between 1938 and 1962.

To deal with the evaluation of effectiveness of these older drugs, the Agency contracted with the National Academy of Science's National Research Council, for panels of experts to review data submitted by companies to support the effectiveness of each active ingredient in their product. This was a huge undertaking that lasted many years. The retrospective effectiveness review included over 16,000 separate therapeutic claims as part of over 3400 NDAs approved for safety between 1938 and 1962. The Agency's administrative processing and implementation of the panel's findings is called

Drug Efficacy Study Implementation, or DESI for short. For the cough and cold drugs, this process spanned many years from the call for data in 1966, to convening the panels in 1967, to the final approval of efficacy and labeling supplements for codeine and hydrocodone antitussive combinations in the mid-1980s.

The actual process involved the panels providing the recommendations to the Agency, which then reviewed the recommendations and published the Agency's findings in the Federal Register. Publication of the Agency's findings that hydrocodone and codeine were effective for treatment of cough occurred in 1982 and 1984 respectively; at which time, efficacy and labeling supplements were required. However, not all of the ingredients in then-marketed combinations were found to be effective. If an ingredient was not found to be effective or possibly effective, in the Federal Register Notice, the Agency requested drug companies to submit further data. In those instances that a final determination was ineffective, products then may have been reformulated in order to complete the DESI process.

The end result of this process was approval of a number of applications or efficacy supplements for both hydrocodone and codeine containing combination products as shown here between 1984 and 1988. You'll notice that I have not presented any of the data or studies that the panels or the Agency reviewed. That's because we're not asking you to discuss today whether these products are effective in the suppression of cough. The Agency accepts that both hydrocodone and codeine are effective antitussives; meaning, that they suppress the urge to cough. And, in fact, one could argue that they do this extremely well. Rather, we're asking you to address the risk/benefit of these drugs, focusing specifically on their use in pediatric patients.

While the focus of this Advisory Committee is not on the over-the-counter cough and cold drugs, it's important to understand that the effectiveness evaluation process for over-the-counter drug products paralleled and was concurrent with the DESI process. And, in fact, the expert panels often overlapped. However, the actual administrative process was quite different because the OTC drugs, on that side, there are no applications. The process involves rulemaking with publication of a drug monograph.

The monograph is essentially a rulebook that lists the conditions manufacturers must follow for each active ingredient. Manufacturers who follow the monograph may market the drug products OTC without first coming to the Agency for approval. FDA first described the monograph process and began to convene panels in 1972. Just as for the prescription drugs, the panels reviewed the existing data and provided recommendations for drugs to be included in the monograph. As part of the process, codeine was proposed for inclusion in the cold, cough, allergy, bronchodilator and anti-asthmatic monograph, or CCABA as we often call it. For the cough and cold drugs, the rulemaking process for the OTC monograph extended from 1972, Federal Register Notice, to publication of the final CCABA monograph in 1987, with multiple iterations, each one including time for public comment.

Now, as the name implies, the OTC cough cold monograph includes groups of antitussive, antihistamine, decongestant, expectorant, bronchodilator, and anti-asthmatic slides. This slide contains the partial listing of those drugs. As I stated before, codeine may be found in both the prescription and the OTC combinations. Whether it's permitted OTC, or must be prescription, depends upon the concentration of

codeine in combination and the other active ingredients included in the combination. The OTC monograph provides for dosing of codeine in adults and children, six years of age and older, although the monograph also contains professional labeling with dosing for children two to six years of age.

Now this slide illustrates concepts codified in the OTC monograph, but which were also applied on the prescription side. On the OTC side, drugs were found to be Generally Recognized as Safe and Effective, or GRASE, when marketed per the labeling requirements and other conditions of use specified in the monograph. One of the concepts that came out of the effectiveness evaluation process, was the idea of rational, therapeutic combinations. A combination is considered rational if each ingredient contributes to the claimed effects and none decreases the safety and effectiveness of the other ingredients. As a result, combinations of certain types of ingredients are permitted in the cough cold monograph, whereas others are not. For example, combinations of an antitussive and an antihistamine are considered rational and are permitted.

Principles applied in the prescription setting included that codeine is an effective antitussive, and that OTC monographed GRASE ingredients could be combined with prescription ingredients as long as the combination is a rational combination. Therefore, to support new combinations of an over-the-counter monographed ingredient with codeine or hydrocodone for prescription use, only bioequivalence or PK data are needed. Finally, the labeling and the dosage of the prescription combinations is based on the labeling of each of the ingredients. So, for example, the indication for a combination of codeine and hydrocodone with an

antihistamine, includes that it's for treatment of cough associated with allergies or the common cold. A similar approach is taken for decongestants and expectorants.

This slide reviews prescription opioid antitussives that survived that DESI process and are currently marketed. As you know, there are two sets of opioid antitussive products, hydrocodone and codeine, in various combinations with antihistamines, decongestants or other ingredients. These are prescription products because during the review process hydrocodone was found to lack sufficient safety to allow it to be in the OTC monograph, or the products contain higher concentrations of codeine than allowed in the OTC monograph.

For hydrocodone, we have a combination with a non-monographed ingredient, homatropine, and a combination of hydrocodone and chlorpheniramine. For codeine, we have combinations with first generation antihistamines, promethazine and triprolidine with or without several monographed decongestants. You see the date of initial approval of the products listed. As shown at the bottom of the slide, the colors reflect whether the ingredient is permitted as part of the OTC monograph or is non-monographed.

This slide represents the current universe of prescription opioid antitussives, which includes all the currently marketed products that were approved with or after DESI. And you'll see that many of these were approved much more recently, particularly since 2011, as new combination products. These drug products triggered the Pediatric Research Equity Act, or PREA, and you'll hear more about the pediatric implications for these products when Dr. Taylor speaks later.

Now I'll talk more about more recent regulatory activities for these

products. Let's start with codeine. As I mentioned earlier, codeine has very weak activity and must be metabolized in the liver to the active metabolite morphine to have its intended effect. This conversion is performed by the CYP2D6 enzyme. However, there is significant genetic variation in CYP2D6 activity, resulting in some patients who are ultra-rapid metabolizers, who are so efficient that they literally get flooded with morphine and can experience toxic effects, including respiratory depression and death. And there are poor metabolizers who get little or no benefit.

This has resulted in progressive prescription labeling changes with warnings being added for respiratory depression and death, warnings for breastfeeding infants whose mothers are being treated with codeine post-delivery pain, and in young children when codeine is used to treat pain after a tonsillectomy or adenoidectomy. A recommendation to not breastfeed if using codeine, as well as a contraindication for use in patients less than 18 years of age post tonsillectomy or adenoidectomy were added. On the regulatory timeline, you'll see the safety issues and new warnings that have been added to the prescription codeine products from 2006 through 2015. As I noted on the last slide, the new warnings included a warning for use by nursing mothers in 2017, and a contraindication for use in post-tonsillectomy and adenoidectomy in 2000.

I think I said this wrong, so let me restate this. The new warnings included a warning for use by nursing mothers in 2007, and a contraindication for use in children post tonsillectomy and adenoidectomy in 2013.

Late in 2014, Health Canada, the EMA and other regulatory agencies began to restrict the use of codeine, either for pain or cough or both, in children under 12 years of age. This culminated in an Advisory Committee meeting late in 2015, which was

convened to discuss the safety of codeine analgesics and antitussive products. This slide summarizes the 2015 Advisory Committee recommendations related to the use of codeine as an antitussive in children. You'll see that the majority voted that the Agency set a contraindication for use of codeine for the treatment of cough in patients less than 18 years of age. Additionally, the Committee recommended that the Agency remove codeine from the OTC cough cold monograph.

Since that time, the Agency has been discussing the most appropriate steps to take regarding labeling, not only for the codeine-containing antitussive products, but also for the hydrocodone-containing antitussives, and several labeling changes have been made since the Advisory Committee meeting in 2015. Respiratory depression and death have long been recognized as a safety issue for opioids, especially when these drugs are used in vulnerable populations such as young children or elderly patients, or when formulated into extended-release formulations, or when combined with other drugs that are associated with respiratory depression.

Specifically, I want to highlight the interaction of these drugs with benzodiazepines and other CNS depressants. Because of the safety concern, last year the Agency required the addition of a boxed warning for all opioids, including the opioid antitussives when used in combination with benzodiazepines or other CNS depressants, including alcohol. As I stated, the Agency has been considering what to do with regard to the prescription labeling of codeine since the 2015 Advisory Committee meeting. As part of reviewing the safety data for codeine, the Agency noted that there are cases of respiratory depression in many age groups, although the majority occur in patients under 12 years of age.

Based on these safety data, the FDA decided to require the addition of a contraindication for the use of codeine for both pain and cough in patients less than 12 years of age. We also added a warning for the use of codeine in adolescents between 12 and 18 years of age, who have risk factors for respiratory depression, including obesity and obstructive sleep apnea, and we strengthened the warning that breastfeeding is not recommended while using codeine. Safety labeling supplements were required in April of this year, and the labeling supplements were just approved on August 29th. So, for many of you, this may be new information.

So, in the regulatory timeline, starting with the last Advisory Committee meeting, you see the new boxed warning regarding concomitant use of all opioid products, including the opioid antitussives, with benzodiazepines or other CNS depressants, the communication for which was published in August of 2016, with the labeling supplements approved in January of this year, and the contraindication that was just added for the use of all prescription codeine products, including antitussives in patients who are less than 12 years of age.

I want to talk for just a moment about Tussionex. Tussionex is an extended-release suspension of hydrocodone polistirex and chlorpheniramine polistirex. In January of this year, UCB, the manufacturer, submitted a labeling supplement proposing among other things to add a limitation of use of Tussionex in patients less than 18 years of age. You see their rationale listed on the slide, and I'll let the company, who will be speaking later, address this, except to make one point. UCB has framed the argument around risk/benefit, which is exactly what we've asked you here to address today, whether the benefit of suppression of cough in this instance, cold and allergies, is

sufficient to outweigh the risks of use in pediatric patients; and whether the benefit/risk ratio has changed over time.

So, back on the timeline, you see the Tussionex supplement, which brings us to this Advisory Committee meeting, and why we've asked you here, namely to discuss the most appropriate approach for labeling of the opioid antitussive combinations, including both hydrocodone and codeine combinations in children, which will also help us decide how to respond to the Tussionex supplement. The Agency has also been discussing what to do about the PREA requirements for the more recently approved opioid antitussive combinations that triggered PREA, particularly in light of the 2015 Advisory Committee recommendations. Your input will also help us to make decisions about the PREA requirements for these drug products.

Now I'll briefly end my talk by outlining the alternative opioid antitussives that are available. First, on the prescription side, we have Benzonatate, which is approved for use in patients ten years of age and older. Benzonatate has a warning about severe hypersensitivity reactions, including bronchospasm, laryngospasm and cardiovascular collapse, which are likely related to sucking or chewing the perles or capsules, so the labeling states not to break, crush or chew the perles or capsules. The labeling also warns that accidental deaths have occurred when this product has been ingested by children less than ten years of age.

This is a listing of the oral over-the-counter antitussives included in the OTC monograph and some of their relevant labeling. And you see listed by active ingredient, class, age and the relevant labeling. This list includes chlophedianol, dextromethorphan and diphenhydramine products. And finally we have the topical

over-the-counter antitussives that are also included in the OTC monograph, namely camphor and menthol. That concludes my talk. Thank you for your attention.

DR. DRACKER: Thank you, Dr. Starke. We'll take two brief questions, if there are any. Yes, sir.

DR. WAGENER: Thank you for a very nice talk. I'm glad to see that the FDA has been doing a number of things since the 2015 committee meeting. I'd like to know why the FDA, however, did not choose to go with the recommendations of that committee, that suggested that codeine be contraindicated for cough treatment in children under 18.

DR. STARKE: That's a good question. Maybe I'll let Dr. Seymour answer it, however.

DR. SEYMOUR: Hi. This is Sally Seymour, FDA. Thank you for that question. It was a difficult decision and it took a bit of time to come to that decision. As you can see, there was a bit of a gap between the 2015 Advisory Committee meeting and our ultimate decision.

In the end, we based the decision primarily on the data and where the cases were for respiratory depression and death. And they were primarily in children less than 12 years of age. And while the Committee's voting overwhelmingly indicated a contraindication in children less than 18 years of age, there were some members who did make comments about concern about availability of codeine in older children, so we were trying to balance the availability in older children versus the safety where the data was primarily in children less than 12 years of age.

DR. WHITE: I don't know if you're the right person to answer this or not,

but one of the concerns I had about codeine is it's considered a pro drug; but do we have any data about the activity of codeine in the absence of metabolism on both suppression of respiration and suppression of cough?

DR. STARKE: Are there any clinical pharmacologists here from FDA?

No.

DR. WHITE: So it's all mediated through morphine?

DR. SEYMOUR: I think you raise a good question. And as we prepare for these Advisory Committee meetings we have tried to look at the literature to elucidate the mechanism of action and how much activity codeine has versus morphine. Same for hydrocodone and its metabolites.

And as Dr. Oppenheimer alluded to, the data is a little bit limited in terms of what is actually the active part. But it appears that codeine has very limited binding for the μ receptor. So, from what we can find from the literature, it suggests that morphine, really the metabolite, is really the primary activity driver at the μ receptor. But the data is not great about whether codeine has a lot of activity or not. But based upon binding, it probably doesn't.

DR. WHITE: Thank you.

DR. DRACKER: All right. One more quick question, please. Yes, sir.

DR. BRENT: And this is a question for both Dr. Starke and Dr. Oppenheimer, and relates a little bit to the discussion we were just having about the μ receptor.

Dr. Starke, you have told us that the mechanism of suppression of cough by opioids, by codeine, hydrocodone, is agonism at the μ receptor. Dr. Oppenheimer, you

have told us that the mechanism of cough is through stimulation of the vagal nerve. And I was wondering what is the relationship between μ receptor agonism and vagal inhibition? Is there any known nexus between the two?

DR. OPPENHEIMER: One of the expert panels did include neurologic intervention of cough. And you need several PhDs to understand that document. But in truth, I don't think we have a firm answer to this. We know it works, as you point out. You can look at models. Capsaicin is a good example to induce cough and show that the threshold changes, but I don't think we really understand where it's coming from.

DR. STARKE: This is Dr. Starke. I don't think I can add anything to what you just heard.

DR. DRACKER: Unfortunately, we're going to have to move on. There will be time for more questions later. Next speaker is Tracy Pham, who will be going over the utilization of opioid and non-opioid containing medications. Thank you, Tracy.

PEDIATRIC OUTPATIENT PRESCRIPTION UTILIZATION OF OPIOID AND NON-OPIOID CONTAINING ANTITUSSIVES

DR. PHAM: Good morning. My name is Tracy Pham. I am a drug utilization analyst for the Division of Epidemiology. Today I will provide the Pediatric Outpatient Prescription Utilization of Opioid and Non-Opioid Containing Antitussives to provide context for today's discussion.

This is the outline of my presentation, with primary focus on the pediatric utilization patterns in the outpatient retail setting, where over 90 percent of antitussives

are sold. Here is the description of the database that we use to analyze the national trends of pediatric antitussive use. We analyze antitussives utilization patterns based on prescriptions dispensed from the outpatient retail pharmacies, with a focus on opioid antitussives containing codeine and hydrocodone. Of note, utilization of codeine and dextromethorphan-containing antitussives are underestimated, as they are also available over the counter. Data on purchases made without a prescription are not available in our analyses.

This figure shows the pediatric antitussive use over time. Prescriptions dispensed to pediatric patients decreased by 18 percent, from 7.1 million in 2012, to 5.8 million in 2016. As shown by the red line, the majority of prescriptions were dispensed for dextromethorphan products. Pediatric use of codeine products, as shown by the green line, and hydrocodone products, as shown by the blue line, were low compared to dextromethorphan products. It is important to note that pediatric use of codeine and dextromethorphan antitussives are underestimated in this analysis, because over-the-counter sales of these products without a prescription are not captured in our database.

This figure focuses on the pediatric use of opioid-containing antitussives. As shown by the green line, pediatric use of codeine antitussives decreased by 61 percent, while pediatric use of hydrocodone antitussives decreased by 71 percent during the same time period. Also noted on this slide, multiple regulatory efforts were taken and may have contributed to the decrease in the pediatric use of opioid-containing antitussives over the years. This figure shows the pediatric use patterns of opioid-containing antitussives by patient age. As shown on the right of the figure, pediatric use of opioid-containing antitussives was primarily in patients six years of age and older.

There was low use of these products in patients less than six years of age. But overall, use of opioid-containing antitussives decreased across all pediatric age groups.

Next I will describe the prescriber specialty data for opioid-containing antitussives. In 2016, family medicine, general practice and internal medicine specialists were the top prescriber specialty at 34 percent of prescriptions dispensed for opioid-containing antitussives in pediatric patients. Mid-level practitioners follow at 27 percent. And general pediatricians follow at 24 percent.

Now I will transition into the Office-Based Physician Survey Data source for insight into products which were mentioned during a physician visit for the diagnosis of cough in pediatric patients. These data were derived from monthly surveys of 3200 U.S. office-based physicians who reported all patient activity during one typical work day each month.

Keep in mind these data are not based on dispensed prescription activity as shown on previous slides. Rather, these are survey results from samples of physicians. A mention of a diagnosis or a product during an office visit may not result in a prescription being generated or dispensed at the pharmacy. However, this data source provides insight to drugs linked with the diagnosis based on the prescriber intent.

In 2016, physician survey data showed that various products such as anti-asthmatics and antitussives were mentioned for cough relief in pediatric patients during an office visit. Budesonide was a top-mentioned drug among patients one year and younger. Dextromethorphan antitussives were the top-mentioned drugs among patients ages two to seventeen years. For opioid-containing antitussives, combination codeine and guaifenesin was the third-mentioned drug for cough relief among patient

ages 12 to 17 years. Although this product was also mentioned among younger patients, the number of patients were very low, reflective of low utilization trends and dispensed prescription data. There were no mentions of hydrocodone antitussives for cough relief in pediatric patients. Although low, other treatments such as antibiotics and non-pharmacological therapies were also mentioned for cough relief in pediatric patients.

I will now go over the limitations of the databases used to conduct these analyses. We focused our analyses on the outpatient retail setting. Although utilization trends presented might not be representative of inpatient or clinic use, the vast majority of antitussive use was characterized in our analyses. Over-the-counter sales data are captured only when prescriptions written for over-the-counter products are filled and dispensed at the pharmacy. Sales of the over-the-counter products to the consumers, without a prescription, are not captured in our analyses. Despite this limitation, our data showed that dextromethorphan accounted for the majority of pediatric antitussive prescription use.

The Office-Based Physician Survey data may not reflect prescribing patterns of physicians who practice in other settings such as hospitals and clinics. And finally, a mention of a prescription or over-the-counter product associated with a diagnosis, during an office visit, may not result in a prescription being generated or dispensed at the pharmacy.

In summary, about 5.8 million total antitussive prescriptions were dispensed to pediatric patients in 2016. Although over-the-counter use was not captured, dextromethorphan-containing antitussives accounted for the majority of total

prescriptions dispensed to pediatric patients. Use of opioid-containing antitussives in pediatric patients decreased over the study time, and was low compared to dextromethorphan products. Aside from antitussives, various treatments such as anti-asthmatics were also mentioned for cough relief in pediatric patients based on Office-Based Physician Survey data. This concludes my presentation. Thank you for your attention.

DR. DRACKER: Thank you, Tracy. I have one quick question myself. The dramatic decrease, or fairly dramatic decrease in prescriptions used for opioid drugs, was that paralleled or even exceeded by decrease in morbidity and mortality associated with the use as well? Was that data tracked at all?

DR. STAFFA: That actually will be talked about a bit in the next presentation.

DR. DRACKER: I did not hear you.

DR. STAFFA: That's actually the topic of the next presentation of what we know about misuse and abuse.

DR. DRACKER: Okay. Thank you. Any other questions?

DR. FISCHER: Is there any information on the length of the prescriptions?

DR. PHAM: So we did not analyze the duration of use for these products. This is analyses from the outpatient retail setting, in which we weren't able to get that information in duration of use.

DR. DRACKER: Okay. Then we'll move on. Next presentation. Dr. Karami will now discuss the poison control data. Thank you.

PEDIATRIC COUGH AND COLD PRODUCTS: ANALYSIS OF AMERICAN ASSOCIATION OF POISON CONTROL -- (AAPCC) DATA 2011-2016

DR. KARAMI: Good morning. My name is Sara Karami and I'm from the Office of Surveillance and Epidemiology. Today I'll be presenting findings on Pediatric Cough and Cold Products: the Analysis of the American Association of Poison Control Data. Above are the disclosures.

The outline of the presentation today includes a brief background of the issues being examined, the purpose of our investigation, the methods used for our analysis, the study results observed, the limitations of our dataset, and the summary of our findings. A recent CDC report, released this August, suggests that the overdose deaths among teenagers 15 to 19 years of age, in the United States, has increased from 2014 to 2015. While toxicological reports can be used to identify which molecules adolescents may be overdosing or dying from, these reports do not provide information on the type of product patients are being exposed to. Use of hospital codes also do not provide details about the type of product patients are being exposed to. However, data from calls to poison control centers often include more details about the specific product as well as the intent of exposure.

Therefore, the purpose of our investigation was to examine rates of exposure to opiate containing and non-opiate containing cough, and cold products among children and adolescents under 18 years of age, from calls to poison control centers while being able to account for a reason for exposure.

We conducted a retrospective analysis of aggregate data using the newly acquired, Agency-wide access to the American Association of Poison Control Centers National Poison Data System. AAPCC captures data on actual or suspected exposures to a variety of substance when a patient, or a health care professional, calls a poison control help line seeking information regarding triage and treatment. Of note, not all calls involve a clinical effect or lead to a medical outcome. American Association of Poison Control's 55 poison control centers serve the entire U.S. population, including the 50 states and the U.S. territories, and capture data on a near real-time basis.

For our study, we conducted a search for all human, single-substance exposures, meaning calls involving only one product, for hydrocodone, codeine, benzonatate and dextromethorphan cough and cold products in children and adolescents under 18 years of age for the time periods of January 1st, 2011 through December 31st, 2016.

We evaluated exposure calls coded by the underlying reason for which the exposure occurred. Specifically, we examined exposure calls coded as “adverse reactions,” which are calls that generally resulted in an allergic reaction or hypersensitivity when exposure involves normal, prescribed, labeled or recommended use. We also examined unintentional exposures which may result from the wrong dose, route of administration or substance, and often includes scenarios where a toddler may have gotten into and swallowed another family member's medication. Lastly, we examined intentional exposures which result when a substance is taken to attempt to gain a high, euphoric effect or to do self-harm.

For our study, we evaluated patterns of adverse reaction, unintentional

exposures and intentional exposure calls; involving cough and cold products by year in children and adolescents under 18 years of age, by calculating age-specific annual call rates per one million population, using age-specific population estimates prepared by the U.S. Census Bureau. Please note that no formal statistical evaluations of trends were performed, and the results presented here are purely descriptive.

The results above illustrates the annual population adjusted call rates involving adverse reactions to cough and cold products in children under 18 years of age. On the Y axis is the call rate per million population. And on the X axis represents the years evaluated from 2011 to 2016. We can see that the population adjusted annual call rates for adverse reactions involving codeine, hydrocodone and benzonatate remained relatively stable. However, for dextromethorphan, cough and cold products shown above in blue, a slight decrease in the annual call rate was observed from 2011 to 2016. We also see a much higher call rate for exposure involving dextromethorphan cough and cold products as indicated by the mean call rate in the box.

The slide above displays the annual population-adjusted call rates involving unintentional exposures to cough and cold products in children under six years of age. For benzonatate cough and cold products illustrated by the dotted black line, a slight increase in the annual call rate was observed from 2011 to 2016. For cough and cold products containing codeine and hydrocodone, illustrated by the green and red line above, a slight decrease in the annual call rate was seen.

A decrease in the annual call rate was also observed for unintentional exposures involving dextromethorphan in blue above. However, a much larger proportion of calls involved dextromethorphan cough and cold products as illustrated by

the wider and different Y/X axis scale as well as the mean annual call rate shown for the different products in the boxes.

In this slide we illustrate the annual call rate for intentional exposures to cough and cold products among adolescents 12 to 17 years of age. For benzonatate cough and cold products illustrated by the dotted black line above, we see a slight increase in the annual call rate from 2012 to 2013, although overall the call rates are small, and subsequently we see a plateauing of the rates.

A relatively steady annual call rate was observed for codeine and hydrocodone, illustrated by the green and red lines above. A general decrease in the annual call rate was observed for intentional dextromethorphan cough and cold products shown in blue. As previously observed, a much larger proportion of calls involved dextromethorphan cough and cold products as indicated by the different and wider Y/X axis scale and as well as the mean annual call rate observed for the different products in the boxes.

Some of the limitations of our study that should be acknowledged include the fact that reference AAPCC data should not be construed to represent the complete incidents of national exposures to any substance. These data only capture events if the exposure resulted in a call to a poison control center. It is unclear what factors influence whether a call is made. However, poison control center data rely on information electively shared by patients and health care personnel. And most substance classification is based on history alone and does not involve biological confirmation.

Changes in poison control center call rates in part may reflect changes in public and professional awareness of risks associated with specific drugs, as well as

awareness of their abuse potential among poison control personnel which could increase the likelihood of an exposure being coded as intentional. Call rates may also be influenced by general changes in the use of poison control center calls over time as a number of human exposure calls has decreased over the past decade.

Lastly, our analysis is purely descriptive and did not statistically evaluate annual trends. In summary, we examined opioid-containing as well as non-opioid containing cough and cold medication in children and adolescents under 18 years of age. Our AAPCC study findings showed relatively small, but stable, or declining annual call rates for codeine and hydrocodone cough and cold products.

We observed a small up-take in rates for benzonatate cough and cold products, but call rates were relatively small. The increase in benzonatate call rates may be simulated by the FDA Drug and Safety Communication issued in December of 2010, on accidental ingestion of benzonatate in children. Furthermore, we saw much higher exposure call rates for dextromethorphan cough and cold products. Overall, the rates have decreased over the past five years, however. The observed decrease in dextromethorphan call rates may be related to the decreased number of calls to poison control centers over the last decade, or due to more recent public health interventions.

With regards to reason of exposure, adolescents 12 to 17 years of age comprise the largest group for intentional exposures, representing 83 to 91 percent of intentional calls, depending on the specific product that we examined; while children under six years of age comprised the largest age group for unintentional exposures, representing 63 to 82 percent of unintentional calls, depending the specific products examined. This concludes this portion of the presentation.

DR. DRACKER: Thank you, Sara. Yes, sir.

DR. MEISEL: Have you attempted to correlate the changes in call center calls with the changing utilization that we just saw from Dr. Pham? I mean, the numbers have gone down, but the number of prescriptions have gone down also. It would be interesting to see the correlation.

DR. STAFFA: It's challenging because so many of the products have over-the-counter availability, so that's why we used -- for the rates we used population instead, just because they're so widely used and we can't get a handle on the exact use of these over the counter.

DR. LIEBELT: Erica Liebelt. Did you break down your intentional exposures and analyze by outcome? Because looking at our poison center data, although the trend is downward, we are seeing an increasing number of calls from health care facilities, and those outcomes that we're seeing are more moderate and severe in the past several years.

DR. KARAMI: So we did look at that, but they're not presented here. And I couldn't exactly tell you what the breakdown is now, but I do believe that -- let's see where -- I do believe they were looked at, but just they're not presented here.

DR. HOEHN: I had a question about why you restricted it to single when they only used a single drug. Because we know with adolescents intentional exposure, there's a ton of poly-pharmacy. So I wonder if that under-represented it or if you had any comment on why it was limited to just a single?

DR. KARAMI: So the majority of calls actually did involve single substance exposures, and I do have a breakdown for that. So, for codeine, that

represented 90 percent; hydrocodone 90 percent; benzonatate 78 percent; and dextromethorphan 84 percent for a single substance.

DR. HOEHN: Thank you.

DR. BRENT: Thank you for that presentation. I know that you looked at the AAPCC data through a contract with the FDA for full access to that data. I believe the FDA also has a similar contract with the Toxicology Investigators Consortium, which has similar information, although it is restricted to cases where there's been significant morbidity. And I wonder if you looked at that database as well?

DR. KARAMI: I have not.

DR. STAFFA: This is Judy Staffa. Our office does not have that relationship, so I'm not sure which part of the Agency has that contract; but, no, we did not look at that.

DR. BRENT: Okay. Thank you.

DR. DRACKER: I think we'll move on. Next presentation, which is Amy Taylor, who will be discussing Considerations of Opioids for Cough.

ADDITIONAL CONSIDERATIONS IN THE USE OF OPIOIDS FOR COUGH

DR. TAYLOR: Thank you. As you said, my name is Amy Taylor. I'm a medical officer with the Division of Pediatric and Maternal Health.

This is an outline of my presentation. I will briefly discuss high level principles for the treatment of acute cough and available treatment guidelines from various organizations, as well as recent global regulatory actions. Then I will present

the current pediatric labeling of available opioid products for cough, and study requirements under the Pediatric Research Equity Act, or PREA. Finally, I will give a summary of the expert roundtable meeting held in April of this year.

For the most part, acute cough in children is self-limited and typically is due to an infection. Because symptomatic treatment of cough in certain situations may be detrimental, one should search for a specific etiology and therapy should be directed at treating the underlying condition.

Over the last decade, there have been changes in the recommendations of various organizations for the management of cough in children. Many organizations are now recommending against the symptomatic treatment of cough in the pediatric population. In 1997, the American Academy of Pediatrics Committee on Drugs issued recommendations on the use of codeine and dextromethorphan for cough. The AAP found a lack of studies to support the efficacy and safety of these products as antitussives in children. They concluded that parents and patients should be educated about the lack of proven antitussive effects and the potential risk. This statement was reaffirmed in 2007.

In 2006, the American College of Chest Physicians recommended against the use of cough suppressants in young children due to the possibility of significant morbidity and mortality. Of note, the World Health Organization has recommended against the use of codeine for cough in young children.

In 2015, the European Medicines Agency contraindicated the use of codeine in patients less than 12 years and recommended against the use of codeine in patients 12 to 18 years of age with breathing problems. Health Canada has cautioned

against the use of OTC cough and cold medications in patients less than six years, and specifically against the use of hydrocodone in patients less than six years and codeine in patients less than 12 years.

The next two slides will touch on the current pediatric labeling for codeine and hydrocodone products. Tables of currently available codeine and hydrocodone products are available in the briefing document. All available codeine products contain a boxed warning regarding deaths related to ultra-rapid metabolism of codeine and a contraindication in children less than 12 years. They also contain a contraindication for postoperative management in children less than 18 years post tonsillectomy and adenoidectomy.

Two available hydrocodone products have dosing information for patients six years and older. They also have a warning to use the product with caution in pediatric patients six years and older. Hydrocodone and homatropine combination has a warning for fatal respiratory depression in children less than six years of age. The hydrocodone chlorpheniramine combination is contraindicated in children less than six years. All other available hydrocodone antitussive products are not indicated for use in patients less than 18 years.

The Pediatric Research Equity Act requires that any application for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration, provide an assessment in pediatric patients unless the requirement is waived. Newly submitted prescription opioid cough products are subject to PREA because combination products containing codeine and hydrocodone are considered new active ingredients. Information under PREA is required to submit

labeling in pediatric patients six to seventeen years for new codeine and hydrocodone prescription products. The studies include a single dose PK study and a large safety study. Efficacy is based on the established efficacy in the OTC monograph or previously approved products. These requirements may change based on the outcome of this Advisory Committee.

A roundtable meeting occurred in April of 2017, consisting of experts in the treatment of pediatric patients with cough, which helped to frame the questions for this Pediatric Advisory Committee meeting. The discussion included representatives of various professional organizations, such as the American Academy of Pediatrics, the American Academy of Family Physicians, the American College of Chest Physicians and the National Association of Pediatric Nurse Practitioners.

The experts stated that in their clinical experience, the use of cough suppressants is situational and should be used only if the cough is causing clinical consequences. They stressed the importance of identifying and treating the underlying cause of the cough. They did not articulate a clear role for the use of hydrocodone or codeine in the treatment of acute cough in pediatric patients. Thank you.

DR. DRACKER: Thanks very much. Are there any questions?

DR. HAVENS: So I was impressed with the earlier presentation saying that the DESI review suggested efficacy, but now later reviews suggest no efficacy. How does FDA balance these two findings? This seems to be a critical question.

DR. TAYLOR: I think I'll let the folks from the pulmonary division answer that.

DR. SEYMOUR: This is Sally Seymour from the FDA. Can you describe

what studies you're saying show there's no efficacy? Is it the statement from the AAP?

DR. HAVENS: Dr. Starke suggested that the DESI reviews showed efficacy. Now, since those have finished, there's 20 years, 30 years of people saying they don't have any benefit. Who's right?

DR. SEYMOUR: So the Agency has made a determination of efficacy based upon the DESI review. I'm not sure exactly what literature you're referring to, to say these products don't work. I know that the AAP has made a statement saying they don't work. I think that's what Dr. Taylor's presentation alluded to.

And so we acknowledge that. That's part of the reason we're here, in terms of understanding the risks versus the benefits. But to our knowledge, there hasn't been any new data to say they don't work.

DR. DRACKER: Skip, did you want to say something?

DR. NELSON: Yeah, just to reframe it perhaps. The issue of efficacy, taken alone, I don't think is on the table. The issue is the risk/benefit as an overall perspective, whether or not it is worth using, clinically given that risk/benefit, even if it could suppress cough from a pure efficacy perspective. So it's putting that balance in. I think that's the way one can see what might appear to be different perspectives on it.

DR. ALEXANDER: If I could just add?

DR. DRACKER: Yes.

DR. ALEXANDER: Sorry. If I could just add to that the whole idea here is sort of the part of what you're asking the committee to weigh in on with regards to the treatment and risk/benefit in a specific circumstance, as opposed to the question of sort of, is there evidence to support efficacy of a drug? Because there may in fact be

evidence to support that the drug is efficacious, it does have an effect on reducing cough and the symptoms of cough; but the consideration of the overall benefits versus risks in a particular situation may not justify the use of the drug, even if it is considered efficacious in that specific circumstance.

DR. DRACKER: I think for perspective reasons, it's become very obvious that first we have to decide what the etiology of the cough is and make sure that's investigated appropriately. And then if medications are used for the suppression of cough, that they're not overused, and that we consider the issue of morbidity and mortality associated with the use.

More importantly, for me, is the issue of the over-the-counter use of these products, which is not regulated, and which is not monitored. And that's something we'll also have a chance to discuss later. Yes.

DR. LASKY: I had the same questions that Peter Havens had. And if we're going to compare benefits and risks, we need to have an agreed assessment of what the benefits are. And I understand that FDA has accepted the DESI conclusions, but I guess we as a committee can also bring in other evidence that's out there. And that's what I've done, as well. Regarding the DESI evidence, it wasn't clear to me, after Dr. Starke's presentation, whether children were in any of the studies analyzed by NAS.

DR. DRACKER: Dr. Starke, do you want to make a comment?

DR. STARKE: Sure. Yes, I've looked at the data themselves, particularly for the hydrocodone products; and there were data in children six and above.

DR. LASKY: Great. Thanks very much.

DR. STARKE: But I need to say -- preface it by -- or encapsulate it with

one other thing. And that is the studies looked at the use of hydrocodone in the treatment of chronic cough, in that setting primarily, rather than in the treatment of acute cough. And if you look at, in fact, at the adult studies, they were in patients with tuberculosis, other long-term cough, and they looked at cough frequency. So, yes, there was -- but there were data in children as well.

DR. LASKY: So that may explain one of the differences in conclusions, that one body was looking at acute cough and another set of reviews was looking at chronic cough. Just so we can understand why we're hearing different conclusions.

DR. STARKE: They did not make a differentiation.

DR. LASKY: Sorry?

DR. STARKE: They did not make a differentiation between chronic and acute in terms of the efficacy assessment.

DR. DRACKER: We'll take two more questions, I think, just to get to the next presentation. Then we have a short break after that. So I just want to keep us on track.

DR. NEVILLE: Hi. I'm the previous chair of the committee on drugs for AAP, so I just wanted to comment on the AAP's comments on cough and cold preparations. A lot of them were centered around dextromethorphan-containing and combination products, and the lack of safety in them. And I want to make a distinction that the AAP's stance has been not per se that they don't work, but that there are no good evidence to say that they do work in children.

And our recent piece on Codeine: Time to Say No was more around the safety of codeine in general as an analgesic and an antitussive, and all of the points that

have been covered are about the variable metabolism. So I don't think that the AAP has said these preparations don't work, and they were not specifically talking about -- or we weren't specifically talking about opiates, more the dextromethorphan combination containing products. And you can see that on healthychildren.org.

DR. DRACKER: Thank you. Go ahead, sir.

DR. MEISEL: I just want to point out that the only indication for codeine anyway is for cough associated with URI. I mean there's a lot of discussion here about chronic cough and cough due to other causes, but the only indication that's on the labeling is for that due to URIs. And so our context of discussion has to be within that, not for the non-labeled use of this, the off-label use of this, which is -- we can get carried away, but that's beyond the scope of our discussion. Isn't it?

DR. DRACKER: That's true, but I'm sure -- you know, we all know that what something's labeled for and what it's used for are very different sometimes.

DR. MEISEL: Right. But our discussion about safety and efficacy has to be within the context of the approved label.

DR. DRACKER: I agree. I think we have to move on. Dr. Starke?

DR. STARKE: One more thing I neglected to add. There was data for acute cough, as well as chronic cough, for both codeine-containing products and hydrocodone products. And you are correct, all of the codeine-containing combinations are labeled for the combination products which all include antihistamines or decongestants, so they are labeled for colds and allergies. Whereas the hydrocodone products, there is one particular product which used to be Hycodan is now generic, as well, which has a combination of hydrocodone and homatropine, and that does not have

a specific subindication of allergies or colds.

DR. DRACKER: All right. I think we'll move on to Mr. Lawrence's presentation, please. Thank you. Mr. Lawrence, if you're present, please come up.

INDUSTRY PRESENTATION -- SOVEREIGN PHARMACEUTICALS, LLC

MR. LAWRENCE: I'm representing an industry, Sovereign Pharmaceuticals, and I happen to have a cold at the moment, and I had a cough, but I didn't get prescribed any cough medicine. So if you could excuse my voice for a little bit, that would be great. I'll take off my glasses so I can actually see.

I would like to thank the FDA and Pediatric Advisory Committee for allowing me to speak today regarding Pediatric Safety Reviews as mandated by the Best Pharmaceuticals for Children Act. I'm speaking on behalf of Sovereign Pharmaceuticals related to a specific requirement for NDA hydrocodone guaifenesin oral solution drug product, which the Agency requested PREA.

The Agency has requested that Sovereign perform a pediatric Phase IV, open label, single arm, single dose, pharmacokinetic study that involves dosing the drug product to children equally between the ages of 6 and 11 and 12 and 17. The study also requires that the children be genotyped for the CYP2D6 and the bioanalytical samples analyzed for hydromorphone.

The Agency has also requested that Sovereign perform a Phase IV study to assess the safety of hydrocodone and guaifenesin to children 6 to 17 ages with symptoms of the common cold.

It's interesting to note that the PREA requirement does not apply uniformly to all NDAs as mandated by the Best Pharmaceuticals for Children Act. The Agency needs to look into this, why this has happened. Specifically, a similar NDA with the same active ingredients was approved approximately six months after Sovereign's approval. The two NDAs are not equivalent, but the other NDA was not required to do PREA studies. I'd like to point out that if the Agency requires that Sovereign's NDA do PREA studies, then both NDAs should be required to do the same studies, in order to be in compliance with Best Pharmaceuticals for Children Act.

We have directly brought this issue to the Agency without proper resolution. Sovereign continues to remain frustrated that the PREA requirement was not appropriately applied to a second NDA.

That said, the new data and information have been made available to the FDA, which has been made public during reconsideration of the possibility of revocation of the Agency's call for opioid clinical studies in children. On April 20, 2017, the FDA issued a drug safety communication. FDA restricts the use of prescription codeine pain and cough medicines, and tramadol pain medicines in children, and recommends against the use in breastfeeding women.

The Drug Safety Communication stated that the codeine-containing medicines carried various risks including slowed and difficult breathing and death, which appeared to be greater risk in children under 12 years, and should not be used in these children. These medicines should be limited in some other older children.

In response to the data information, FDA added its strongest warning called a contraindication to the warning labels of codeine and tramadol, alerting that codeine

should not be used to treat pain or cough in children younger than 12 years old. At the same time, we are required to do clinical tests on these age children.

The Drug Safety Communication also added that the new warning to the labels of codeine and tramadol, to recommend against their use in adolescents between 12 and 18 years of age, are obese or have conditions such as obstructive sleep apnea and severe lung disease as been presented earlier today.

Sovereign understands that for this pediatric subgroup, hydrocodone is not directly contraindicated, but believes that FDA's warning is sufficient to warrant reconsideration of the appropriateness of performing the PREA required pediatric studies in adolescents between 12 and 17 years old.

Hydrocodone is synthesized, as previously discussed, from codeine. Hydrocodone is a metabolite of codeine and combines to the significant respiratory depression of all age groups, but is especially dangerous to children and adolescents. Hydrocodone is currently contraindicated in children at this age due to respiratory failure.

As previously discussed, the Tussionex labeling states that under pediatric use, in pediatric patients as well as adults, the respiratory center is sensitive to the depression action of narcotic cough suppressant in a dose-dependent manner. Caution should be exercised when administering Tussionex, Pennkinetic extended-release solution to pediatric patients six years of age and older. It goes on to state that hydrocodone affects the center of the controls of respiratory rhythm and may produce irregular and periodic breathing. It is Sovereign's belief that hydrocodone products be contraindicated for pediatric population under 18 years of age, and that Tussionex

labeling should be revised to reflect such stance.

Sovereign contends that the performing the PREA required PK study and safety studies isn't appropriate and places both children and adolescents at undue risk. There is no evidence that the conduct of such a study would provide any data that would add value to the contraindication or warnings that FDA has already implemented. Sovereign's product currently contains the warning for children under six, and the safety and efficacy is not shown in patients under 18. Based on the most recent statements regarding codeine, Sovereign would welcome working with the Agency to make stronger statements regarding the use of hydrocodone in the pediatric population.

Furthermore, Sovereign is concerned that the IRB would not be able to prove the proposed studies, given the additional safeguards required for children in clinical investigations. Additionally, if these studies were to be performed and an adverse reaction or death occurred, is the FDA prepared to take full financial responsibility because the Agency has required that these studies be performed? This full responsibility needs to be provided by the Agency, in writing, prior to any opioid drug dose to pediatric populations. I know this is non-standard, but you are putting a population at significant risk doing these type of studies.

In particular, because there is more than a minimal risk to children and adolescents in taking an opioid drug, an IRB, would have to employ an exception for the study to be performed; yet exceptions are applicable here since a single dose, which is important to recognize, pediatric study would not provide a direct benefit for the individual subject, nor would yield generalizable knowledge about the subjects' disorder or condition.

As a result, a clinical study could proceed only if the IRB and FDA found that the study presented a reasonable opportunity to further the understanding of prevention or alleviation of a serious problem affecting the health and welfare of children. And that is in 21 CFR 50.53. Opiates that provide adequate relief of cough do not qualify for serious health problems exceptions. Thus, there is no medicine reason for an IRB to approve the dosing of children with opioids as subject human precaution should not be granted. Sovereign believes that the FDA and the Pediatric Advisory Committee reconsideration should lead to a revocation of the PREA opioid requirement for all pediatric age groups. Thank you very much.

DR. DRACKER: Thank you. You haven't coughed once, so you won't be able to get a prescription for the medication. Are there any questions?

DR. PATRICK: Just curious, for the folks in the FDA, if there is a contraindication from whatever group for these products, would they still have to do these studies for PREA?

DR. SEYMOUR: So the contraindication that I think he was focusing on was for codeine. Their product is actually a hydrocodone-based product. But in the codeine-based products, when we did the contraindication in children, less than 12 years of age, we asked the companies to amend their pediatric studies so that they're only doing them in children 12 and older. So we would not ask for them in that contraindicated age group.

DR. PATRICK: Just a quick follow-up. So if from this group or another group there was a similar contraindication for hydrocodone, then there wouldn't be a requirement for those studies for PREA?

DR. SEYMOUR: That would be my understanding. I mean, if we ultimately contraindicated the use of these products, or said they shouldn't be used, some kind of labeling, I think it would be a very unusual situation that we would ask for pediatric studies in an age group we didn't think they should be used.

DR. PATRICK: Thank you.

MR. LAWRENCE: One comment is that the clinical studies required a single dose, not a steady state, effect of hydrocodone on pediatric studies. So, the reality is you are getting a PK number off a single dose, which I understand the significance of that. But as far as doing safety studies, you're doing one dose and you're evaluating a safety on one dose. It doesn't really make a lot of sense to put those children at risk for such a type of clinical study.

If you want to do a steady state or those type of things, maybe, but then you'd have to be really careful to make sure that you were monitoring those children very well, so that there was not any adverse event to occur. Serious one, anyway.

DR. DRACKER: Yes.

DR. CUNNINGHAM: So you gave us the information for 50.53 with the potential of no direct benefit. But if all of these children are symptomatic, isn't there actually the possibility of direct benefit from the treatment of these symptomatic children?

MR. LAWRENCE: I have a question for you. If you're going to -- I'm not a doctor, so I'm sorry, I represent a pharmaceutical company, but -- when you dose a child, you give them one dose of hydrocodone, is that going to be really effective? Because I know that my wife has had pneumonia before and she's received Tussionex

for that. And she received it for a length of time to kind of subdue the pneumonia effects, and took many doses of that. So, is a single dose really going to be appropriate for that?

DR. CUNNINGHAM: Others can weigh in, but yes, I think a single dose can be effective. And I also think it may be in the context of giving the single dose as part of the study, but then continuing the therapy if it's thought that that would be effective from a symptomatic standpoint.

MR. LAWRENCE: Okay. Because that technically is not in the protocol currently, that they would have that option.

DR. DRACKER: The biggest issue we deal with clinically is children not sleeping at night. And so for many parents I commonly get the request to use something for cough at nighttime more than any other time. And so it is, I think, feasible to consider single-dose use when the child is going to sleep. And that's the time most parents seem to want to use medication. Yes?

DR. NEVILLE: I have a question, just to clarify. The compound we're talking about is codeine containing?

MR. LAWRENCE: Codeine and guaifenesin.

DR. NEVILLE: I would argue that a single dose does provide safety information based on polymorphisms in children, and you can detect sleepiness, et cetera. And if the dose is low enough, it can still be safely given, yet PK can be extrapolated to steady state. I would argue that's the safest way to study it in that age group, as a pharmacologist.

MR. LAWRENCE: Okay. Thank you.

DR. DRACKER: Any other questions? Okay. We'll take a break and we'll reconvene at 11:05 for the next presentation. Thank you for your participation.

MR. LAWRENCE: Thank you.

[BREAK]

DR. DRACKER: The first presentation after the break is by Dr. Sloan, who is an industry representative for UCB Pharmaceuticals. Thank you.

INDUSTRY PRESENTATION -- UCB PHARMACEUTICALS, LLC

DR. SLOAN: Thank you to the Advisory Committee of the FDA for allowing us the opportunity to speak. Good morning. My name is Victor Sloan. I'm a rheumatologist and Development Strategy Lead in the Immunology Patient Value Unit at UCB. I also hold an appointment as Clinical Associate Professor of Medicine at Rutgers Robert Wood Johnson Medical School. I'm here today to tell you about UCB's position on the use of Tussionex for cough in children.

At UCB, we're committed to ensuring that all of our products bring value to patients. An integral part of this commitment is the regular review of all of our products, using both routine pharmacovigilance and our senior level benefit risk board which has overall governance for benefit risk assessment across UCB, and of which I am a member.

In 2016 we undertook a review of Tussionex, considering modern pharmacovigilance methods, changes in clinical practice, and review of literature using up-to-date methods. The conclusion of this review was that the benefit risk ratio for

Tussionex in children was no longer favorable. I'd now like to take you through the process that led us to this conclusion.

Here's a brief regulatory history of Tussionex. Hycodan was the first hydrocodone product approved in 1943. In 1976, there was a determination that hydrocodone was not appropriate for over the counter use, but was "safe and effective" if given by prescription. In 1982, a DESI evaluation found that Hycodan was effective for cough but would have to go through the NDA process. In 1983, an NDA was filed under 505(b)(2) referencing both Hycodan and the monographs for hydrocodone and chlorpheniramine to support safety and efficacy. The NDA for Tussionex was approved in 1987. And as a reminder, all of these actions occurred prior to the Pediatric Rule in 1998, and PREA in 2003.

At present, Tussionex is indicated for relief of cough and upper respiratory symptoms associated with allergy or cold in adults and in children at least six. As of 2008, following a proactive labeling supplement submitted by UCB, Tussionex has been contraindicated in children, under six, due to the risk of fatal respiratory depression. In 2011, following an FDA recommendation, UCB adopted a unit of use presentation and discontinued the 473ml bottle.

As part of our benefit risk assessment, we queried our internal safety database. Since approval, we have received 391 individual safety case reports. Of these, 35 or nine percent were in children. The cumulative exposure in adults and children was approximately 673,000 patient years, based on UCB sales data. This database does not allow us to determine how much of this exposure was in children.

Of the 35 safety cases in children, 18 were serious. None of the 35 cases

occurred after the introduction of the unit of use presentation. Of the 18 serious cases, 11 were in children under six. And of the 18 serious cases, ten were fatal. And of these ten, nine were classified as overdoses or had toxic levels of hydrocodone at autopsy. Six of the ten deaths were in children under six. One occurred post-contraindication. Of the 17 non-serious cases, 14 involved medication errors. And all of the medication errors prior to the introduction of the unit of use.

Our comprehensive review looked at the totality of evidence regarding opioid use for cough and/or cold in the pediatric population. This review included internal safety data, medical literature, such as a 2012, review of studies of cough medications in children, the 2015 joint meeting of the Pediatric and Drug Safety Advisory Committees, the 2015 EMA report, and the 2016 American Academy of Pediatrics Clinical Report.

As mentioned, it's now generally accepted that the best treatment for acute cough in children is treatment of the underlying disease. Of note, while hydrocodone is metabolized by Cytochrome P450 2D6, this pathway is only one of the Cytochrome pathways involved, and therefore rapid metabolism by Cytochrome P450 2D6 appears to have only a minor impact on the metabolism of hydrocodone. Nevertheless, we believe this to be an additional risk factor that we considered as part of our overall benefit risk assessment.

As mentioned, in January of this year, UCB filed a label supplement proposing limiting Tussionex to patients 18 years or older. Of course, the contraindication for children under six will remain in place.

As previously noted, current best practices and evidence suggest that the

best treatment for acute cough in children is management of the underlying disorder. Our comprehensive review revealed no new safety concerns, but also did not demonstrate any robust evidence for efficacy in the relief of cough or upper respiratory symptoms in children.

Applying modern evidence and pharmacovigilance methods, we determined that the benefit risk ratio for Tussionex in children was no longer favorable. Even though the risk minimization measures, contraindication under six and unit of use, reduced serious and fatal cases, cases still occurred. And therefore, as previously noted, UCB has submitted a prior approval supplement proposing limiting use of Tussionex to patients at least 18 years of age. Thank you for your attention and I'd be happy to take any questions.

DR. DRACKER: Thank you. Questions?

DR. WAGENER: Given the fact that historically this drug has been used in under 18-year-olds, what would be the company's plan for avoiding that use if the label was changed to be 18 and above?

DR. SLOAN: As I mentioned, based on our benefit risk assessment, we've proposed limiting use to patients over 18. We've proposed label language to the Division, and that label language as well as any communication or risk minimization measures would be the subject of discussions with the Agency.

DR. DELOST: I was reviewing your safety information and you said you have 391 reports to you?

DR. SLOAN: Correct.

DR. DELOST: Was that included in the FAERS reporting system?

DR. SLOAN: I would have to defer to someone at the FDA to answer about question about FAERS. Those were spontaneous safety reports to us. Obviously, all serious cases are reported to the Agency.

DR. DELOST: Okay.

DR. STAFFA: I can just add in that when manufacturers are required to submit reports, there are regulations governing that. So those would go into the FAERS system. But FDA also receives reports directly from providers and patients as well.

DR. DELOST: Okay. Because I was looking at the numbers, and the literature that we reviewed did not have that many cases from the FAERS report going back to 1969. I was wondering, we only had 64 cases of codeine and 38 cases of hydrocodone in the FAERS report.

DR. STAFFA: I think it highly depends on how one does the search and identifies the cases, so you'd have to get into the details to compare the two.

DR. SLOAN: And I should also clarify that those 391 were also in adults. Only 35 were in children.

DR. DELOST: That's a good clarification there.

DR. SLOAN: Other questions? I'll give you the gift back of a few minutes.

DR. DRACKER: Okay. That was -- we went easy on him. Next presentation is by Dr. Sharon Levy, reporting the Opioid Misuse and Opioid Use Disorders in Adolescents. Thank you.

OPIOID MISUSE AND OPIOID USE DISORDER IN ADOLESCENTS

DR. LEVY: So I want to thank you for inviting me. My name is Sharon Levy. I'm the Director of the Adolescent Substance Abuse Program at Boston Children's Hospital and an Associate Professor of Pediatrics at Harvard Medical School. And I have nothing to disclose for this presentation.

So, as this panel is well aware, this picture just reminds us of the distinction between opiates, which are naturally occurring compounds such as codeine derived from the opium poppy, and opioids which are semi-synthetic or synthetic products such as hydrocodone. All of these products, though, have the same effect on the μ -opioid receptor, so they bind to the same receptor and cause all of their mechanism of action through -- primarily through, there's more than one opioid receptor, but primarily the clinical and the misuse types of symptoms are all modulated through the μ -opioid receptor.

This is a picture of the central nervous system showing places that have very high density of μ -opioid receptors, and these correlate to the effects that we see from opioids. So, for example, the spinal cord is of course associated with the analgesia we get from opioids. The brain stem for respiratory suppression and also central cough suppression, which is the topic of conversation for today. The areas of concern for addiction medicine primarily involve the limbic system, which changes there are thought to be related to the obsessive use of substances that develop with addiction in the prefrontal cortex.

And in this cartoon, I'm just showing what happens with heavy exposure,

exogenous exposure, of any compound and we get some tolerance. I've actually shown it in this cartoon as the cells developing more receptors, thus making them a little bit harder to trigger from a single receptor. And of course, when we take the exogenous chemical away, what happens is that we're left with this altered cell which is now harder to trigger, and this can lead to cravings and is associated with compulsive use.

And this loss of control or addiction can happen in any age, but it's notable that adolescents are developmentally primed to use drugs, to initiate drug use. And as a developmental behavioral pediatrician, I want to make the argument that the reason that adolescents use drugs is really largely driven by developmental neurobiology.

I'm showing here scans of human brains. These are MRI scans and the arrow is pointing to ten years old because at that age the brain is generally the same size and weight as it is in adults. And actually, for most of human history, the age of about 12 or 13 was considered the age of majority, with the concept of adolescence being relatively modern.

Now that's really interesting because I did a Google image search under the term "adolescence" and these are a couple of the first pictures that came up. And you can look at them and go, how is it that we didn't recognize adolescence, you know, before the very recent times. You know, they do seem, on a quick glance even, to be a little bit different from fully mature adults.

The answer is that they are neuro-developmentally quite different from adults. Even though the brain might be the same size and weight, it functions quite differently, as we all know. This is a slide showing the basic stages of neuro-development. On the left we see a brain slide at birth, few neurons and few connections

between them. In the first phases of development, what happens is you get rapid development of both neurons and their interconnections. And the middle panel is showing this phase with what looks like a dense tangle of neurons.

And then as development progresses, we actually see pruning and we end up with a brain that actually has far fewer connections, fewer cells and fewer connections, but that then get myelinated so the connections are larger and faster. So, there's no net change in weight, but there's very significant change in function.

And as a developmental behavioral pediatrician, I want to point out that these steps of brain development don't happen in the entire brain at the same time or at the same rate. In fact, what's been known for a long time is that there's an orderly progression, generally thought of as from back to front. And here we can see MRI scans showing brain development. On the left you have the brain of a five-year-old. The blue areas are developed, where the green and red are still immature. And you can see that there's this orderly progression. And in this line, you can see that even at age 20 there's still a fair amount of green and still some development to go. This process is now thought to come to its conclusion sometime in the middle 20s.

And if we look at the area that's developing, what's really interesting is that we can actually predict something about typical behavior of children at that age. In fact, in pediatrics, we tend to use these ages as a guide to determine whether a child is developing typically. So, for example, in the first year of life, one of the very active areas of brain development is in the cerebellum, which is of course responsible for gross motor control. And this is just happening right as children become very focused on learning to walk, right? This is during toddlerhood. And so, the brain development and

the behavior development go exactly together.

When we look at the preschool years, a very active area of development is the amygdala. This is responsible for emotional regulation and control. During this phase, we see those preschool tantrums, the terrible twos, which really largely go away by the school age years. Again, we would consider tantrums in a first-grade classroom to be something a little bit unusual, and suggests some sort of atypical or delayed development.

Now the nucleus accumbens, which is like a critical part of the reward pathway and thought to be very involved in the development of addiction, is part of the brain that undergoes maturation largely during the school-age years. And this part of the brain is responsible for salience. It helps us to distinguish between important rewards and unimportant rewards. And I'm going to get back to that a moment later, but this is thought to be very important for motivation and drive.

And then, finally, the last area of the brain to develop, prefrontal cortex, which is of course the seat of executive functioning and responsible -- it helps us with our good decision making. Things like self-monitoring, error correction, impulse control. Not well developed in teens, and so as all of those functions are developing, we see a lot of bad decisions being made.

But I want to get back to this issue of salience. This is a slide of an experiment. It was published over ten years ago now, but it makes a very important point.

In this experiment, researchers brought in children and adults of different ages. They gave them a simple task to do and then they watched what was happening in

the reward center of their brain as they were receiving a reward. What's really interesting is that youngest children are shown in blue and you can see that their response was the same whether they received a small reward or a large reward, because they haven't developed salience yet, right? To them, if you tell them it's a reward, it's a reward. Which is why we always tell parents of young children just give your kid a sticker to reward them, right?

And actually, it works very well. In fact, my son who's now 16 said to me the other day, "Hey, Mom, remember when we used to be on long car rides and you used to make me look out the window and count birds and give me a point for each bird?" And I said, "Yeah, I remember that." He said, "You know, I never got anything for those points." I said, "I owe you."

If you look at the green line, that's adults. And they do what you would expect. With a small reward, they give you a small positive bump in activity in the reward center. A large reward, you get a proportionally larger response. But what's really interesting is if you look at adolescents, with a small reward, they actually deactivate that part of the brain. They're actually like physically unhappy with small rewards. And again, when I look at my adolescent children and see them roll their eyes, I think it's nothing personal. It's really just brain development.

When you look at a large reward, though, what happens is you get this tremendous bump in the reward center. And this is what's driving behavior. There's a tremendous drive towards things that will stimulate the pleasure and reward center in the brain. And you can actually think of adolescence as the time period between the nucleus accumbens, or that pleasure and reward system, being really developed with the

prefrontal cortex still developing.

And so, there's a relative imbalance there and that puts kids at risk, particularly of drug use. Because if your goal is to increase signaling in the reward center of your brain, the best way to do it is by using substances of abuse, all of which have a final common pathway through dopamine, increasing dopamine in the pleasure system.

So, whether they get there directly such as, you know, cocaine or amphetamines, or indirectly, alcohol or the opioids, they're all going to cause these increases of dopamine firing in the nucleus accumbens and ventral tegmental area. And so, kids are actually quite a setup if drugs are available. They will use them. I'm not talking about individuals, but as a population. You can see that it would be a very good way to address this very normal neurobiologic drive.

And, in fact, not surprisingly, most drug use starts in adolescence. This is a graph from SAMHSA that shows us the peak ages of initiation are sometime between age 16 and 20, right as these processes are resolving. So that is an issue when we're prescribing medications with potential for misuse or diversion. This is a graph that shows the growth in opioid prescriptions from 1991 to 2013. This is largely for pain.

And this is a story that's well known to everybody. But what all of this prescribing has done, is it's created a tremendous reservoir. And if we look at youth use rates of opioids, you could see that it generally follows the pattern of the prescription rates, and because a big component of -- because it's creating this reservoir that kids can access. And developmentally, we know that they're going to be tempted to do that.

Now the red line is from the Monitoring the Future study, and this does not

distinguish between different opioids. So, the question asks, "Have you ever used an opioid?" And then they give examples. And they include codeine and Percocet as part of the examples. But we cannot really distinguish. It's harder to get data on individual substances. Codeine and hydrocodone are generally thought to be weakly reinforcing relative to the other opioids, but they certainly can be misused.

This is a picture of something that's called "purple drink" which has become popular. This is cough syrup containing codeine mixed together with Sprite. In my neck of the woods, this is referred to as "lean" by my patients. And so even though codeine and hydrocodone might both be weakly reinforcing, they can certainly be misused. And they are certainly used in this way.

Beyond misuse and the temptation to try something, I also want to make the argument that adolescents are developmentally vulnerable to developing substance use disorders upon exposure. And so, if you think that prefrontal cortex, you know, you can think of it as almost like a protective roof over the lower centers of the brain because it sends inhibitory signals down to lower parts of the brain. And, you know, in this way it regulates behavior. And because that inhibitory signaling is not strong in adolescents, they are much more prone to develop substance use disorders or loss of control over use upon exposure. And so, this is a big problem.

These are graphs showing that the age of initiation for alcohol and marijuana both are highly, highly correlated with the risk of developing a substance use disorder later in life. And the same pattern is true with use of prescription medications, including opioids. And the effect size appears to be similar, somewhere in the range of four to five times.

What's the mechanism and how big of a deal is prescribed opioids for this age group? Well, prescribed opioid use can certainly lead to opioid misuse. And, in fact, this is a study published in Pediatrics a couple of years ago. And what it showed was that even when -- this is pain medications, but opioids, even when they're appropriately prescribed, there's about a 33 percent increase in the risk of later misuse. Now that doesn't necessarily mean addiction. But kids who get these prescriptions are more likely to report having used an opioid non-medically. And that, in fact, almost always follows the prescription rather than the other way around.

So, it does increase the risk somewhat. There are other things that increase the risk as well. So prior history of alcohol, tobacco and marijuana use all substantially increase your odds of opioid misuse, trying an opioid.

And then how about the pathway from opioid misuse to opioid addiction? Well, there are a couple of mediators of that pathway. Younger age, genetic vulnerability, mental health disorders, and motivation for using substances all can increase your risk for developing an addiction. The best data we have is that the younger you are, by each year of age, your risk for developing addiction to opioids is about five percent. So, every year we can delay exposure to misuse of opioids, decreases your risk of addiction later in life by about five percent. These, depression, family history, post-traumatic stress disorder and other mental health disorders are all harder to control, but all have significantly increased the risk of developing addiction upon misuse.

And the motivation for misuse is also important. So, in this study, kids, about half of them who misused opioids reported that they were doing so to relieve pain,

even though they had not been instructed to by a physician or medical provider. I don't know that anyone reported that they were misusing for cough suppression. The other half were using to get high, or experiment, or because of the feeling it caused. And not surprisingly, the risk was elevated in both groups. Even people who were using it for its standard indication, but without medical supervision, they had about an observation of about 1.8 of developing addiction, compared to those who were using it recreationally had a much higher odds ratio.

Where does this leave us in terms of benefits and risks, because that's really the question for today. This will be the question to ponder. And I heard some of the earlier talks, so I know that this will be the discussion later this afternoon. But the benefits for cough suppression, I suppose, are questionable and still a matter of discussion. The risks are actually fairly substantial. All of these products have the potential for misuse and will be misused by the group of adolescents more likely than any other age group, and that is exactly the group that is at risk of developing addiction.

And so, how do you manage all of that? I don't know. But one thing I will toss out there is that it's not clear to me that changing the age will have the largest impact on this, because most of the misuse that we see in adolescence is actually due to diversion. And so, it's not necessarily that kids are misusing the medications prescribed to them. They're misusing the medications that they can get their hands on that are in those medicine cabinets. There's a small increase in risk for having your own prescription, but that's relatively small. And so, whether you can really change this balance just by deciding to limit the indication by age, to me, remains a real question mark and something I put out there for the committee to struggle with.

And finally, I want to end there, but I do want to just point out on a completely separate topic, the good work of the American Academy of Pediatrics in working to identify and treat opioid use disorder. Thank you.

DR. DRACKER: Thank you. Go ahead, Michael.

DR. WHITE: I was looking at the papers, and I've listened to you before speak about this. And a lot of data that we use is based on nonmedical use, and a lot of it is, have you used, within a period of time, an opioid that was prescribed without a prescription?" And it doesn't really quantify that very well. It could be one tablet or two tablets or three tablets. At what point do we go from using one dose of a medication because, God, my leg hurts and I've got some, to addiction and the definition of an addicted person? Because it seems like the literature that we have available to us is not terribly clear on that point.

DR. LEVY: I think you make a really excellent point. The literature often confuses the distinction between misuse and addiction, which are two completely things, right? Misuse is typically any non-recommended use; so, it's either not prescribed to you or used more than or by a different route than was prescribed to you. Whereas, addiction is compulsive, repetitive use or loss of control over use of a substance. They're not the same thing. You can't get to addiction without starting really by misuse.

So, obviously, reducing misuse, cutting it off, will ultimately reduce the pathway to addiction. But they're not the same thing, and it's not clear. I showed a paper that showed an increase of risk of misuse for people who've had prescriptions, but it's really not clear whether that increase in misuse actually leads to addiction or not. Like you said, it could just be because these kids have access to the medication right in

their medicine cabinet, and so, you know, they have a headache and they take it. And whether that means they're going to end up with an addiction, you know, is not clear.

DR. WHITE: Can we say that reducing the availability will reduce the risk for addiction? Since addiction is related to poverty, it's related to educational status, it's related to so many other factors. Can we tease out and say if we prescribe instead of a week's dosage, a three-day dosage of an opiate-containing drug, that we're going to decrease the risk for addiction in the future?

DR. LEVY: These are questions that I think we're all struggling with as a society. You know, I think when you're talking about adolescents, a big part of the issue is access to a reservoir. And whether that's because -- and that has to do with the vast overprescribing, over the past more than a decade, of opioids. We have scattered around the medicine cabinets of the country, we have a vast reservoir.

Now anything that we can do to reduce that reservoir, I would say will make an important impact. None of this has ever been studied, of course, but it stands to reason that prescribing smaller numbers and smaller amounts, shorter courses, would all make a difference.

DR. WHITE: But we made that argument for prohibition and alcohol, and we made that argument for marijuana, and we're rapidly approaching legalization of marijuana. Yes, it seems obvious, but do we have data? We're supposed to be looking at data. Do we have data to drive that as a process that we can rely upon?

DR. LEVY: Well, if you look at the other substances, a lot of people would argue that prohibition worked, depending on what you mean by worked. Alcohol consumption rates were much lower during prohibition. And with regards to marijuana,

we know that changing policies -- so I know that there's been a lot of confusing reports out there, but there are some really nice reports showing that places with the more liberal policies -- and this really isn't surprising -- have a lot more marijuana use, both in adults and in adolescents.

Access is without question, and availability is without question, related to risk of initiation. I think if you're asking about whether those two are correlated, I don't think that there's any convincing argument that they are not. There are other pieces of it, which is, you know, a lot of people consider alcohol prohibition a social failure, not because it didn't reduce rates of alcohol consumption, it did, but because of other issues.

DR. WHITE: Thank you.

DR. DRACKER: Yes.

DR. BRENT: Thank you very much for that presentation. It was extremely interesting. I'd like to explore a little bit the paradigm that you are putting forth, because I think this is fundamentally crucial to the issues that we are considering here.

You have these very nice graphs of availability leading to misuse, leading ultimately to addiction, and arrows going very clearly in one direction. But what do those arrows actually imply? Are they implying with certainty, in your mind, that this sequence of events naturally follows in a causal way, that the availability causes the misuse, which causes the addiction? Or are we saying that we know there are people that are predisposed to misuse, and predisposed to addiction, and they are going to follow this sequence, and it's just the natural course of their disease, and it's not because we did this by making the drugs available?

DR. LEVY: Thank you for the clarification. The model is clearly -- that I put up there with the arrows is clearly an oversimplification. I just wanted to show where the data shows where the associations are. So, you know, my clinical experience, I can tell you that having your own prescription is not at all the driver for ending up with an opioid use disorder. So most adolescent use is actually coming from diversion.

Now, why is there so much diversion? You could argue quite logically that because there's just a lot of this stuff around. So, why are kids using opioids? Because that's what's easily available to them. And if you look back at the studies from 10 or 15 years ago, you'll also see that there was reduced -- the perceived risk of harm with use, and that was partly due to the idea that these were prescription medications so they'd be safer to use. And that is something that is very tightly correlated with increased use.

We have big reservoirs. We had kids, at least, believing that they were safe, and you have a part of the population that I would argue is developmentally kind of prone to look for things that are going to cause large brain reward. We had, I would say, a perfect storm in that case. But that certainly doesn't mean that, you know, it's a linear track from having a prescription, to starting to misuse, to addiction. Not by any means. That's a vast oversimplification, and I didn't mean to imply that with the slide.

DR. BRENT: Thank you.

DR. TURER: This is more a comment about the diversion, and I had pulled the percentage of patients prescribed drugs, and the top 15 drugs prescribed by age. And it was really fascinating. In 1999, as well as 2002 to 2010, the number 12 and number 13 prescriptions for children are for hydrocodone and for codeine. And actually, it's codeine number 12, hydrocodone number 13.

And then data from 1999, which I have not been able to find updates, it appears that for those age groups, are number 12 to number 13. But as you go up the age groups, the narcotics become the number one prescription for men in the 45 to 54-year-old age range. And so, they're like number 12, number 13, both girls and boys. They increase to the number six prescription, 13 to 17. 18 to 24, number 4. And then it drops to number one by 45 to 54.

So, for diversion, we've got a really good case; these are being prescribed in amazing numbers. And we should get updated numbers. I believe these came from FDA.

DR. DRACKER: Yes, sir.

DR. MEISEL: In about half of the states, codeine syrup is available over the counter, Schedule V, about half the states, they're not. That presumably one would assume in the states where it's available over the counter makes it more available. Is there any data in the states that have it available over the counter, versus those that have restricted it to Schedule III, that differentiates the future abuse, addiction, whatever, in this population? Does that make any difference, in other words?

DR. LEVY: Yes, so that's a good question that I can't answer off the top of my head. There is a survey that's the Youth Risk Behavior Surveillance system, that's given statewide. I believe they ask a question, at least in recent years, about opioids. So, it's something that can be looked at.

One of the things to remember, though, is that we don't really distinguish between which opioids kids are using. It's like one combination question. And how much, you know, what proportion codeine and hydrocodone play in that. You know,

clearly, they're being misused, but whether it's -- how much of that opioid misuse represents codeine and hydrocodone, I don't know. And that might obscure those kinds of relationships.

DR. DRACKER: I just want to comment first, and it's something that we're dealing with, at least in the Central New York area, is the explosive number of children born to mothers who are addicted to opioids. The opioid use, primarily because of the availability of heroin, both easy access and the inexpensive cost of heroin, which is a fraction of what it costs for diverted oxy and hydrocodone, is really problematic.

And the problem we're having these newborn children who are on scores for days after they're born is just really very significant. And unfortunately, we're not discussing the newborn child addicted to these drugs, but it's really a major issue for us.

DR. PATRICK: Stephen Patrick. Great presentation. Just a quick question. Do we have any data on -- and you've alluded to this a couple times -- on type of opioid? Does the National Survey of Drug Use and Health have anything or other surveys on codeine specifically, or anything like that? Or is it all just super general?

DR. LEVY: So I went back and I looked again in preparation for this presentation, and really there is not much that looks at specific opioid. And I've got to tell you, working with kids, I'm not sure that they always know.

DR. DRACKER: Any other questions? All right. Thank you very much for the presentation, and we'll reconvene at 1:00 for the afternoon session. Thank you.

[LUNCH RECESS TAKEN]

OPEN PUBLIC HEARING

DR. DRACKER: We are going to start the afternoon session with the open public hearing session. We have two presenters for the open public hearing. We also have a statement that I think the committee members received from law firm of Hyman, Phelps and McNamara.

First let me read the same about the open hearing. Welcome to the open public hearing. Please state your name and your affiliation relevant to this meeting. The Food and Drug Administration believes that the Agency, and public benefits, from a transparent process that helps ensure that the FDA decisions are well informed by the advice and information FDA receives from its advisory committees.

If you have any financial interest relevant to this meeting, the FDA encourages you to state that interest as you begin. Such interest may include a company's or group's payment of your travel or other expenses, or, grant money that your organization receives from a sponsor or a competitor. If you do not have any such interest, you may wish to state that for the record. If you prefer not to address financial interests, you can still give your comments.

Regarding the statement which was received from Hyman, Phelps and McNamara, I have to read a statement, which is in response to that and relevant to that statement. One comment was submitted to the docket in reference to today's advisory committee from the law firm of Hyman, Phelps and McNamara, PC. The committee has received the written comment prior to the meeting, and the public has access to the comment through the FDA's website for this AC meeting. No other comment is made

for this.

We have two speakers today as stated. Could you please approach the microphone and state your name and background.

DR. ZUCKERMAN: I'm supposed to be speaker number three, but if you want me to go first I'm happy to. I do have slides however.

DR. DRACKER: John, what would you like me to do?

DR. ALEXANDER: Sorry. You can get the slides up and we can go ahead.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman. I'm President of the National Center for Health Research. And I do have stock in Johnson and Johnson which may or may not be relevant to my comments today. While we're waiting, I'll just say that the National Center for Health Research is a private nonprofit organization. We don't take money from pharmaceutical companies. As a center, we have no conflicts of interest.

And the center conducts research and scrutinizes research conducted by others with a particular focus on looking at safety and effectiveness of various medical treatments. And also looking at conflicting evidence and making sense of why some data seem to indicate whether something is safe or effective, and it may conflict with other research. And I'll start as soon as my slides are up. Great. Next slide please. Thank you.

Okay I'm going to start out by looking at the effectiveness issue which was raised this morning. I was a little surprised that the Corcoran Reviews were not mentioned. Corcoran did do a systematic review just last year looking at data on

codeine for children ages 0 through 18, for chronic cough, and they found no data -- I shouldn't say no data -- to support; they actually found no data that they thought was relevant because they were particularly focused on randomized clinical trials. They had done a systematic review a couple of years earlier on codeine for children for acute cough, and in that case, they actually found no data to support effectiveness as well as no data to support not being effective.

The European Medical Agency Review also look at codeine as a cough suppressant, focusing on quality studies, and found that there was no difference compared to placebo. There were two studies that found that codeine was as effective as other non-opioid cough medications, but had worse side effects. And then an even older Corcoran Review had looked at adults and children and found no difference between medications with codeine and placebo for acute cough. Next slide please.

Just to remind you that there is this issue where 1 in 12 people, adults and children, have a gene that causes the enzymes that transforms codeine into morphine; it causes it to be overactive and that can be very dangerous. So, that's 1 in 12. And just to remind you that, of course, children are less capable of metabolizing codeine, and that too much morphine can slow down the respiratory function and can be fatal. Next slide.

You know the risk. Just going over them a little bit. Can be fatal, but there are other risks as well. And so when we look at effectiveness, and of course, as has been mentioned, we have to look at benefits versus risks. There are a lot of risks, and benefits are questionable whether you focus on the Corcoran Review or the other reviews.

Just want to remind you that the standard for the FDA is not whether a product is proven to not work, the company has to prove -- the companies in this case --

that their product actually does work. So, the effectiveness issue, even if there's no data or if the data are conflicting, I think it's safe to say that there's not clear evidence of benefit for cough either acute or chronic.

And I just want to mention another thing. That it has been said that, of course, a lot of times children and adults, for that matter, like to take cough medications with codeine at night because it helps them sleep. But I would call that a sleep aid. I would not call that a cough suppressant. Next slide please.

Another issue that was raised, in the documents that you were provided, was that cough medication with codeine can be particularly dangerous for children who are obese. And that therefore, there was some question whether they should be particularly listed as not taking medication of this type.

This pie chart represents all children in the United States. And even in this day and age of obesity, two thirds of children are considered either healthy weight or underweight. And you can see that 15 percent are listed as being obese, but are perceived by their parents as being a healthy weight. And 14 percent are objectively overweight, but again are perceived by their parents as a healthy weight. And only that small little sliver, four percent, are children that are either obese or overweight whose parents recognize them as such.

We have to deal with the fact that first of all parents are not aware, or don't want to recognize, that their children are obese or overweight. And clearly their pediatricians are not telling them that, or at least not to the point where they're registering that. When we look at potentially treating children that are obese differently than other children, we have to consider the fact that their parents, and to some extent

perhaps their doctors, haven't really acknowledged the fact that they're obese.

That's my last slide. And overall, I just want to say that I appreciate the opportunity to be here today. I think the discussion has been really helpful and interesting. But I have been very concerned about the fact that, in the lack of clear data that taking opioids as children has any result in opioid abuse as teens and adults, that's been questioned. And of course, we don't have good data, but it seems to me logical that when we have a society where so many young children and teenagers are being given opioids, that we have to really rethink that. Particularly, given the total lack of evidence that these drugs are effective for cough suppression. Thank you.

DR. DRACKER: Thank you very much. There was someone else that wanted to speak today. If they're in the audience, please come to the microphone.

Okay, I guess that will close the public hearing period. John, should we just move on to the next part? Okay.

ADVISORY COMMITTEE QUESTION AND ANSWER PERIOD

DR. DRACKER: We have five items for discussion before we get to the question period. John, would you prefer I listed each discussion point first and we discuss it? Or, go through all five at this point.

DR. ALEXANDER: I can basically go through the questions first if you'd like. But I want to make sure that you spend enough time on sort of each of the sub-questions; but I'm okay with sort of going over them all.

DR. DRACKER: Okay.

DR. ALEXANDER: Can we have the slides put up?

DR. NELSON: Yeah. We should post the slides that John had.

DR. DRACKER: First item is, what are the benefits and risks for the codeine hydrocodone products intended for treatment of cough associated with allergy or the common cold? In your deliberations, include the benefits and risks of these products for the patients, as well as the wider public health impacts of opioid-containing medications. Should we stop there and discuss that first?

DR. ALEXANDER: Why don't you just go over the rest of the questions; and if you cover some of the other topics, while you're sort of discussing each one, then that's fine.

DR. DRACKER: B) Does the benefit risk assessment change for treatment of cough and other specific circumstances? C) Are there important differences in the benefit/risk, between hydrocodone and codeine, that would affect the recommendations about use in pediatric patients? D) Are there differences in the benefit/risk assessment for a specific pediatric age groups? E) How do the wider public health concerns, of opioid containing medications, impact your benefit risk assessment of codeine, and hydrocodone products, intended for the treatment of cough?

DR. MCGOUGH: I have a question of clarification to Dr. Starke. I just want to be sure I understand the DESI process correctly. My impression is that given the needs of the time that was probably reasonable and the best way to approach that -- but basically it sounds to me as that was really expert consensus of available evidence which would be a level B or C level of evidence, I think by our standards today. My impression, and correct me if I'm mistaken, is again at the time, that was probably a reasonable standard and the FDA determined efficacy based on that.

But today in 2017, we've got 20 to 30 more years of experience, and our standards today in terms of looking to double blind placebo-controlled studies that are adequately powered, that have reasonable effect sizes and significance, et cetera, would be different than what was probably done in 1967 and '72, et cetera. Is that a correct impression?

DR. STARKE: Overall, I'd say yes. But it all depends upon what -- for the effectiveness evaluation, primarily, there were publications that were used to evaluate any individual component in a drug combination. Whether those studies would match today's requirements, that's a difference issue. Overall, when you look at them, many of them weren't placebo controlled. Some were, but they might not reach the rigor of today's studies.

DR. MCGOUGH: Well, and given that the pediatric rules didn't really come in until the '90s, I mean, were there actual placebo-controlled studies in children in that review? Or, are we really talking case reports, letters to the editor, personal convictions? It is what it is, but I think as we assess risk plus benefit, we have to really have a sense of how solid the benefits are.

DR. STARKE: There's different levels here. What we would ask for now is a far different level than what was probably accepted at the time. Even if you say a drug is efficacious in children, the level of evidence in terms of PK data, safety data, efficacy data, may have differed.

Certainly, there have been, since that time, multiple advisory committees in the '90s -- and I can think of at least two or three -- that discussed just the issue of dosing of pediatric drugs. And this is what's most of these drugs; the adult dose and

then half for children approximately 12 to 18 years of age, and then half that dose for younger. That's the approximation of the dosing that's been used, whether that was the correct way to think about it. So, we've come a long way over time.

DR. DRACKER: Dr. Havens.

DR. HAVENS: In a certain way, arguing about the DESI findings doesn't make any sense. Because at best it was old studies done inadequately, which did not show clear benefit. And since that time there's many reviews. The AAP in 1997, says demonstration of the efficacy of antitussive preparation in children is lacking. The World Health Organization says no benefit in 2001. Corcoran does it twice, most recently last year. The best we could be doing is arguing about the difference between marginal effectiveness in narcotic preparations and dextromethorphan, one of which kills you and one of which doesn't.

If we were faced in any other setting with two potentially arguably, marginally effective drugs, although the data are not absolutely clear, one of which has lethal side effects and the other one doesn't, it wouldn't be a discussion. I've been at these meetings where those are the questions, and the drug with potentially lethal side effects doesn't get approved.

So right, DESI's not the point. The data from DESI are not available. The review data are given in the Backgrounder and in multiple references in the Backgrounder, and I can't see that they support, for any single person, use for what we're asked in allergy or the common cold, or even cough for that matter, in children.

DR. TURER: At best in terms of risk from acute cough it seems that the data we have heard today it's just quality of life. This isn't a life threatening illness. It's

a self-limited illness that is not life threatening. Risk of the drug versus the risk of the illness you're treating seems so disproportionate here. And we have other data regarding use of something as simple as honey that improved one of my favorite outcome measures, which was parental quality of life and sleep duration.

We have effective alternatives that have been tested. We have a disease with a very low-risk profile, yet we're looking at a drug that has a risk of death. That to me seems very disproportionate; that the risk of the drug far exceeds the benefit it would provide to the patient.

DR. DRACKER: Thank you. That was very succinct. Thank you. Any other questions? Comments? Yes.

DR. LIEBELT: I think that we're all familiar with the immediate risks of the drug itself. But I would like to just offer my opinion when you think about other risks. Whenever a medication is prescribed, it goes through a series of different steps. And certainly, as a pediatrician, as somebody who's involved in safety and quality, we know that errors can be made along that cycle. Errors can be made in the writing of a prescription. Errors can be made in fulfilling that prescription accurately. Errors can be made in what the caregivers, or the patient, or child themselves are given from the medication.

Those processes and the medication-management fulfillment cycle are all prone to risks that the patient will receive an unattended amount that could cause effects. And although the medication reconciliation process is sound, and makes good sense from a rational standpoint as a safety measure, again as a practicing pediatrician, we see that the process is not perfect. People don't remember what their children are taking.

And in our healthcare environment now, where children many times have to go to multiple different places for care, redundant prescriptions, redundant medications with the same components are being written with a lack of understanding from the caregivers about those potential redundancies. And it adds yet another risk to the child in giving a medication, as was nicely just stated, for a self-limited symptom, for a self-limited illness. Thank you.

DR. MCGOUGH: I just want to make one more comment. Actually, in response to you raising the issue of other negative results. I'm a child psychiatrist and basically an international ADHD person. So, I am prescribing all those other drugs that are inappropriately diverted. I fully agree. I thought Dr. Levy's presentation was spot on. I think the risk for initiation of drug abuse is very high in these developing brains. I think we can come up with innumerable examples where increased supply means increased diversion.

Marijuana's legalized for adults, kids start using it. You raise taxes or cost of cigarettes and alcohol, kids use it less. I mean, there really is a real difference between the more something is available, the more it is going to be misused and, in some cases, lead to adverse impact. I think the motivation is to minimize, to the extent that's medically necessitated, the use of these drugs. And I'm not hearing anything that really creates a strong argument for using these drugs in this age group.

DR. DRACKER: Any other comments? Yes?

DR. JONES: I just wanted to comment. I think we discussed a lot today about efficacy of whether it's actually efficacious in stopping cough. I think there's a big difference between efficacy and benefit, where we're being asked to say whether or

not these medications are beneficial for treatment of colds in children and allergies in children, cough related to allergies.

Dr. Oppenheimer presented a really great presentation that went down all the difference causes of acute and chronic cough in children, and outlined kind of what are the standard therapies for those, and these drugs are not included as part of standard therapy. And I think that the use of them is antiquated and now we have lots better therapies to treat coughs in children. I think from that standpoint, and the other data that we saw today, we can summarize that they are not truly beneficial for treatment of colds and allergies in children.

And also with the added risks related to the exposure to these drugs, having them in homes, being available for abuse, but also related to the alterations and how some children handle these drugs, which vary by race and ethnicity. You know, with the changing demographics of our country, there are some groups that may be at higher risk for these ultra-rapid metabolizer types and we should also consider that. And also with the increasing prevalence of things like obesity and obstructive sleep apnea, that's also a major concern.

I think there's a lot of things on the side of benefits where we see that these medications truly aren't beneficial for colds and for allergy-related coughs. And there are significant risks that should be considered.

DR. DRACKER: Yes?

DR. LASKY: Normally I think when we do a benefit/risk analysis we should be able to have in one column under the benefits what the benefit is actually. And be able to quantify it so 50 percent of the time children will see a decrease in their

cough, lasting from 10 days to 6 days, or whatever we're finding the benefit to be. So we're not in that position, I don't think, unless I've missed something, to be able to describe what the benefit is. If we can't describe the benefit, of course we can't contrast it to the risks.

The other point I want to make, which I think people have gotten at, is we're in a situation where I think we're lacking evidence. And lacking evidence of course is not the same as, you know, there is a possibility that codeine and hydrocodone are effective; it's simply that we're lacking high-quality evidence. When I looked at the evidence -- and this is just briefly -- there is the systematic review from Corcoran, which is high-quality evidence, but they did not find any RCT. So that's absence of evidence. And that was for codeine and chronic cough only.

And there was a Corcoran Review that was for OTC codeine for acute cough, but we're not looking at OTCs today. I'm not sure, with my brief look, whether there's an overlap of those drugs with the drugs we're concerned about today. I haven't seen the DESI analysis, and I can't say whether that's a high-quality or poor-quality evidence. And the expert opinion from April 2017, agreed that there was no effect but unfortunately expert opinion is at the very bottom of the hierarchy for quality of evidence. Again, does not mean it's wrong? It just means we are definitely facing the situation of no or poor-quality evidence.

I'd probably be cautious about making any statement about any kind of benefit. And that would apply to codeine. And I think there's even less of it in the materials that I've seen for hydrocodone.

In terms of risks, the evidence for respiratory distress is primarily case

series, and adverse events reports, which is an extension of case series. That's the next level up. It's slightly better quality of evidence, but we still can't quantify a risk. And in terms of widening the misuse of opioids, that seems intuitive that if the drug is more available, there's more opportunities for people to use it. And I don't even know how I would categorize that piece of information. It's not part of the evidence hierarchy, but I am considering it in terms of risks. Those are the kinds of issues I'm reviewing in my mind.

DR. DRACKER: Yes sir.

DR. PATRICK: It strikes me that the reason that we're here discussing this, is a combination of history and clinician inertia. And that, you know, this wouldn't get approved today. And I think we've seen overwhelming evidence, thus far, of very limited data on benefit and some concerning reasons for risks. In my clinical practice, and the bit of general pediatrics I did before my specialty training, I never prescribed this.

And it's true that opioids do suppress cough. I had a colleague once have a family member say to them that liquid Lortab works best for their daughter's cough. I mean, I think this is the issue that we find ourselves in. It seems to me we've heard overwhelming evidence today for lack of benefit and certainly; we know the risks of having an opioid prescribed.

DR. DRACKER: Thank you. Yes?

DR. HOEHN: I certainly agree with everything that everybody else has said in terms of the clinical inertia that was just mentioned and the lack of benefit. I think we need to be mindful here that there's very clear evidence of harm coming to

children. And to me there's no evidence of benefit from anything I've seen anywhere. We're treating a parent; we're not treating their children.

And if you go back to some of the data that was presented this morning, the vast majority of the time, it's not being prescribed by a pediatrician, it's being prescribed by family practice doctors and nurse practitioners who are probably responding the parent's need. What do I do, my child coughs all night? Yes, it's painful. Kids cough. I have three. Mine cough for about eight months of the year. But you know what, they've never had codeine and they never would have codeine, but I'm just saying it doesn't make any sense.

And I think to allow it to exist on the market, the FDA is giving everyone a false impression. It's giving parents a false impression. And it is leading providers, who are not following AP recommendations, to be prescribing the use of medications that are dangerous. That's my two cents.

DR. PATRICK: Can I ask you quickly, just for some clarification, why we're not talking about the OTC preparation of this as part of this meeting?

DR. DRACKER: Go ahead John.

DR. ALEXANDER: Sure, I can address that. Part of what we're doing here in trying to sort of address the prescription products, is we have made changes to the labeling, we've tried to address the information that we had based on the safety concerns. And I'm interested in hearing a little bit more discussion from people about what are the different risks that are being seen. The issue is in part for -- at least for codeine -- the recent changes that we made with regards to a contraindication for patients less than 12, as well as sort of the additional warnings for children that are in the

12 to 18-year-old age range, is based on the data that we had and the information that we had about safety.

Now there still seems to be a lot of concerns about sort of what the risk is overall of respiratory depression, even in the older age groups. But that's part of what we are trying to tease out from you. Is how much you are looking at this, as there's an individual risk to those older patients, that they would still have the same problems with regards to respiratory depression. Does it differ for hydrocodone versus codeine where it appears, at least from the data that we have, that the issue with regards to hyper-metabolism is more of an issue for codeine than it is for hydrocodone? Trying to sort those out.

In response to your question. We're trying to get the answer for the prescription products. We do think that ultimately, whatever decision that you make today with regards to what you would recommend for the prescription products, we will try to apply those consistent determinations to what is done with the OTC products. But the issue that we have there, is mainly that the monograph products are regulated differently. And our ability to sort of affect change in that is not as easy as it is for the prescription products. By focusing on this we're hoping to get the answers that we need about what direction to move forward.

DR. PATRICK: Thank you for that clarification. The one last point I would point out about the clinical inertia piece, as it's approved for even older kids if we look at some of the surveillance data that we got earlier, there were like 3000 prescriptions for codeine for infants. And so I think this is part of the broader conversation that we have in this group. But also dissemination of this because clearly,

some providers are still prescribing codeine cough syrups to infants.

DR. DRACKER: He had a question?

DR. MEISEL: Just to follow up on. It would be a peculiar public relations nightmare, don't you think, if the agency withdrew its approval for the prescription product, but the OTC product remained on the market.

DR. WAGENER: I'm going to bring this back a little bit to the questions. Specifically question 1a. I totally agree with Dr. Lasky. I see sort of three steps. First is the drug efficacious? And I don't think we need to even address that issue because the FDA has asked us not to. They've said let's assume it's efficacious, which means if you give enough to a person who's coughing, they'll decrease their cough. That's all it means. Doesn't mean that it's effective, which would imply that when used in the general population that people benefit from it. It just says it does something.

Number two is, what is the benefit from it? And if you look at question 1a, it specifically uses allergy and common cold as the argument for benefit. I think we've heard plenty of information. There's quite a bit that was referenced that would say that for allergy and common cold, both acute issues, that the management is not a cough suppressant, period. That in those situations for an acute disease, it's finding the etiology. Treating that or allowing time to pass. In that sense for question 1a, there's no benefit.

As far as risk is concerned I would point out that if overnight this suddenly became not used in people under 18, let's say, that has no reason to think that it's going to decrease the availability to the under 18 year old. They're still going to be available in the adults. You could still go to a grocery store and buy it over the counter. You can

still get a prescription for it if you're an adult. The adolescent can still find it left over in the adult's medicine cabinet. I really don't know if we should say risk is that kids are going to get a hold of it, and we're going to suddenly stop that. We haven't done that with marijuana. We haven't done it with alcohol. I don't see how it's going to happen with this drug.

As far as risk for mortality, we didn't see any data presented to us as far as the alternative drugs. They may have a higher risk for mortality for all I know, or at least a higher number. There are a hundred fold as many episodes of inappropriate use and side effect as there are with codeine. If there are a hundred fold of those events, there's probably some mortality there. I don't think it's going to change mortality much as a risk.

But I bring this back to benefit. And if benefit is zero, the ratio of zero divided by any risk is not calculable, and it shouldn't occur. I think in question 1a the answer is for allergy and common cold there is no indication, period.

DR. DRACKER: Skip, did you want to make a comment? Don't hesitate next time.

DR. NELSON: I was just going to comment that we do recognize that there would be an apparent inconsistency. But I'm reminded of the 10-year odyssey of the meetings that this committee has had over the years around the OTC monograph. It's not lost on us that there would be implications, as John said, for that discussion. But the process is much more complex in terms of rulemaking.

DR. DRACKER: Thank you. Yes?

DR. HOEHN: I just wanted to point out. I was doing some math from one

of the FDA presentations this morning, and one of them showed how they've decrease in one of the -- I believe it was one of the OTC preparations -- down to 200 mg and 100 cc of codeine. But that still means that a 20 kg child, which is the average size of a 5 year old, in 2 teaspoons gets a full dose of codeine, because that's one 1 mg per kg. So, it's not a negligible or homeopathic amount that's out there, if a 5-year-old can go get two teaspoons and that's equivalent of a full dose of codeine.

DR. DRACKER: Michael White. Thank you.

DR. WHITE: For those of us with ADHA, this list of questions is really difficult. I'm going to start with I don't think codeine and hydrocodone carry the same risk profile at all. Codeine is basically a prodrug. And I think that using prodrugs is often fraught with danger to begin with. And the danger is that you'll convert codeine to morphine at an inordinate level. In the data that we were given one to ten percent of Caucasians are rapid metabolizers, three percent of African Americans, somewhere between 16 and 28 percent if you're from North Africa, Ethiopia or you're Arab in origin.

Potentially this drug could be available to patients that have a one in three risks of being rapid metabolizers, which puts them at risk for death from respiratory depression. It seems a really high risk for a drug that may or may not have any potential benefit. And as to the benefit, the benefit has been reviewed by the American Academy of Pediatrics whether the drug is beneficial or not. And it's found that cough suppression for any of these issues is not even indicated by a fairly reasonable review group, I would say. Many of us are members of the American Academy of Pediatrics. And Dr. Johnson's our representative.

This issue has already been reviewed, and Dr. Turer pointed out nicely that you really don't even need to do cough suppression, except the parents really want you to. I would just wipe codeine out from the start because it carries much too high risk. And the only way we can assess that risk, is to know what CYP2D6 is, your status as an ultra-metabolizer.

And at the last meeting we reviewed this, there is no test to know if you're a rapid metabolizer or not. So, what you're supposed to do is, if you've had a previous bad reaction that suggest you're a CYP2D6 rapid metabolizers, such as death from respiratory suppression, you shouldn't take it again. I think without having a test that we can do to tell you that you're at risk for a drug that has risks, that doesn't really do much good, we shouldn't even be having this discussion.

Then we would go to the hydrocodone where there's still some risks if you inhibit the metabolite, because the hydrocodone itself is the active ingredient. I don't even know this other CYP, whatever it is. And I'm sure we have no way of assessing that one either. So again, we're going to give a drug to a group of subjects that are high risk -- and I don't know how common that one is. We weren't given numbers on how common that particular cytochrome is in the population, but it's got to be a reasonable number. So, again, we're going to be giving a drug, but in this case one that we want you to get rid of more quickly, that might make you get too much of it. Where the only way to know if you're going to have a bad reaction is to have had one in the past. Again, which is respiratory depression. And so if you die from using that drug, you shouldn't be taking it either.

I'm having a real hard time supporting either of these drugs for antitussives.

And then I think you haven't posed the question about use for pain control. Is that part of what you're going to ask later? I don't remember. No? Okay. So, we're just going to ignore that part. Okay. Thank you.

DR. DRACKER: Thank you. Yes?

DR. CUNNINGHAM: I had a couple of responses to the sub-questions, but also in response to the question about its use in pain. We in palliative medicine know that it's converted to morphine and don't use codeine. Many Children's Hospitals in particular have taken codeine completely off the formulary for that question.

If I look at the sub-question, so sub-question (b) does the benefit/risk assessment change for treatment of cough in other specific circumstances? I think if we had any data that said that these treatments were effective, then yes, it probably would change for patients with chronic cough. Where chronic cough is the equivalent detriment in your quality of life to severe COPD. That's (b) for me.

And (c) Are there importance differences in the benefit/risk between hydrocodone and codeine that would affect our recommendations? I think if either of them were effective, I think the hyper metabolizer would change that risk benefit. But since they're not effective, it's kind of a moot question in my view.

And then (d) Are there differences in the benefit risk assessment for specific pediatric age groups? And it comes back to the same thing for me. And then if we think of chronic cough and the detriment in quality of life, then we're looking at treating someone palliatively for chronic cough if it truly decreases their quality of life. And we have other options as we talked about; we have morphine that is the drug itself and we know how to dose that.

DR. DRACKER: Thank you. Yes?

DR. NEVILLE: If I could just comment. I want to go back to the indication because as a member of that round table, hydrocodone may be effective in end-of-life cough as an oncologist. And we talked a lot at that meeting about often you're using narcotics, who have other benefits, for things at end of life. But the point here is we're not talking about that. Perhaps there are other specific circumstances where these medications might be of benefit.

But my understanding was, today we're talking about cough and cold. And in the acute cough setting, I don't think we can answer the chronic cough question, because there are so many reasons, like Dr. Oppenheimer said, for chronic cough. And you have to diagnose the underlying reason and then treat that. But for me, going back to the original question the benefit/risk assessment -- of course unless you're the one coughing -- isn't there. But I don't want to get off track and generalize that to all populations, because narcotics do work as cough suppressants. It's just not appropriate for a self-limited, low-risk illness.

DR. DRACKER: Yes?

DR. CUNNINGHAM: The question (b) actually asks, in other specific circumstances. So I felt like we should at least open that up and address that sub-question, even though I'm in agreement with your assessment.

DR. DRACKER: If I could just make one comment. The years that I have been part of this committee, I've always experienced that we discuss medications, devices and treatment either for a specific disease treatment or prevention such in the case of vaccine. This is a curious discussion because we're discussing the use of a

medication for a symptom, not a disease state. And this is very different. Typically, we don't adequately address the cause of the cough. The cough is just a symptom.

And so we're discussing a treatment for a symptom which doesn't get to the etiology of the symptom. And a treatment for the symptom which has very significant inherent risks. So this is very different and I think something we have to keep in perspective, that we're discussing the treatment of a symptom with associated risks, which I consider to be unbearable. Yes, John.

DR. ALEXANDER: If I could just comment on that. I would point out that there are other symptomatic treatments and that is allowed. There are antipyretics that are approved for treatment of fever, without necessarily sort of specifying what the underlying condition is. There are treatments for pain that aren't necessarily specific to one type of pain or one source of pain. There is the idea that there can be a benefit in terms of alleviating a symptom that might be caused by more than one condition.

DR. DRACKER: I wasn't suggesting this wasn't a purview. What I was suggesting was that the treatment's much worse than the cause in this case.

DR. TYLER: I would like to offer a couple parallels that I think may help us. You know, when I first started practicing, how we treated asthma was with Theophylline. And no one today would think of treating asthma with Theophylline because we now know it is an inflammatory disease and we need to use inhaled steroids, and have to address the underlying inflammation.

It's harder not to use something than to use something. But really, when you think about what we know about cough -- so in some ways we don't know a lot about the symptoms, but we do know a lot about the diseases that contribute to cough.

We know a lot more about asthma than we did 20 years ago. We know a lot more about GERD. We know a lot more about bronchitis. But the reality is, if you look right now, this treatment doesn't offer anything to coughs. Yes, it treats the symptoms, but it is not looking at the underlying etiologies. We would never approve it for cough today. The idea that this is really antiquated really captures this. I mean, this is what we thought was the best thing 30/40 years ago. But today it's not the best thing.

The other analogy I'd like to use, is the use of antibiotics in otitis media. So, 30 years ago, somebody shows up with otitis media, they always got antibiotics. And now we're really rethinking that and the new guidelines are coming out and saying it's a viral disease the majority of the time. And that maybe antibiotic isn't what we should be using. How we use antibiotics has huge implications for the sensitivities. And we now have superbugs. And so now there's a huge push to really decrease the amount of antibiotics we use.

It's very similar with opioids. In many ways, we don't have data, but what we do know is when we decrease the availability of opioids in our community, we decrease the other problems and the other risk points. And we're also coming to understand -- and it had to take an "opioid crisis" to get us to kind of like pay attention to this. But we have to start thinking about the impact of opioids in our community and figure out ways to decrease them at all levels.

I understand that OTCs is not the point of this and we have lots of regulatory problems with OTCs. But on the other hand, another way of attacking this is codeine is a controlled substance. Change the schedule. We've changed the schedule on other drugs. But we have to think about ways to get it off OTC status. And I realize

there's regulatory hurdles, but we have to tackle that. We cannot continue to have this drug that's a risk point as OTC status.

DR. DRACKER: Yes?

DR. DELOST: I'm going to be the one that everyone tars and feathers when we're done. I'm Kort and I'm Kort Delost pharmacist. You're making all good points about the toxicity versus what perceived benefits are. But along Linda's point, you still have a choice to use Theophylline if you have to. You still have a choice to use an antibiotic if you have to. If you take this and restrict it totally in children, you won't have the opportunity to use it in any circumstance.

The reason I brought that up is, if I'm looking at the risk factors, the reason I ask that question earlier is the risk factor from codeine cases for respiratory depression, from 1969 to 2015, were 64 cases. I know that's way under reported, but it's still very minor. Hydrocodone cases 1969 to 2015, 38 cases. Twenty-three deaths in that, 24 deaths in the other group. In the codeine base, it's less than 12-year-olds mostly. And in the hydrocodone, it's mostly less than 6-year-olds.

That's not a real high risk I perceive. To blanketly take something out, that's been around for 43 years or whatever, you might want to rethink that before you totally annihilate availability of that drug. There are some cases where it might need to be used.

Also, if UCB believes Tussionex should be contraindicated in anyone less than 18 years old, what's that going to do -- and we talked about pain control a little bit. It's sort of a slippery slope. Because you're talking about the same side effects you're going to get from hydrocodone for pain as you are for cold and cough. If you feel

comfortable using it for pain, why don't you feel comfortable for cold and cough. Even though it's a symptom you're treating, some of those parents and people that are suffering from those symptoms might be able to benefit from it. I just wanted to throw those out there, let you think about it.

DR. WADE: Just in response to that, and kind of an epiphany I had reviewing these documents, is that I haven't heard anyone or ever been taught that morphine is an appropriate anti-cough medication. And I think if we were to go to parents and say, here's some morphine for your child's cough, they might fall asleep better, none of us would do that. And I don't think parents would accept it.

I think this is really a historic and antiquated cough medicine. And today we asthma therapy, we have gastroesophageal reflux therapy, we have pulmonary function tests, spirometry, and all these different ways to evaluate the etiology beyond a chronic cough. And I think if a child or adolescent, or young adult for that matter, is coughing really terribly and having difficulty sleeping and having life consequences, I think they should be in their doctor's office having further evaluations.

But when I converted this in my mind to would you use morphine for cough, or would morphine be an appropriate over-the-counter medication, the answer to me feels pretty obvious that that is not an over-the-counter substance, nor a product that I would be wanting to use for a symptom of cold or cough.

DR. CALLAHAN: As many of us in this room do, we have to use prescriptions off label like in epilepsy and other difficult conditions, when nothing's actually approved for that age group. So, then it's on us to explain to the parents why are we prescribing this off-label drug to their child. What are the risks and benefits? Is

there anything approved?

Where I find it easy when parents make requests of me for a prescription that is not FDA approved for some other condition, it's very easy to say well that drug is not FDA approved for your child or for that indication. And they usually accept that very quickly. They're usually very knowledgeable. A lot of times they'll call me and ask me why are you approving this? This isn't approved, and then I have to explain it.

I think it's very helpful to have an appropriate label. And right now, the label is that these medications are effective and approved for children, which I find is terrible. I've been reading about these medications for 25 years since I had my own children, and I'm always trying to convince parents that these aren't effective, and they're not necessary, and you don't want to take the risk. You're often talking to somebody that doesn't listen because then they go to the ER, or they go somewhere else, and they get prescriptions for these medications.

DR. DRACKER: Michael.

DR. WHITE: In response to what you had to say. I had this same comment, that I made at one of the meetings, when we were talking about the OTC drug which is the numbers that we have are small. I agree. From 1960 something, until today, it's only like 60 kids. But why? I mean, there doesn't need to even be 60 kids. Because, as I say, codeine -- exactly what she says. Why don't I just give morphine? And in some, that's what we're doing because of the high metabolizers. And hydromorphone the same sort of thing.

I'm not sure that these drugs have any benefit or any indication for this particular set of symptoms. That doesn't mean they can't be used for pain. But even in

pain, codeine's not that helpful as she alluded to. It's not even available in many pediatric hospitals. I don't know; does anyone use hydrocodone for pain in kids? Do you use it for pain?

DR. HOEHN: I use it for palliative care patients.

DR. WHITE: Maybe there's an indication there. But I don't think we should even be talking about whether this has got a benefit/risk ratio that one should assume for children with cough. I think the real argument is what kind of honey; Texas honey or should you get sourwood honey from somewhere up in the mountains.

DR. DRACKER: Thank you for that Michael. There was a question down there?

DR. PATRICK: Yes. In response for something that has no benefit, one death is one death too many. And I think that as we look at this more broadly, I mean that should be part of it. And the other thing is that people can use things off label. Otherwise, we would have no prescriptions for 1-year-olds for codeine these days. But they take that risk upon themselves. And what you do is you credential providers to change the scope of practice. To change how we see this.

I think one of the things that needs to be reframed, is that you go see your pediatrician to diagnose the underlying cause, not to get a prescription. And some of that's a cultural change that is taking some time.

DR. DRACKER: All right, who was first? We'll go down there.

DR. PLUMB: Hi. I work in pediatric emergency medicine and in opioid overdose prevention. I'm finding a lot of things spinning in my head. But I would love to sum up a couple of things. I think that Dr. Patrick alluded to something. It is so

important to those of us who see patients that we don't see regularly, and don't have routine relationships with, to be able to fall back on things like FDA recommendations. And to be able to say, you know, I don't think it's safe because of X, Y and Z. Or why, because of X, Y and Z. Oh, and by the way the FDA backs me up on that. That is such a tremendously important factor for people in my field.

Hydrocodone is prescribed tremendously in the world that I work in, both in emergency medicine as well as in trauma. The Children's Hospital, where I work, the top five prescribed out of our outpatient pharmacy include oxycodone, hydrocodone, Tylenol, and ibuprofen are in the top four of those five. It is prescribed tremendously, largely for pain more so than for cough.

I also think that, as I look kind of within my own mind to wrap my head around this, we have to start somewhere with getting people to think differently about opioids in children, and opioids in the home where children exist. I pulled the data from the Children's Hospital where I work from 2010 to 2015, just out of my own curiosity. Who am I seeing that's opioid overdoses? And admittedly, that's a skewed population, right. Because a 17-year-old heroin overdose is going to go to the closest hospital, not necessarily to the Children's Hospital. But 87 percent of the kids we saw in our tertiary care, Children's Hospital were zero to five years of age.

So again, I understand that just taking away the prescription to a child for these substances is only a bit of the messaging that needs to happen. But perhaps it will assist in those who prescribe to adults as well, in the way that they think about prescribing these substances where there are children in the home. Thank you.

DR. DRACKER: Thank you.

DR. TURER: I wanted to address some of the other questions. I addressed 1(a). In terms of 1(b), I think the comments about when might this drug be indicated are important. And part of me felt, well I think if one of the risks is death, children who are facing death in the setting of palliative care, it would make sense. However, I don't believe -- and maybe my palliative care colleagues can fill me in on this -- that there are kids out there who are suffering cough absent of pain. Most of those kids, you'd actually be probably treating with hydrocodone for cough associated with metastatic disease to the lungs and they've got pain.

The other thing is, I don't think that codeine would make good sense because of all the risks with it being a prodrug. I think you'd use a longer duration drug because of their chronic disease. So for (b), I don't think that keeping the indication for cough makes sense even in the setting of palliative care, because you'd be treating pain and you'd have a different indication.

For (c), in terms of important differences, I just mentioned I think codeine is different and I won't belabor that. In terms of the differences by age groups, it says specific pediatric age groups. I would actually push that beyond the pediatric age groups. I'd say what are the data in the adults. As an internist, I can't tell you the number of patients who ask for these cough syrups by name. By name.

And so when I read those data about the number 1 through 15 drugs prescribed nationally, and saw that narcotics are number one in 44 to 50-year-old men, I went, I'm seeing that. I'm actually seeing it younger than that. Perhaps it shouldn't be FDA approved for that.

While we've been talking I went to Micromedex. And when you pull up

Micromedex, and FDA uses for Tussionex, it says FDA approved adult, yes. Pediatric, yes, six years or older. Efficacy in adults, evidence favors efficacy. Pediatrics, evidence favors efficacy. As we've discussed today, I don't think those data are quite that black and white. But that's what our clinicians are going to see out in the public.

Finally, regarding the how did the wider public health impacts of opioid containing medicines effect the benefit/ risks, I think Dr. Levy very pointedly indicated this is a real concern. And I wasn't present for the discussion, but it sounds like people had said let's not have these drugs be FDA approved, but they still are for the 12 to 18. Somebody should let Micromedex know, because it hasn't been updated to reflect that. Also, it sounds like there may be greater risk in treating adolescents with these drugs.

I think we should actually have our colleagues in internal medicine review these data and maybe even remove the indication for adults. Or, another idea would be to list both codeine as well as hydrocodone as tier 2 drugs. That has had a remarkable impact on reducing prescription of hydrocodone. We had found many of our residence, under the attending, were prescribing these at unprecedented rates. Just by making that a tier 2 drug, they now have to come to us. We have to prescribe them and we don't. That really ramped down on the proportion of our patients in a safety-net system receiving drugs they shouldn't have been receiving at all. Thank you.

DR. DRACKER: Sarah.

DR. HOEHN: I just wanted to make a quick comment. Someone mentioned earlier about otitis and antibiotic use. I just wanted to point out that we're talking about just essentially cough, which is the common cold. And the natural history of a cough is just a cough. And there's actually more risks with masking that cough if

for some reason the pediatrician is missing whatever the underlying diagnosis is. There's actually more harm from masking it, but there's not anything that's going to come from un-treating it, that wouldn't merit its own treatment. And it's not going to be treated with codeine. I don't know if that makes sense or not.

But there's essentially no harm to not treating it; where you could make an argument with otitis, as an ICU doctor, it will spread, you'll get mastoiditis, you'll get a bit of abscesses. There's all these bad things that can happen. There's not really any bad thing that can happen from cough, not treating it. And the only thing that would happen would be that you'd miss the symptoms, but if you treat them with codeine, you're more likely to mask the symptoms for whatever the cause is anyway.

I think there's really no indication. And as a palliative care doctor, I have no concerns because we're keeping it very focused on cough, and I don't think we need to be worried about everything else with pain. Because I think that's a whole separate thing. But there's no reason in 2017, ever, why it needs to be used for cough.

DR. DRACKER: Melody.

DR. CUNNINGHAM: Just to the comment if Theophylline is still available for off label use. I would argue, since codeine is converted to morphine, that even if we completely eliminated codeine, we're not actually eliminating the downstream drug that would be used to treat. So, we are still leaving morphine on the table.

And then just to clarify -- put on my palliative care hat -- because you talked about you wouldn't be treating cough in an end-of-life situation without treating pain. I think since we're the sister hospital to St. Jude, where the majority of oncology

patients are, we occasionally see them, we do have patients who would be treated for cough at end of life and not pain. I think we equate palliative care with cancer patients. And I can tell you from the number of consults per year, that that's not the case. There are lots of non-oncology patients and patients without pain at end of life.

DR. DRACKER: Yes?

DR. BRENT: In many ways we're saying some conflicting things here. On one hand a number of people are saying, look these drugs are not efficacious. Why are we even talking about this? Why would we want to continue to use a non-efficacious drug? Other people are saying, look we know opioids suppress cough. And there's no question that they probably do. They probably do it in sort of a secondary manner by causing relaxation and sedation, and that by itself is something that reduces cough.

Efficacy is really, I think, somewhat of an open question. Although I think we could all agree, to the extent that there is efficacy, it is probably low. Granted there may actually be circumstances where we would want to treat cough. A child who is coughing so severely that they may fracture a rib. A child who's been up two or three nights coughing because of pertussis. There are the occasional cases where we might want to treat cough.

But it's important to realize -- and I think the wording of the questions that have been posed to us are very insightful. Because they're not asking is it right to continue to use these agents. Or, is it wrong to continue to use these agents. We're talking about a risk/benefit ratio. There's no absolute right. There's no absolute wrong. But there certainly are risks and benefits that we can weigh. Where it becomes pretty

clear that although there are these isolated circumstances where we may want to use opioids, and they may in fact be, under some circumstances, efficacious, these are kind of few and far between. And for the most part, they really don't enter everyday practice.

It would be nice if there was a mechanism whereby physicians did have these drugs available to them to the extent that they might want to use them. In the great majority of cases, I think there is a clear-cut consensus, in this room, that they shouldn't be used. And probably I think we've beat this to death a little bit. To the extent that we talk about -- we make a distinction between hydrocodone or codeine, it's probably not that necessary.

The point about codeine rapid metabolizers is a very important one. It always seemed to me that the black box warning -- I realize why it's there and it's a good reason for it to be there, but it's a very unfair black box warning. It's a very unfair black box warning to the prescribers. It basically says to the prescribers, look there's a substantial number of cases -- it might be single digits if we talk about the American population, but it's not less than 1 percent. There's a substantial number of people out there who, if they take the drug, are going to be ultra-rapid metabolizers. And they're going to generate morphine. You don't know who they are, but we just want to warn you that this may happen.

That's not a very helpful thing for prescribers. It puts the prescribers in a really difficult situation. Usually black box warnings are there because they can offer some advice. If your patient is not opioid addicted or opioid tolerant, don't put them on fentanyl. That's something we could actually do something about. But you're saying this is just a warning. Just a heads up guys. You may kill your patient when you give

them this drug, but it's up to you if you want to give it to them.

I think codeine, under any circumstances, should be totally off the table. In terms of hydrocodone, for all the reasons we talked about -- it may have some place in therapy, but once again we're not talking about whether it has an absolute place or not an absolute place. We're talking about a risk/benefit ratio. It really seems to me that a very clear-cut consensus has evolved here that the risk/benefit ratio leans more on the side of risk than of benefit.

DR. DRACKER: Yes?

DR. SEYMOUR: Can I respond briefly. This is Sally Seymour from the FDA. I just want to respond to some of the statements about the box warning for codeine. We are very careful about what information we put in the label and are very thoughtful about our approach. The box warning for codeine doesn't just say your risk of ultra-rapid metabolizers, it actually identifies the high-risk groups that we have identified based upon the data. And that's the patient's post tonsillectomy and adenoidectomy. That's really where the data showed that there was the highest risk.

Beyond that, we didn't see risk initially. When we looked broader, that's when we decided to take it to an advisory committee meeting in 2015. And that's where we had the majority of cases less than 12. If we had lots of data in cases in older children, we probably wouldn't be here. We would have contraindicated in children less than 18. It's sort of this lack of these cases that is part of the issue.

There's an OSC review in here, as well, in the briefing document that really, they look for cases. And there's not really compelling cases with hydrocodone in kids. I think your deliberations, your discussion, mirror some of the discussions we've

had internally that the drug has an indication, has efficacy. There's been questions about it. There's not great data in terms of risks. And so, I think you're having a similar discussion.

But in terms of the box warning, in all fairness, I think we tried to identify which were really the highest risk groups, to try and guide you based upon the data we have. It's not every child. It seems to be that there are patients particularly prone to respiratory depression if they have another risk factor, obesity, sleep apnea. Kind of a two-hit sort of mechanism, ultra-rapid metabolizer and another predisposing factor.

DR. DRACKER: Could I remind all of you to please state your name clearly for transcription purposes. Thank you.

DR. MEISEL: I agree with virtually everything that has been said here today, but a couple of things. First in terms of the codeine. I think it's pretty clear that if we were faced with an NDA today based on what we know, we would not approve or vote to recommend approval of codeine-containing cough syrup for kids. But 85 or 90 percent of the prescription cough medicines is neither of these drugs. It's dextromethorphan, and we're not here to talk about dextromethorphan.

But I'm not aware of any evidence, or even much of a suggestion, that codeine is superior to dextromethorphan in suppressing cough. And so again, it goes back to relative risk. I know there's risks of abusing dextromethorphan. That's out there, but it's different than the risks of abusing a real narcotic that converts to morphine, and the rapid metabolizers and all that sort of stuff. And so when you look at relative risks of codeine-containing cough syrup, versus a DM containing cough syrup, it's night and day.

When you've got the situation where the kid is up coughing all night and you just need to deal with that symptomatically, there are options; that's DM, and we don't remove that option. So, I want to make sure that we are clear on that; this is not a zero something game here, there is something else out there that's available.

And in terms of the hydrocodone, gosh we heard before lunch, that different manufacturers, that they'd like to change the labeling so that we remove the approval. Who are we to tell the manufacturer, no you've got to still market it to kids. If the manufacturer believes that the benefit/risk profile is no longer favorable, then it seems to me that -- I'd be hard pressed to suggest that indeed it is.

DR. DRACKER: Anything else? Yes, Michael.

DR. WHITE: This is an aside on the history of the FDA, which was known as the Food, Drug and Insecticide Administration until 1927, when they had a discussion about Mrs. Winslow's Soothing Syrup for teething and colicky babies. We're kind of having that same discussion again. This instituted the formation in the Food and Drug Administration because Mrs. Winslow's Soothing Syrup was mostly morphine. And we're basically having that same discussion over again. And it's about time we settled it I think.

DR. DRACKER: Yes sir.

DR. WAGENER: In some ways having practiced for 35 years, and talking care of kids with cough that whole time, I remember a couple decades ago the big issue was isoproterenol versus albuterol. And I look at codeine in the same way. It's a drug that's been around for a long time. We now, with history, have much better identified its risks, its benefits, that certain patients that are not easy to identify are at particularly high

risk.

I remember sitting with Jackie Joyner Kersee, for any of those that know her, and she used isoproterenol and almost died once in a stairway running up and down stairs. You finally had to sit there and say, look this is just a drug that shouldn't be here. And we have better things now. We have better treatments. And the question is, how can the FDA, or whatever other process there is, go about getting rid of an archaic drug.

I think hydrocodone's different. I'm sort of sorry that the FDA tied the two together in this case. Because I think we should be talking about them maybe differently. But certainly, codeine is a drug that simply has had its past and it now should be filed away.

DR. DRACKER: Yes sir.

DR. HAVENS: I'm interested to hear a little bit more about the 12 to 18 year old direct risk to the patient taking the drug. There's two issues that have come out here. One is a public health concern, that if we have too many opioids in circulation, that's bad for adolescents who, 50 percent will use whatever's in the medicine cabinet. But if we think that that's not -- well, I don't know.

Number one, is that the rule of the FDA, to use public health concerns from that perspective in this kind of labeling decision? Or, should it really be a question of personal harm. And if so, do people in general believe that the personal harm to the older age -- which we've heard some people think is probably small -- is so great as to need to remove both codeine and hydrocodone.

DR. DRACKER: Okay. Anyone else? Yes?

DR. DELOST: They did separate that out as far as the question on voting.

We'll have our choice to do that. And I agree codeine is not the one that I was talking about mostly. What I was concerned about was the hydrocodone part.

DR. HAVENS: But you and others have said that the actual risk to the person taking the drug is pretty low in the 12 to 18-year-old group. Do you believe that that risk is so low that, just based on risk of personal harm, those drugs should be removed? Or, does the risk of population harm come into that decision for you?

DR. MCGOUGH: Well, I think I have not been impressed with the benefit side of the equation. It sounds to me that the indications to treat are very small, there are alternatives. Any risk, with almost an absence of benefit, favors a no. I guess it really is a social question. But again, in the ADHD world, this is a big concern of having formulations that are less available because there is a relationship with pills floating around schools, et cetera, et cetera, and then misuse. If it has no effect, we're at the starting point. But any effect is in the positive direction.

DR. DRACKER: I do think it is a matter of perspective. And again, that's what we'll be considering in our vote; looking at both the risks and benefit and what the ratio is for all of us. Yes, Michael.

DR. WHITE: We kind of alluded to dextromethorphan, which you can buy freely, anywhere mostly, no matter what your age. We're talking about taking a drug with small usage really under prescription for the most part; because we're not talking about over the counter. And if we're going to discuss it in terms of the opioid epidemic, how much does this really impact the opioid epidemic in difference to dextromethorphan, which is perfectly available in purple drink. We've lost a football play at LSU because of that.

That was part of the question that you guys were asking us to look at. And I'm not sure that we have any idea how much this is really going to affect the opioid epidemic. You had some comment Skip.

DR. NELSON: It's not an answer to that question. It was to be clear when you're using the language "remove" that you're clear about what that means. Because the way these questions are framed is, they're focusing on the indication for the treatment of cough associated with allergy or the common cold. What's not on the table is that these products are removed from the market.

DR. WHITE: Thank you for clarifying that. But removing that indication will decrease the prescriptive amount given out not very much, do you think?

DR. ALEXANDER: Let me address that. I do think that in terms of the issue of availability, while FDA has been trying to sort of look at what the public health issues are with regards to these opioids, especially with opioid epidemic over the past couple of years -- so that that's part of the reason that we are sort of bringing these types of questions to you. I do think that it's a fair question. And I do think that it is likely that if what we're doing is simply removing the indication for children -- we've already seen the data with regards to drug utilization -- we'd probably be reducing the amount of prescriptions of codeine and hydrocodone by a relatively small amount. But that's still something that we view is better than nothing.

At the same time, I do think that you're making a fair point that, with the availability of all of the medications and certainly the amount that's prescribed for adults, that we probably wouldn't be having a great impact on what's available for an adolescent to get to, that's in the medicine cabinet.

DR. DRACKER: I could comment that anecdotally a pharmacist had mentioned to me, that since this discussion started a few years ago there's been a significant increase in dextromethorphan, guaifenesin and Benadryl use by parents for cough preparations.

MS. CELENTO: Regarding the topic of what's available in the medicine cabinet. I think change it to what's available whereby prescription for children or over the counter for children. There's certainly an opportunity to use this as a public relations messaging opportunity, in terms of getting the word out to parents that any medication has to be secured. Whether it's pills or a liquid. Whether it's cough suppressant for a parent. There's always the opportunity to continue to relay that message to the public.

DR. DRACKER: Yes?

DR. WAGENER: This goes back to your question a minute ago. I find the difficult group is the 12 to 18-year-old in the question of the hydrocodone cough medicines. It's interesting that the company has offered to take this as a non-indication age group. I'm sure that a large part of that had to do with their financial assessment of what profits they're making in that age group versus what potential risk there is.

But be that as it may, that age group can suffer life-disabling cough for a variety of different causes, and that is not controllable by trying to control those causes. I can use a patient with cystic fibrosis as an example. So, we're not talking about oncology, we're talking about a different disease. And they do respond to cough suppressants. It's a very, very last choice in a patient like that, but they do respond.

The question is what to use in that age group. We'll use morphine as our drug of choice, usually if we really want to suppress cough. Is dextromethorphan the

way to go? Possibly. It's a difficult one. And I guess the question comes back sort of to the pharmacist perspective. And that is, do you want to take the hydrocodone off the market and realize that, in those limited cases, something else is going to replace it. Or, in large number of cases, dextromethorphan is going to replace it. I just find that a very difficult age group to question what would happen with these prescriptions.

DR. DRACKER: Michael.

DR. WHITE: Dr. Nelson, just because I'm not so good with my language, no matter what our vote is, our vote is going to be -- if there's a recommendation it's going to be that this not be recommended for use; and the warning will be put out that it's not. But that doesn't preclude you from using it. A warning just is a warning. Is that a correct statement? No matter what our decision or recommendations are, we're not going to preclude the use of these drugs. And if you do have a particular patient, where you think it will be beneficial, you still could use it. It just is with knowledge that it carries risk, pretty high.

DR. DRACKER: Michael, thank you for clarifying that for everybody. We'll take one more question and then it's time for the vote in consideration of the questions please.

DR. DELOST: Just a little follow up onto that comment I heard earlier. Of course, codeine is one of those things that's a major problem. I was more focused on the hydrocodone part. But since those new regulations were passed, we've seen a lot of self-regulation anyway, much downward trends. Dr. Pham said it's trending downward. Also Dr. Karami said there was a low overall incidence of adverse reactions with the unintentional exposures comparatively.

I think everyone's got the message. What you have to decide is do you have codeine at all. What age group do you have hydrocodone. That's the questions we're going to answer.

DR. DRACKER: Okay. I guess we're at the point we're going to consider the questions. Dr. Alexander, you want to help with this. I'll read the questions and then we can take a vote. Again, please once I pose the question we'll go around the table and then state your name and then whether you concur or not concur or abstain please. Yes?

DR. JONES: I just wanted to comment regarding the 12 to 18-year-old group, and just reiterate again that we're talking about cough for allergy and a cold in this age group. I just wanted to emphasize that again.

DR. DRACKER: Yes, Skip.

DR. NELSON: If I'm not mistaken, when we had the automated voting systems, so the voting process is you vote yes, abstain, no, first. And then you go around the room after everybody's vote is recorded just for clarity.

DR. DRACKER: That's fine. Thank you for helping me with that.

DR. ALEXANDER: We'll start out with the voting question on codeine. The question is, is the benefit/risk favorable for use of prescription codeine cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients 12 to less than 18 years of age; yes or no, and provide the rationale for your vote. I just want to make sure that this is stated clearly; that if you're voting yes, you're voting that the benefit/risk is favorable for the use of cough. And if you're voting no, then the idea would be that the benefit/risk is not favorable.

ADVISORY COMMITTEE VOTING

DR. DRACKER: Let's start at the left side of the table please. We can come around the table.

DR. KELLY STONE: I voted no. I have to say this rather challenging in that there isn't an increase in safety signal on (inaudible) indication. In an idea world, if it were used for those patients who truly had unexplained, cough after going through proper algorithms, it would be nice to keep it in the armamentarium. But I'm not convinced that that's the way that it's been used. And given the risks, I don't think that there's a favorable profile.

DR. PLUMB: I voted no. I also believe that I don't perceive there to be a benefit that could possibly in the -- what was it? The zero over anything is incalculable. That stuck with me. I don't believe that there is a favorable benefit/risk ratio.

DR. PATRICK: I voted no. There's no clear benefit and clear evidence of harm.

DR. NEVILLE: I voted no for the reasons that have been stated. But feel especially enthusiastic in that I think codeine, in particular, is an antiquated drug.

DR. MEISEL: I voted no for all the reasons that have been described.

DR. MCGOUGH: No as well, for the reasons that have been stated.

DR. LIEBELT: I voted no for all the reasons stated, as I find no benefit at all, and much more risk in terms of the indication for a symptom that is self-limited for a self-limited disease.

DR. LASKY: I voted no and hope that it registered. I saw some votes that didn't register. But I pressed no. And my reason was lack of evidence of efficacy, effectiveness or benefit.

DR. FISCHER: I also voted no for the reason that therapy for acute cough isn't indicated. And there's no clear benefit to the patient, but there are risks.

DR. DELOST: I voted no because codeine's unpredictable.

MS. CELENTO: I voted no in line with the reasons already stated.

DR. CAMPBELL: I voted no as well. I think the FDA, from the DESI process, has to presume it's efficacious; even in that the lack of further evidence doesn't necessarily negate that -- but that for such a minor symptom, such as cough -- that the risks well outweigh the benefit.

DR. BRENT: I voted no because I do think that there is some potential use of opioid related antitussives. But the question specifically stated allergy or the common cold. I don't think there's really much of a role under those circumstances. Even if there was, codeine would not be a good drug, because the active principle in codeine is morphine; and we don't know what the dose of morphine anybody will get, when we give them codeine, because of their 2D6 polymorphisms.

One other thing I should add, that hasn't been mentioned yet, which is a real concern about these drugs being out there, is that we have to realize that in these age groups, as in the rest of society, we're seeing obesification. And as we're seeing obesification, we're seeing an increase in obstructive sleep apnea. We're actually evolving into an error where we're having a population of patients now who are much more sensitive to opioid type of agents. And that actually enhances the risk associated

with them.

DR. WHITE: I voted no. I don't think that we've proven efficacy in the particular circumstances listed. I think we should follow the pediatric guidelines for treatment of cough. And I don't think this precludes the use in exceptional circumstances where it might be useful.

DR. WADE: I voted no for the reasons previously stated, that opioids have too great a risk to the individual and the population. Particularly, in reference to the cough associated with the common cold.

DR. TURER: I voted no for many of the reasons already stated.

Dr. SAYEJ: I voted no for the reasons that were stated by all the experts in this room. I don't believe that narcotics are a way to treat a common cold or allergy symptoms. We have a major narcotic epidemic in the country and across the world, and fueling the fire doesn't help. This is one of those things that we can do.

DR. HOEHN: I voted no. I think we've talked about it a lot today, but I just think there's no indication for treating the common cold. And I just think it gives the wrong impression to families and caregivers.

DR. HAVENS: I voted no. There are safer alternatives available and these drugs are not needed in this context.

DR. CUNNINGHAM: I voted no for the reasons in our discussion as well as the reasons stated by the other voters.

DR. CATALETTO: I voted no. The risk/benefit profile is unfavorable, and I would not use it for either a cold or an allergy symptom of cough.

DR. CALLAHAN: I voted no due to the potential risk and the principle of

do no harm.

DR. WAGENER: I voted no. I agree with the multiple international consensus conferences, that feel that cough suppressant should not be used with allergy and the common cold. Plus, I think that codeine has some risks that could easily be avoided.

DR. TYLER: I voted no as well. I too agree that there are no benefits to these, and there are many guidelines that have reviewed them and incorporated that recommendation as well.

DR. DRACKER: Thank you for your comments and your votes. The summary is 24 no votes, 0 yes votes and 0 abstain. Thank you. Next question.

DR. ALEXANDER: The next question is related to hydrocodone. We are going to ask you to vote separately on the different age group. So, the question is, is the benefit/risk favorable for use of hydrocodone cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients. I ask you to vote in part (a) for 6 to less than 12 years of age. And then part (b) for 12 to less than 18 years of age, and again, provide a rationale for your vote.

DR. DRACKER: Just to clarify we're taking two separate votes, correct? So, please vote for part (a) first.

DR. NELSON: What did you say about tar and feathers.

DR. DELOST: Got to stick by my principles.

DR. DRACKER: I knew who that green vote was. All right should we go the other direction please.

DR. TYLER: I voted no. I do not believe there's evidence to support that

it has benefit and there are risks.

DR. WAGENER: I voted no entirely based on benefit. There's no evidence that the management of allergy or the common cold should include cough suppressants.

DR. CALLAHAN: I voted no for reasons stated in prior discussions.

DR. CATALETTO: I voted no for exactly the same reason.

DR. CUNNINGHAM: I voted no for the lack of benefit and some data on risk.

DR. HAVENS: I voted no for no benefit and potential harm.

DR. HOEHN: I voted no for the same reason, that there's no indication for treating the common cold.

DR. SAYEJ: I voted no for the same reasons stated.

DR. TURER: I voted no, same reasons.

DR. WADE: I voted no. I don't believe in the use of opioids given the risk associated with them for the common cold.

DR. WHITE: I voted no.

DR. BRENT: Since this analysis is restricted to cough and allergy or common cold, I voted no.

DR. CAMPBELL: I voted no for the same reason.

MS. CELENTO: I voted no for the same reason.

DR. DELOST: I voted yes because the risk is relatively low. Most of the problems are in less than the six years of age. And I've personally seen benefits from the use of it, in my practice.

DR. FISCHER: I voted no for reasons previously stated.

DR. LASKY: I voted no because I didn't see evidence of a benefit.

DR. LIEBELT: I voted no because I saw no evidence for the benefit in the treatment for common cold and allergy. and there is potential harm for opioids in children.

DR. MCGOUGH: To echo everyone no indication, no clear benefits, some risk of harm.

DR. MEISEL: I also voted no. Again, no evidence that it's any more effective than dextromethorphan in this population for these reasons. And the manufacturer also concurs that the risk profile is negative.

DR. NEVILLE: I voted no. To Dr. Wade's earlier point hydrocodone is metabolized to hydromorphone and I would not give Dilaudid for a cough.

DR. PATRICK: No for reasons previously stated.

DR. PLUMB: Also no for reasons that we have all elucidated.

DR. KELLY STONE: I voted no for the same reasons that have already been stated.

DR. DRACKER: Again, thank you for your votes and your comments. We have 23 no votes, 1 yes vote and no abstain. Thank you. I'd like to open up voting for the (b) section of the question, which is the older age group please.

Well, that was a surprise. All right, shall we go around the other way?

DR. KELLY STONE: I voted no. Again, the safety profile is better than for codeine, but benefits in the setting aren't apparent.

DR. PLUMB: I voted no. I think that if there is to be a cough suppressant

in the 12 to 18-year-old group, there are much safer alternatives than hydrocodone.

DR. PATRICK: I voted no. There is still reported deaths in this population with, again, no clear benefit.

DR. NEVILLE: I voted no for the previous reasons. And also, while the drug may be safer in this population than the younger population, I think the FDA making a statement, it is not indicated, does help pediatricians with prospect for why they're not prescribing opioids.

DR. MEISEL: I voted no for all the reason described.

DR. MCGOUGH: Again, a lack of an indication for cough suppression in these conditions. Inappropriateness of using opioids to suppress cough. And any risk will be greater than the real lack of any benefit.

DR. LIEBELT: Again, for the same reasons. No indication. No role. The risks are there and there's not a need to treat for a self-limited symptom in a self-limited illness.

DR. LASKY: I voted no because I didn't see evidence of a benefit.

DR. FISCHER: I voted no because therapy for acute cough isn't indicated and there is a potential for harm.

DR. DELOST: I voted yes for the same reasons I stated before.

MS. CELENTO: I voted no. No indication for a cough and the risk is way greater than no benefit.

DR. CAMPBELL: I also voted no. I think I was also swayed by the evidence that exposure to substances as teens increases your likelihood of misuse of the substance later.

DR. BRENT: I voted no for reasons previously stated.

DR. WHITE: No.

DR. WADE: No for the reasons previously stated.

DR. TURER: I voted no largely because of the concern of using opioids in adolescents.

DR. SAYEJ: I voted no for the same reasons everyone has expressed. I echo Dr. Campbell's and Dr. Turer's comments about the potential for misuse in adolescents.

DR. HOEHN: I voted no for the same reasons everybody already said.

DR. HAVENS: I voted no. No new reasons.

DR. CUNNINGHAM: I voted no for all the reasons previously stated.

DR. CATALETTO: I voted no as well.

DR. CALLAHAN: I voted no for prior reasons.

DR. WAGENER: I voted no for lack of benefit for these specific indications.

DR. TYLER: I voted no as well. Also, no benefit and I too was persuaded by Dr. Levy's comments around the special issues in the adolescent population.

DR. DRACKER: In summary, we have 23 no votes, 1 yes vote, no abstinence. Thank you again for your votes and comments. The final question?

DR. ALEXANDER: The last question is actually a little bit more general question with regard to use of prescription opioids as a more general concept for treatment of cough, without the specification of the use for the common cold or allergies. Is the benefit/risk favorable for use of prescription opioid cough suppressants

for treatment of cough in pediatric patients, yes or no? And please provide your rationale.

DR. DRACKER: Well, it's a little more interesting this time. We'll start at the right-hand side.

DR. TYLER: I voted no. I believe that there is little to no evidence of benefit. Lots of risk. I think as we've described today there's lots of reasons that when people present with a cough, either acute or chronic, that those patients needs to be evaluated. I think the labeling should reflect that.

DR. WAGENER: I voted yes. As is often the case with FDA questions, this was a tough one because it's so broad. I certainly would not have voted yes if the question was related to codeine, which I definitely would have voted no. But in the case of the hydrocodone, I think that physicians need the option of cough suppressant. It's reasonable in under 18-year-olds.

And the risk of that drug, as was presented to us, has not been shown to be significant in certainly the older age group. I'm not sure about the addiction issues. If there's any relationships, certainly there's a lack of data there. But I think the relationship is more likely to be related to any medication used as opposed to specifically opioids.

DR. CALLAHAN: I voted no because of the broad nature of the question. A yes vote would give favorable use to any opioid including codeine. It would also give approval for use of treatment of cough, and of any allergy, in any age pediatric patient. And so, I don't know how anyone could vote yes on such a broad question.

DR. CATALETTO: I voted no. This was a broad question. And

when you think about cough as a broad category, I think you have to treat the underlying cause. So, I voted no.

DR. CUNNINGHAM: I voted no. I agree that this was a little more difficult question because it is so board. However, I think saying no in the vast majority of situation is the correct answer. And then I think you leave it to the folks who've ruled out other causes of the cough, and to very discrete sub-specialty groups to recommend it in these situations.

DR. HAVENS: I voted no. Focusing my attention on the fact that this was about cough suppression and not treatment. And in that context, there are better suppressants of equal efficacy with fewer side effects than narcotics.

DR. HOEHN: I voted no. Again, because I think the focus should be on the underlying cause. And some of the few examples that people brought up about end-stage disease, whether it's oncology or cystic fibrosis, I think there's other drugs that are better choices.

DR. SAYEJ: I voted no. Again, this was a slightly more difficult question because it was board. However, I would like to make a comparison here. Giving narcotics to a patient with acute gastroenteritis is not the best or smartest thing to do. Cough in some ways is a defense mechanism in our body, and suppressing that is not always the best thing to do either, especially in the setting of an acute respiratory illness or an infectious process.

Also in the setting of cough in the absence of an infectious process, we have to be careful. In patients who have obstructive sleep apnea, in patients who have neuromuscular disorders, in patients who have asthma, suppressing their cough could

potentially be very detrimental.

DR. TURER: I voted no. I found the evidence presented by Dr. Oppenheimer, that up to 100 percent of cases, the etiology of these cases can be identified, go after the cause. As a follow up to your comment, I've had numerous patients who request, by name, belladonna alkaloids for their GI issues. So, it does happen.

DR. WADE: I voted no, consistent with prior votes. That we have many other options, and children with chronic cough or difficult cough should be further evaluated for other medication options. And the risk profile of opioids is too great, the individual and the population.

DR. WHITE: I voted no. I think that these drugs should be used with careful attention to why they might be used in this population. And certainly, this does not preclude your use if you feel strongly that, in an individual patient, it needs to be utilized.

DR. BRENT: I am Jeffrey Brent, and I have officially defined myself as the wimp in the room by abstaining. I think there are circumstances where we want to use these kinds of agents to suppress cough. I total agree that if somebody has a significant and chronic cough that they need to be evaluated. But I think everybody here in this room knows that evaluations don't happen instantaneously. It takes a while.

Sometimes, there is some serious quality of life issues in the interim. And although it is rare, I think there are circumstances where physicians might want to use these kinds of agents to suppress cough. I'm not sure that there are really a whole lot better agents around. So, giving difference to clinical judgement of physicians, I have

voted to abstain.

DR. CAMPBELL: I voted no as well. While there may be small patient populations that would benefit from narcotics, I think it's either incumbent to the judgement of the treating physician or to a pharmaceutical company, who can identify that patient population and do proper studies to show efficacy in that particular patient population.

MS. CELENTO: I voted no in line with my previous votes.

DR. DELOST: I voted yes. I just like to see people be able to have the choice, to use what they think they can use their common sense to use. Thank you.

DR. FISCHER: I voted no. I do agree that there might be a rare patient who opioid suppressants are a viable second line therapy for refractory cough; but in the vast majority of cases, it's either not indicated or we have better alternatives.

DR. LASKY: I also found this broad question difficult. I voted no because I felt evidence of a benefit was not provided or presented regarding this broader category. And that evidence of risks associated with this broader category was not provided or presented.

DR. LIEBELT: I voted no, focusing on the benefit/risk ratio. Although this is more general for prescription opioid cough suppressants, like a previous panel member, I don't believe there are any benefits as a -- excuse me, limited benefits as a cough suppressant for a very, very small patient population. However, I think the risks and the potential risks are much higher, not only because of the drug itself, because of other patients with specific risk factors, of which some evidence was present, we may not be able to easily identify when prescribing these drugs.

DR. MCGOUGH: I voted no. A broad question. Broadly speaking, I think as with our other questions, the benefits are scant. The indication to treat generally are scant and there are some risks. However, judicious physicians, who do a proper assessment, are still free to prescribe off label and can address those, I think, more idiosyncratic cases that don't read the books and do what they're supposed to do. We're not denying good physicians the ability to treat their patients.

DR. MEISEL: I voted no. I think, as was just stated, we have seen no evidence and have had no discussion today about the real benefits and risks in this population. I know of no evidence that either of these narcotic drugs or any other narcotic drug is more effective than dextromethorphan. And if we want to vote on something like this, I would want to see an NDA with the right kinds of data presented to us, for and against.

DR. NEVILLE: I voted no. And I actually have treated some of the patients with end-stage, malignant cough without pain, and have found that narcotics do work. But cough alone was too broad of an indication for me. And as was stated previously, this doesn't preclude and I would feel comfortable using this drug off label in the patient population I treat.

DR. PATRICK: I voted no. I think codeine overall is dangerous and that's included in this group. But even if we have some group of patients that may be needed treatment, it could be as off label. But as a population, I think we have compelling evidence that there's very little benefit and clear evidence of harm.

DR. PLUMB: I voted no. I do believe that there is a tide turn that needs to be reached where we start to think different about opioid substances. And there is no

better place, in my mind, than for that to be in the pediatric population. Cough is not the right indication for opioids.

DR. KELLY STONE: I voted no, consistent with the previous votes.

DR. DRACKER: In summary, we have 22 no votes, 2 yes votes and 1 abstain. Is that correct? No, I'm sorry, 21 no votes, 2 yes votes, 1 abstain for a total of 24.

There are obviously no wimps on this committee and we have never tarred and feathered anyone that I've seen in the past. But I want to thank all of you for your comments and your care for the children of our country. And I appreciate your involvement. The meeting is now over, I believe, and we will meet again tomorrow morning at 8:30. Thank you.

[MEETING ADJOURNED FOR THE DAY]