FOOD AND DRUG ADMINISTRATION

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

ABUSE POTENTIAL OF DEXTROMETHORPHAN

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P R O C E E D I N G S

(8:03 a.m.)

DR. KRAMER: I'd like to welcome everyone to today's Drug Safety and Risk Management Advisory Committee. I have a statement to read that is a prepared statement, many of you have heard before. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum at the meeting. We are aware that members of the media are anxious to speak to with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain

from discussing the meeting topic during the breaks or lunch. Thank you.

We will make every attempt to stay on time today to allow the very expert panel members to express themselves, to ask all their questions, to clarify anything the speakers have said and hopefully to exchange views among the different disciplines that are represented on the committee.

So with that, we'll start with the FDA.

MS. FERGUSON: Introductions.

DR. KRAMER: Oh, yes. We didn't introduce ourselves. So, let's start on the right-hand side with Edward Nelson. We'll go around the table and have everyone introduce themselves and state where they're from and their particular expertise.

DR. EDWARD NELSON: Ed Nelson, industry representative, Medical Director, Martek Biosciences, retired Vice-President, Medical and Research, Johnson and Johnson, McNeil Consumer and Pharmaceutics.

DR. HENDELES: Leslie Hendeles, Professor of Pharmacy and Pediatrics at the University of Florida. My expertise is clinical pharmacology.

DR. HONSINGER: Richard Honsinger, clinical professor at the University of New Mexico. I practice

allergy, immunology, and internal medicine in Los Alamos and Santa Fe, New Mexico.

DR. WALKER: Leslie Walker, Professor of Pediatrics and Chief of the Division of Adolescent Medicine at the University of Washington.

DR. WOODY: George Woody, professor, Department of Psychiatry at the University of Pennsylvania and addiction medicine.

DR. ENGLE: Jan Engle, I'm a pharmacist. I'm the Executive Associate Dean at the University of Illinois at Chicago, College of Pharmacy.

DR. KRENZELOK: Good morning. I'm Ed Krenzelok. I'm a professor of pharmacy and pediatrics at the University of Pittsburgh and director of the Pittsburgh Poison Center.

DR. LEWIS NELSON: Lewis Nelson. I'm an emergency physician and a medical toxicologist at Newark University, School of Medicine and the New York City Poison Control Center.

DR. MORRIS-KUKOSKI: Hi, Cynthia Morris-Kukoski. I'm a forensic examiner in toxicology at the FBI laboratory, Department of Justice and a clinical pharmacist, toxicologist United States Navy Reserve.

DR. WINTERSTEIN: Almut Winterstein. I'm a

associate professor at the college of Pharmacy and the College of Public Health and Health Professions at the University of Florida. I'm a pharmacoepidemiologist.

DR. HERNANDEZ-DIAZ: Good morning. Sonia Hernandez-Diaz, Associate Professor for Epidemiology at the Harvard School of Public Health and Director of the Pharmacoepidemiology program at Harvard.

MS. EICHNER: Marilyn Eichner, FDA patient representative. I'm also a registered nurse in pediatrics.

DR. STANCLIFF: Sharon Stancliff, family physician. And I'm currently medical director at the Harm Reduction Coalition in New York City.

DR. WOODS: I'm Jim Woods, Department of Pharmacology, University of Michigan. I don't have any expertise.

MS. FERGUSON: Elaine Ferguson, designated federal official.

DR. KRAMER: Hi, I'm Judith Kramer. I realized I never introduced myself at the beginning. I apologize for that. I'm an associate professor of medicine at Duke University. And I'm the acting chair of the Drug Safety and Risk Management Advisory Committee. I have a background, training, and have practiced both pharmacy and general internal medicine. For the last 25 years I've been

involved exclusively in clinical research. And in particular for this meeting, I've had an abiding interest in balancing benefits and risks of therapeutics and assuring patient safety.

DR. VAIDA: Allen Vaida, I'm a pharmacist and the executive vice president at the Institute for Safe Medication Practices.

DR. COOPER: Bill Cooper, I'm a professor of pediatrics at Vanderbilt University. And I practice in a general pediatrics there as well as conduct research in pharmacoepidemiology.

DR. MORRATO: Good morning. I'm Elaine Morrato. I'm an epidemiologist in the Department of Health Systems Management Policy at the Colorado School of Public Health. And I'm also the assistant director of our Children's Outcomes Research Program at the Children's' Hospital in Denver.

MR. MULLINS: Good morning. I'm Rodney Mullins. I'm National Director of Public Health Advocates. And my specialty is public health. Thank you.

DR. MAXWELL: Good morning, I'm Jane Maxwell. I'm senior research scientist at the University of Texas in Austin. And my specialty is monitoring trends in substance abuse.

DR. KOSTEN: I'm Thomas Kosten, Professor of Psychiatry, Pharmacology, Neuroscience at Baylor College of Medicine and MD Anderson and also associate dean at Baylor. And drug addiction is my area.

DR. CARTER: Lawrence Carter, Assistant Professor in the departments of psychiatry and pharmacology at the University of Arkansas for Medical Sciences. My expertise is behavioral pharmacology and abuse liability assessment.

DR. OLBRISCH: Mary Ellen Olbrisch. I'm Professor of Psychiatry and Surgery at Virginia Commonwealth University. And I'm a clinical health psychologist.

DR. BICKEL: Warren Bickel, Professor of Psychiatry, Director of Center for Addiction Research, University of Arkansas for Medical Sciences.

DR. SCHIFFERNBAUER: Joel Schiffernbauer, Deputy Division Director, Division of Non-prescription Clinical Evaluation, FDA.

DR. GANLEY: I'm Charlie Ganley. I'm the Director of Office of Drug Evaluation IV in the Office of New Drugs, FDA.

DR. FURNESS: Scott Furness, Director, Division of Non-prescription Regulation Development, CEDR, FDA.

DR. KLEIN: I'm Michael Klein, Director of the

Controlled Substance Staff at FDA.

DR. THROCKMORTON: Good morning. I'm Doug Throckmorton. I'm the Deputy Director in Center for Drug Evaluation Research, FDA.

DR. CURRY: Good morning. Denise Curry, Deputy Director, Office of Diversion Control, Drug Enforcement Administration.

DR. KRAMER: Thank you very much.

We're now going to start with a statement from our FDA representative, Elaine Ferguson.

MS. FERGUSON: The Food and Drug Administration, FDA, is convening today's meeting of the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethic and conflict of interest laws covered by but not limited to those found at 18 USC, Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, FD&C Act, is being provided to

today's participants, the meeting, to the public.

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

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

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

employment.

Today's agenda involves discussion of abuse potential of the drug dextromethorphan and the public health benefits and risk of dextromethorphan use as a cough suppressant in prescription and nonprescription drug products. The Department of Health and Human Services received a request from the Drug Enforcement Administration for scientific and medical evaluation and scheduling recommendation for dextromethorphan in response to the increased incidence of abuse, especially among adolescents.

This is a particular-matters meeting during which general issues related to the abuse potential of the drug dextromethorphan and the public health benefits and risks of dextromethorphan use as a cough suppressant will be discussed. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Edward Nelson is serving as the nonvoting industry representative acting on behalf of regulated industry. Dr. Nelson's role at this meeting is to represent industry in general and not any particular company. Dr. Nelson is currently employed

by Martek Biosciences.

We would like to remind members and temporary voting members that if the discussions involve any products or firms not already on the agenda for which an FDA participant has personal, imputed financial interest, the participants need to exclude themselves from such involvement. And their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. KRAMER: I think we're ready to start to stay on time with the presentations. And we're going to start with opening remarks from Dr. Michael Klein the Director of the Controlled Substance Staff.

DR. KLEIN: Good morning. Dr. Kramer, members of the committee, and invited guests, welcome to this meeting of the Drug Safety and Risk Management Advisory Committee. Today we will discuss the abuse potential of dextromethorphan-containing drug products. And following the provisions of the Controlled Substances Act, the CSA, the Drug Enforcement Administration has gathered and reviewed available data on dextromethorphan abuse. DEA has reported to us increasing problems related to the drug's

abuse. In so doing, DEA requested a scientific and medical evaluation and scheduling recommendation for dextromethorphan from the Assistant Secretary for Health at the Department of Health and Human Services, HHS.

The responsibility for conducting the scientific and medical evaluation of substances for control under the CSA is delegated to the FDA. The National Institute on Drug Abuse, NIDA, participates with FDA on drug scheduling recommendations. The HHS scientific and medical evaluation is binding on the DEA insofar as our recommendation limits the level of CSA scheduling. DEA cannot place a drug into a schedule that is more restrictive than the one we recommend. Additionally, DEA cannot schedule a drug if our recommendation is that it not be controlled.

After receiving DEA's request for scheduling a recommendation on dextromethorphan, FDA began to collect information to support an agency assessment to respond to the request. A senior FDA attorney, Lynn Mehler, will today discuss the statutory and regulatory issues related to drug scheduling. The CSA regulations that result from scheduling are also in the background package. Dextromethorphan is extensively available in OTC products for the treatment of cough as well as in a number of prescription products.

Ms. Mehler's talk will address the provision of the CSA that speaks to the exclusion of non-narcotic substances that are sold OTC without a prescription. The abuse of dextromethorphan products was discussed in two previous FDA advisory committees. Details of these meetings, as well as a history of dextromethorphan and approval of dextromethorphan products by the OTC monograph process will be described by Dr. Ayana Rowley with the Division of Non-prescription Regulation Development.

The first advisory committee on dextromethorphan in 1990 was convened because of reports of abuse of dextromethorphan-containing cough syrups by teenagers and was asked to help FDA develop a strategy for assessing the problem and discuss possible solutions. The committee recommended that the sponsor provide additional data on the toxicity of the substance, especially in the higher-dose range and that additional epidemiological data be gathered so that FDA could better assess the scope and significance of abuse and the risks to the public health.

Two years later in 1992, the advisory committee reconvened and discussed several proposed epidemiological studies on dextromethorphan abuse including conducting a national survey from interviews with drug-free school coordinators, evaluating attitudes and behaviors of

potential and actual dextromethorphan abusers and abuse prevention programs. Although no clear consensus on the extent of the problem or solutions came out of this meeting, there was a general recognition in this early pre-Internet era that outbreaks of abuse occurred in some small communities, that the dextromethorphan-abuse problem had not risen yet to the national level and further studies should focus on areas where abuse outbreaks are occurring.

Clinical investigators were again encouraged to collect clinical behavioral pharmacology data of high-dose dextromethorphan. However, in 2005 the issue of dextromethorphan abuse was brought to national attention. Five teenagers from the states of Washington, Florida, and Virginia were reported to have died following ingestion of dextromethorphan. In each case, the deaths were attributed to the toxic effects of dextromethorphan. In each case, the decedents had ingested elicit powered, nonpharmaceutical dextromethorphan from an Internet resale company.

Additionally, four case reports of overdose were associated with these deaths. In response, FDA published a talk paper in May 2005 entitled, "FDA Warns Against Abuse of Dextromethorphan." These reports will be discussed in the FDA presentations. The abuse-related pharmacology of

dextromethorphan is an essential part of the scheduling assessment. Assessing the experimental effects of dextromethorphan in animal and human studies as well as case reports of abuse, misuse and overdose will be covered by Dr. Katherine Bonson of the Controlled Substance Staff.

The clinical data related to the medical use of dextromethorphan will be described by Dr. Priscilla Callahan-Lyon from the Division of Nonprescription Clinical Evaluation. The CEDR office of Surveillance and Epidemiology, OSE, will discuss drug-usage data and examine databases for reports of abuse of dextromethorphan and these will include FDAs adverse events reporting system errors and SAMSHA's drug abuse warning network DAWN data.

The OSE speakers are doctors Tracy Pham, Sara Camilli, and Catherine Dormitzer. Poison Control Center data are also included in the background packages.

Following the conclusion of FDA presentations, the Consumer Healthcare Products Association, CHPA, will describe voluntary programs they have initiated to reduce the abuse dextromethorphan by teens. The CHPA Website describes steps aimed at preventing abuse and is supported by data from the Partnership Attitude Tracking Study, PATS, survey. The agency has reviewed information provided on the CHPA Website and will be available to respond to

questions from the committee.

Through this advisory committee, we are today requesting that you help us determine if the pharmacology and epidemiology data presented are sufficient to demonstrate that dextromethorphan has abuse potential and if the data identify a particular population at risk for abuse. We also welcome your evaluation of the effectiveness of the CHPA voluntary efforts in reducing dextromethorphan abuse and your recommendations for any new approaches that could reduce abuse and misuse of these products.

Additionally, we would like you to consider the impact of risk-management measures on drug availability and patient care. Finally, you will be asked for your recommendation on whether dextromethorphan should be placed under control of the Controlled Substances Act.

We thank you in advance for participating in this meeting and providing us with your expertise and insights on this important public health issue. Thank you.

DR. KRAMER: Thank you, Dr. Klein.

MS. MEHLER: Good morning. I am Lynn Mehler, an attorney with the FDA, Office of the Chief Counsel. And as Dr. Klein mentioned, I'm going to give you a brief overview of the statutory framework for scheduling a substance under

the Controlled Substances Act.

The CSA was first enacted in 1970 to regulate the manufacture, importation, possession, use, and distribution of certain substances. DEA is primarily responsible for interpreting and enforcing the CSA, but HHS has a number of responsibilities under the CSA, several of which are performed by the FDA. One of these responsibilities is the process for scheduling or controlling a substance under the CSA. As Dr. Klein mentioned, before a substance can be scheduled, FDA must complete a medical and scientific assessment and a scheduling recommendation for HHS with a concurrence of NIDA. The HHS scheduling recommendation is binding on DEA as to scientific and medical matters. And DEA cannot schedule a substance if FDA recommends that it not be scheduled.

HHS sends the analysis and recommendation to DEA, and DEA must go through rule-making before scheduling. There are five schedules -- sorry, there we go -- there are five schedules under the CSA. Schedule I is the most restrictive. Substances in Schedule I are not available for medical use. FDA-approved products are controlled in Schedules II through V. A substance's schedule dictates the requirements regarding physical security, quotas, prescription, and registration requirements. Section 202

of the CSA establishes the schedules.

The DEA regulations list the substances that are controlled in each Schedule. In doing the FDA and HHS scientific and medical evaluation, we must consider eight factors. And the factors are on the slide. They are actual or relative potential for abuse, scientific evidence of pharmacological effect, state of current scientific knowledge, history and current pattern of abuse; scope, duration, and significance of abuse; risk to the public health; dependence, liability and whether or not the substance is an immediate precursor.

After considering the eight factors, HHS must make a recommendation as to the appropriate schedule for the substance. Each schedule has three findings that must be made to recommend placement of a substance in that schedule. The findings are set out in the CSA.

As I stated before, Schedule I substances have no currently-accepted medical use and treatment in the U.S. They have a high potential for abuse and a lack of accepted safety for use under medical supervision. Schedule II substances have a high potential for abuse, a currently accepted medical use and treatment in the U.S. or a currently accepted medical use with severe restriction, and abuse may lead to severe psychological or physical

dependence.

Schedule III substances have a potential for abuse less than substances in I or II, a currently accepted medical use, and abuse may lead to moderate or low physical dependence or high psychological dependence. Schedule IV substances have a low potential for abuse relative to substances in III, a currently accepted medical use and treatment in the U.S., and abuse may lead to limited physical dependence or psychological dependence relative to those substances in III.

Schedule V substances have a low potential for abuse relative to substances in IV, a currently accepted use and treatment in the U.S., and abuse of the substance may lead to limited physical dependence or psychological dependence relative to those substances in IV. As you can see, determining whether to recommend Schedules II through V is about comparing the substance to substances that are already controlled under the CSA.

All right. Let’s talk about dextromethorphan. Currently, it’s not controlled in the CSA. When the CSA was enacted, it was specifically excluded from being a controlled substance. But the CSA provided that it could be scheduled through the scheduling process I outlined previously, if the science dictated.

There is an exclusion in the CSA for non-narcotic OTC drugs. Section 201(g)(1) of the CSA provides the following: The Attorney General shall by regulation, exclude any non-narcotic drug that contains a controlled substance from the schedules if the drug may, under the Federal Food, Drug, and Cosmetic Act, be lawfully sold over the counter without a prescription. So, obviously, a key determination is whether or not the substance is a narcotic drug. You can see the full definition of a narcotic drug from the Controlled Substances Act in the slides.

But in essence, a narcotic drug includes opium, opiates, derivatives of opium and opiates, poppy straw and concentrated poppy straw, cocoa leaves with some exceptions, cocaine, ecgonine, and any compound mixture or preparation containing any of those substances.

So where does that leave dextromethorphan? It does not meet the definition of a narcotic drug under the Controlled Substances Act. It is available in FDA-approved prescription products as well as lawfully-marketed nonprescription or OTC drugs. The DEA regulations at 21CFR130821, set out a process for applying for exclusion from the schedules for any drug product that meets the criteria in that provision I just mentioned.

So in summary, before dextromethorphan can be

scheduled, FDA must complete a medical and scientific analysis and scheduling recommendation. And DEA will have to go through rule-making. If the substance dextromethorphan is scheduled, sponsors of lawfully-marketed OTC products containing dextromethorphan will be able to apply to DEA for an exemption. If DEA grants the exemption, the OTC drug will not be scheduled. If the substance dextromethorphan is scheduled, dextromethorphan in bulk in FDA-approved prescription products or in drug products that are not lawfully marketed, will not be eligible for the exemption from scheduling and will be required to comply with the requirements of the CSA and DEA regulations for the relevant schedule. Thank you.

DR. ROWLEY: Good morning. My name is Ayana Rowley. And I'm an interdisciplinary scientist from the Division of Nonprescription regulation development. This morning I will describe the regulatory requirements for bringing an OTC drug product to the marketplace. Next I will provide a summary on the regulatory history of OTC dextromethorphan. And finally, I will summarize the two previous advisory committee meetings on the issue of dextromethorphan abuse.

To begin, let's look at what the consumer sees when they go to their local pharmacy. Currently, there are

over 100 OTC dextromethorphan-containing cough and cold drug products. Dextromethorphan is available in single NAD products or in combination with other active ingredients. These products are available as suspensions, capsules, tablets, and syrups as oral solutions. They are available as immediate and extended release formulations.

Now looking at this display, one might think that all these products are approved by the FDA in the same way. But they are not. So let's take a closer look. Here you can see two OTC dexamethorphan-containing drug products. One is marketed under a new drug application or an NDA. And the other is marketed under the cough and cold drug products monograph. Can you tell which is monograph and which is NDA?

Now you may ask, are they really different? How are they different? Well, the product on the left in the red box is an immediate release formulation which is marketed under the monograph system. And the product on the right in the purple box is the extended release formulation which is marketed under an NDA.

So what exactly is a monograph? And how is that different from an NDA? All over-the-counter drugs are regulated by one of two means under a new drug application or under the monograph system. NDAs are submitted by drug

manufacturers. The NDA must be approved prior to marketing. NDAs are for specific drug products. And the information submitted under an NDA is confidential. And finally, under an NDA, a sponsor will sometimes be granted marketing exclusivity for the product.

In contrast, monographs do not require prior approval before product marketing. Also, monographs are active ingredient rather than product-specific. Under the monograph system, anyone can market a drug product if the active ingredient is listed in a monograph and the product is listed as stated in the monograph. Monograph development is a public process. And the rule-makings are published as public documents in the federal register. Finally, unlike NDAs, no marketing exclusivity is granted.

Most people are familiar with the NDA process, so I'll spend a little more time discussing the monograph process also called the OTC drug review. In 1938, the Federal Food, Drug, and Cosmetic Act required that all new drugs must be proven safe prior to marketing. It was not until the 1962 Drug Amendments Act that evidence for both safety and effectiveness was required before a new drug could be marketed. At the time of the 1962 Drug Amendments Act, there were approximately 300,000 OTC drug products on the market. Of those, only about 500 have been approved

for marketing as safe under an NDA. And of those, only 25 percent have found to be effective for one or more of their intended uses.

Thus, an extensive review known as the OTC Drug Review of all over-the-counter drug products was initiated on May 11, 1972, to determine their safety and effectiveness. The review originally included only over-the-counter drug products that were marketed in the United States prior to the 1972 initiation date. But this was subsequently extended to December 4, 1975. The review was conducted by expert review panels consisting of healthcare practitioners and scientists which is similar to today's advisory committees.

The panels consider active ingredients rather than drug products. These were divided into 80 different therapeutic categories which included up to 800 active ingredients which ranged from acne to weight-control drug products.

After the panel reviewed all the proposed active ingredients, they classified the active ingredients in one of three ways. Category I, GRASE, generally recognized as safe and effective for the intended use and is considered not to be misbranded, or Category II, not GRASE, not generally recognized as safe and effective for the intended

use. It's considered misbranded. Or finally, Category III, which means that there was insufficient safety or efficacy data available to permit classification. However, the manufacturer has several options to pursue following this classification. They can submit additional data to show that the ingredient in a product was safe and effective. They could reformulate the product. Or they could appropriately re-label the product.

The panel's recommendations are then published in the Federal Register as an advanced notice of proposed rule making or an ANPR. The purpose of this notice is to alert the public the FDA is developing a rule and inviting public comment on the subject matter. This is the first step of the three-step rule-making process for monograph ingredients.

After the FDA reviews the panel's recommendations and public comments, FDA generates a proposed rule of a tentative final monograph also abbreviated as TFM. The TFM is published in the Federal Register for comment. The TFM is FDA's first stated position on the safety and effectiveness of a particular active ingredient. This is the second step in the three-step rule-making process. The final step comes after FDA reviews the public comments and any additional data that were submitted in response to the

tentative final monograph. FDA formulates a final rule also called a final monograph.

The final monograph is published in the Federal Register. This final monograph becomes the effective regulation for the Category I active ingredients in that particular therapeutic category. The codified section of the final monograph is then added to the Code of Federal Regulations.

You have just heard about the monograph process. So what exactly is in a monograph? First are the permitted active ingredients which are generally recognized as safe and effective. For each ingredient, the monograph specifies the permissible dosage forums, dose, and/or concentration as well as the permitted combinations with other active ingredients.

Finally, the monograph includes the required labeling which includes the uses, warnings, and directions. No one is allowed to deviate from this labeling under the monograph process. The labeling is found in the drug facts panel on the marketed product.

This concludes my summary of the OTC drug review and the monograph rule-making process as well as the required labeling for OTC drugs.

Now I'm going to give you a brief regulatory

history of over-the-counter dextromethorphan. On September 9, 1976, FDA published the cough, cold, allergy, bronchodilator, anti-asthmatic, AMPR for OTC human use. In this initial rule-making -- this initial rule-making highlighted the findings from the panel's acceptability on dextromethorphan as an over-the counter drug product. The panel concluded that dextromethorphan is a non-narcotic, antitussive agent by selective suppressive of the central cough mechanism and has no significant abuse liability. The panel thereby classified that dextromethorphan and dextromethorphan hydrobromide as Category I, GRASE active ingredients.

After the publication of the ANPR, FDA published a tentative final monograph for antitussive drug products proposing that dextromethorphan in itself as a Category I antitussive active ingredients with labeling and directions for use based on the panel's recommendations on October 19, 1983. In that tentative final monograph, FDA noted that dextromethorphan has a wide margin of safety with respect to its potential to cause poisoning through accidental overdose, that no fatalities have been reported even in doses in excess of 100 times the normal adult dose, and then the agency tentatively concluded by concurring with the panel's findings that due to the low order of toxicity,

dextromethorphan is probably the safest antitussive presently available.

On August 12, 1987, FDA published the final monograph for antitussive drug products. In this monograph, dextromethorphan was labeled as a cough suppressant with directions for adults and children over two years of age. Included on the slide for your reference is the maximum daily doses for children and adults.

Since the publication of the final monograph, there has been an increase of reports of dextromethorphan abuse which has resulted in FDA holding two advisory committee meetings to discuss the issues and possible solutions to this concern. The first AC meeting was held on August 6, 1990. The meeting was held in response to citizens' petitions from Pennsylvania and Utah, specifically focused on the abuse of dextromethorphan-containing cough syrups by teenagers in communities located in rural areas. Here I have included for your reference some of the common slang terms used by teenagers which was discussed at the meeting.

In the opening remarks the following objectives were outlined and the committee was asked to help FDA identify and better define the extent of the problem, develop a strategy for assessing the problem and to

identify and discuss the pros and cons of possible solutions that could be applied. Invited speakers gave presentations and presented data on the nature of the problem, the areas affected, the characteristics of those local areas, and the information regarding the drug or the manner in which it was being used that made it a problem.

The reports of teenagers abusing dextromethorphan were sporadic. And they could not conclusively show that it was a health-hazard problem. Thus, the committee recommended that the major manufacturer of dextromethorphan provide additional data on the toxicity of the substance in higher dose ranges and that additional epidemiological data be gathered. As a result the committee held a follow-up advisory committee meeting two years later.

On July 14, 1992, a follow-up meeting was held to assess the scope and significance of abuse and the risk to public health. At the end of this second meeting there was no clear consensus of the extent and problem or what actions should be taken to control it. In addition, FDA commented to the sponsors that future studies are needed to focus the attention on the areas where the outbreaks were occurring and also to collect clinical behavior and pharmacology data as part of the clinical studies using the higher doses of dextromethorphan.

This concludes my presentation regarding the OTC drug review, the regulatory history of over-the-counter dextromethorphan, and the two previous advisory committees on dextromethorphan abuse. I thank you for your attention. And I turn the podium over to the next speaker.

DR. KRAMER: Before we go to the next speaker, I think we have time set aside on the agenda, I think it would be good to pause at this point and give the committee members a chance to ask any clarifying questions of the first two speakers. And I'll kick it off with one for Lynn Mehler, if I could.

It would be good if both of you just stood up here so the committee members could clarify questions.

Ms. Mehler, you stated unequivocally when you were explaining the definition of a narcotic that dextromethorphan is not a narcotic. And if I could just question the Category A on your slide states that included among narcotics are opiates including their isomers. And from our background materials, dextromethorphan was clearly described as a dextrahereditary (phonetic) of levomorphine (phonetic) which is a Schedule II drug. And I recognize that dextromethorphan is not a precursor of levamothorphan (phonetic), but it is a dextrahereditary isomer. And if you read that literally, I could imagine that it could be

defined as a narcotic. And I recognize it's not an opioid receptor antagonist, excuse me, agonist, but it doesn't actually state that as a requirement in the definition.

MS. MEHLER: Well, my first slide was that I'm a lawyer. So I'm going to have to maybe refer that to, possibly to my FDA colleagues. But I relied on, you know, their analysis in the determination that dextromethorphan is not a narcotic. So I'm not going to be able to get into the details obviously.

DR. KRAMER: Is there someone who could from FDA? I think this is a critical point to start out the meeting and state that it's not a narcotic if it could be interpreted that way through defining it as an isomer, dextarotory (phonetic) isomer of a Schedule II opioid.

DR. KLEIN: Well, historically it's been recognized as not being a narcotic. There's a special provision that describes its use in the CSA that draws attention to the activity of dextromethorphan. And what we're going to present is data that shows that it doesn't have narcotic properties.

DR. KRAMER: So, I'm just trying to be literal, since the regulation itself is the reference to defining something as a narcotic and not the science, maybe one of our pharmacologists could comment? Yes.

DR. HENDELES: I think the fact that it doesn't bind to the new receptor is the reason why historically it's classified as a non-narcotic.

DR. KRAMER: I understand scientifically, but if you're a literal interpreter of the regulation, you could interpret that it is covered, although, historically, it wasn't looked at that way. Is that not correct?

DR. HENDELES: Pharmacologically, it doesn't behave as an opiate or as a narcotic.

DR. KRAMER: Any other comments? I'll tell you what, let's make sure in order to get people to speak when they have something to say, if you raise your hand until Elaine writes your name down, we'll take it in the order that people have raised your hands so we can make sure that we get you all. And I hear something -- yes.

MR. MULLINS: I had a comment also. But from what I understand about the characteristics of this and the biokinetics of the drug is that it is in the same family as phencyclidine, PCP, and ketamine; correct, it is in that same family? So it's my understanding that it has characteristics of PCP.

DR. KRAMER: It activates the same receptor that PCP.

MR. MULLINS: Right, activates four receptors --

DR. KRAMER: NMDA receptor --

MR. MULLINS: NMDA and also three other receptors also.

DR. KRAMER: Your question is?

MR. MULLINS: I think that I believe that it is -- we should define narcotic because I think it has the characteristics of -- it is a derivative of morphine and the morphine family. So I think it has characteristics of a narcotic.

DR. KRAMER: So, Elaine?

DR. MORRATO: Are we able to ask other questions?

DR. KRAMER: Yes.

DR. MORRATO: I just wanted to make -- this is also for Ms. Mehler, I wanted to make sure I understood the kind of legal-regulatory consequences of these schedulings. So in practice is -- if we schedule DXM, is that, or any product, is that synonymous with requiring that it can only be sold through a prescription?

MS. MEHLER: No, that's actually -- there's a different determination under the Food, Drug, Cosmetic Act which is FDA statute, that says whether or not a drug is a prescription or available over the counter, which is a different legal inquiry. There are controlled drugs that are -- sorry, there are OTC drugs that are scheduled. So

it can be both. DEA has some regulations on if you are an OTC drug and you are controlled and you don't trigger this exemption. So with their available, it does not mean, once you schedule it does not trigger a requirement under the Food, Drug, and Cosmetic Act that it be prescription.

DR. MORRATO: And then I had a follow-up so that if it's scheduled, I think I understood you to say that the manufacturers have the right to petition for an exemption, but that if an exemption is granted that the bulk substance would still be required to be controlled; is that right?

MS. MEHLER: That's my understanding that the exemption would only be for the product that meets the definition which would -- assuming that it's a non-narcotic and that's it's legally marketed under the FDC Act. So only those products that are legal OTC products under FDA's statute would get the exemption. So clearly a bulk substance doesn't meet that definition. A prescription product doesn't -- or a product that may be sold outside the monograph and without an NDA.

DR. MORRATO: Okay. So that if I understand correctly that this might be an alternative legal path to getting the bulk product controlled as an alternative to seeking new legislation that's under consideration; is that correct?

MS. MEHLER: Yes.

DR. MORRATO: Thank you.

DR. KRAMER: Lewis Nelson.

DR. LEWIS NELSON: Well, I actually raised my hand to support your point because it seems very clear to met that, at least based on this tiny little bit of a definition we have here, that its clinical effects don't really weigh into the -- for example, nobody would suggest that cocaine, the derivative of cocoa leaves bond to the opioid receptor. So it can't -- excuse me -- it can't simply be opioid activity defines a narcotic. And if they're really basing it on structural characteristics, admittedly, the dextrorotatory axomers (phonetic) don't bind to new receptor and activate it. But that's not really what's suggested here. So it would be important from a -- from a real stickler point of view to define that a little bit better because I guess it does play into the ultimate decision that has to be made.

DR. KRAMER: Richard Honsinger.

DR. HONSINGER: And to further -- further along with Elaine's question, that is if we do make this drug a scheduled narcotic and we give exemptions and there's a hundred different companies that happen to make -- to use this drug or a thousand different companies that use this

drug in their products, does that mean that there will have to be a thousand applications or can it be a product by exemption?

MS. MEHLER: I'm not going to be able to speak to that because that's a DEA decision. And I did reference the DEA regs. They outline how one would apply for this exemption. And if you read the regs it seems to be a product-by-product application. So that's the process that is out there now. That's really -- I can't go really beyond that.

DR. KRAMER: I have a clarifying question on that same point. And then Tom Kosten has a question. I'm a little confused by the -- your describing the possibility of exemption. As I understand it, the DEA asked the FDA and the FDA has asked this committee to consider the scientific evidence to make a recommendation on scheduling. If I understood correctly what you said that even if this committee recommended that there should be a schedule substance, that the manufacturers can apply to be exempt from that requirement which seems to counter the whole purpose of having a committee make a recommendation on scheduling. So could you explain what we're doing?

MS. MEHLER: Well, obviously, as we discussed before, that would only be the OTC products that apply for

the exemption. It would not --

DR. KRAMER: Which is everything, almost everything on the market.

MS. MEHLER: But it would not cover the bulk, it would not cover prescription. It would not cover any illegal product that's out there. So to the extent that's an issue that needs to be discussed, then that's, I think, what we're here for.

Also, I mean, I think the specific questions don't go to the ultimate decision of, you know, what does DEA do. But I think some of the discussion about the science and what really is the problem and I think the attempts at risk management so far.

DR. KRAMER: But despite the science and despite the recommendation, there's an opportunity for it to be -- for an end-run around the recommendation; is that correct?

MS. MEHLER: That is my understanding of the Controlled Substances Act.

DR. KRAMER: Tom Kosten.

DR. KOSTEN: This is a history question. Back in 1992 there was a review of the data at that point which suggested there was unclear evidence about its abuse, liability or what kind of a public health problem it was. Were there other scientific data in that discussion that

led them to have such a interesting conclusion?

DR. ROWLEY: So if I understand your question correctly, you want to know if there was any other studies that they discussed at the time of that meeting?

DR. KOSTEN: Well, what was the, just a brief summary, what was the epidemiological data? I mean, there was at least two states already that were saying this was a problem. Was every other state in the union saying there was no problem whatsoever with this drug? Because I think this contradicts some data that I would think are from Texas and a few other states.

Just a little bit more detail about what happened in '92, I mean, what was the quality of those data they were looking at.

DR. ROWLEY: From my understanding from reading the transcripts, there were four studies that they presented. However, at the time of that meeting, only one of the studies had been conducted and the data wasn't available. So the rest of the studies were just proposed and there wasn't any data. They were going to do the follow-up between -- the meeting was in August -- July of 19992. So the follow-up data was going to occur between the 1992-1993 school year.

DR. KOSTEN: And that data was never looked at?

DR. ROWLEY: We have never received any follow-up data for those particular studies.

DR. KOSTEN: Are we going to get any from those studies at this hearing?

DR. ROWLEY: Not to my knowledge.

DR. KRAMER: Dr. Maxwell.

DR. MAXWELL: Yes. I'm aware of who were on those committees. I did not talk to them about their findings. I would be very interested in actually knowing the quality of the epidemiologists who were on it, actually learning a little bit more about what happened and why -- how they could meet twice and not have any data. I don't understand.

DR. ROWLEY: Unfortunately, all we have from that 1992 meeting is the transcripts from the meeting. So that's the available data we were able to gather that occurred at that time. We don't have any follow-up information for you.

DR. KRAMER: Lewis Nelson.

DR. LEWIS NELSON: I'll pass my question for now.

DR. KRAMER: Rodney Mullins.

MR. MULLINS: My question is on the history of dextromethorphan. I wanted to clarify this issue with Ms. Cowley. And I wanted -- Ms. Rowley, excuse me, I wanted to

clarify the history of dextromethorphan. It seems like it was introduced as Romilar in 1960, correct? And it was then banned. And then it was re-introduced; is that correct? Because Romilar was the original -- was the original form of dextromethorphan, and then it was re-introduced with a distasteful agent and then it then transformed into different forms as far as cough syrups and things like that.

I wanted to ensure or just clarify the history of the therapy.

DR. ROWLEY: I'm going to have to defer that comment to my FDA colleagues.

DR. FURNESS: We'll have --

DR. KRAMER: I didn't hear you, I'm sorry.

DR. FURNESS: We'll have to look that up.

DR. KRAMER: Okay. We'll get back to you on that question. And next we have George Woody.

DR. WOODY: About terminology, from the material we've seen, it looks like you might be able to -- we could probably make a case for abuse. But throughout the regulations, there was a reference to physical or psychological dependence. In DSM-IV, abuse and dependence are separate, they're two different cause tracks. However, in what the American Psychiatric Association has put out

for DSM-V, they're going to get rid of the abuse criteria and it's all going to be dependence but with varying levels of severity. So, I was just sort of curious how we should think about that dynamic.

DR. KRAMER: Michael Klein.

DR. KLEIN: Another section of the Controlled Substances Act defines an opiate as having addiction-forming or addiction-sustaining liability similar to morphine. And subsequent studies that were conducted on dextromethorphan, which will be discussed in the next presentation, examined whether dextromethorphan had similar activity to morphine. And the results were negative.

DR. KRAMER: We have one more question then we're going to the next presentation.

Sharon Stancliff.

DR. STANCLIFF: Thank you. I'd like to get a little more clarity on what the scheduling options are and perhaps it would helpful to explain how pseudoephedrine went from over-the-counter in the front of the pharmacy to behind the counter; would you be able to clarify that for me?

MS. MEHLER: By federal statute, the federal statute put several requirements on the sale of pseudoephedrine. So it's not a controlled substance. It's

got its own, sort of, set of rules and regulations about where it's sold and how you get it and sort of all those record-keeping requirements. So it was not administratively scheduled. And what I walked through was what does FDA, HHS, DEA do when we have a drug of abuse or a potential drug of abuse and want to administratively schedule it and the process we have to go through. So pseudoephedrine didn't go through that process, Congress can put whatever they want in whichever schedule. So you'll see, if you see a list of schedules, there's some substances in there that weren't put there through the administrative process. For example, I think steroids are Schedule III, we didn't go through our eight factor analysis and make the findings. Congress just put them there. So, that's why pseudoephedrine has its own set of, sort of, regulatory requirements and regs and all that.

DR. KRAMER: If I could just -- you just make a statement that steroids are Schedule III, could somebody from FDA clarify that statement?

MS. MEHLER: Sorry.

DR. KLEIN: They were placed by Congress under Schedule III.

DR. KRAMER: What steroids?

DR. KLEIN: All anabolic steroids.

DR. KRAMER: Glucosteroids? Thank you.

We'll go on with the next presentation.

Katherine Bonson.

DR. BONSON: Good morning. I'm Katherine Bonson, pharmacologist in the Controlled Substance Staff. I'm going to be talking today about the abuse-related pharmacology of dextromethorphan. I'm not sure where I press to. In the next 20 minutes I'm going to give you a very brief overview of the chemistry of dextromethorphan, its receptor binding, preclinical behavioral studies, human pharmacokinetics, human experience and clinical studies, and human deaths and over doses as well as human adverse events.

I want to say something about the information that we utilize though. We have not actually received any primary data from any assessments of the abuse potential of dextromethorphan either preclinically or clinically. Thus, this presentation relies on publicly-available information found in the scientific and medical literature. This information includes information from well-conducted studies as well as from anecdotal case reports.

So let's go to the chemistry of dextromethorphan. As we've been talking about, dextromethorphan is the methylated dextrorotatory analog of the synthetic Schedule

II opioid levorphanol, which is a derivative of codeine. Levorphanol can also be converted to the Schedule II opioids, racemethorphan and levomethorphan, the racemic and dextrorotatory forms of dextromethorphan.

Under the Controlled Substances Act definition dextromethorphan is not a narcotic drug and is not currently scheduled under the CSA. Thus, dextromethorphan is different from the Schedule II narcotic compounds to which is it structurally related such as levorphanol, levomethorphan, and racemethorphan.

Let's go now to the receptor binding studies. Even though dextromethorphan is derived from opiate drugs, it has no significant affinity for mu-opioid receptors. Dextrorotatory drugs typically do not have high affinity for the mu-opioid receptor unlike levorotatory drugs. Although dextromethorphan has no affinity for mu-opioid sites, opioids that are structurally similar to dextromethorphan such as levorphanol, levomethorphan, and racemethorphan do have high affinity at the mu-opioid site.

So what is the mechanism of action to dextromethorphan? Well, there are five mechanisms that have been identified thus far. These are as an NMDA receptor channel blocker; as a sigma-1 receptor agonist; as a calcium channel blocker; a serotonin reuptake inhibitor;

and a nicotinergic antagonist.

Dextromethorphan binds with moderate affinity at the PCP site of the NMDA receptor channel complex. And dextromethorphan acts as a non-competitive antagonist at this site. And this is thought to be the primary mechanism of action of dextromethorphan. It also acts at sigma-one sites where it acts as a high affinity agonist. It also induces inhibition of voltage-dependent calcium channels creating a functional antagonism. It also has high affinity binding for the serotonin transporter producing serotonin reuptake inhibitory activity. And finally, dextromethorphan acts as an antagonist at nicotinergic acetylcholine receptors. So out of these five though, the NMDA antagonism seems to be the primary mechanism.

Let’s go to the preclinical behavioral studies that have been conducted with dextromethorphan. General behavioral effects of dextromethorphan have been investigated in animals. And dextromethorphan at doses of 60 to 100 milligrams per kilogram, i.p., produce stereotypy in rats that is similar to that produced by the NMDA antagonist, PCP which is Schedule II, and ketamine which Schedule III. Dextromethorphan at doses of 15 to 120 milligrams per kilogram, i.p., also produces hyperactivity in rats that is similar to that produced by PCP, a Schedule

II drug.

Self-administration studies have also been conducted with dextromethorphan so let's just go over that method. Self-administration is a method that tests whether a drug has rewarding properties in animals. Animals are trained to press a lever a certain number of times to receive an intravenous dose of a known drug of abuse. A test drug is then substituted and if that drug has rewarding properties it will maintain lever-pressing in the animals.

So in animals trained to self-administer the NMDA antagonist PCP, the Schedule II drug, dextromethorphan will maintain self-administration in monkeys at moderate doses of 100 to 300 micrograms per kilogram per infusion. But it does not maintain self-administration at lower doses, 30 micrograms per kilogram per infusion or at higher doses greater than 1,000 micrograms per kilogram per infusion in monkeys and in rats. Self-administration has also been produced by other NMDA antagonists including PCP, the Schedule II drug, and ketamine, the Schedule III drug.

Drug discrimination has also been conducted with dextromethorphan in animals, so let's go over that method. In drug discrimination are trained to differentially press one of two levers after administration of a training drug

or placebo. If a test drug produces similar interoceptive cues, that's how the animal thought to feel, to the training drug, more than 80 percent of the animals' response will be on the training drug-associated lever. In this case, the test drug is said to generalize to the training drug.

In animals trained to discriminate, the NMDA antagonist PCP, Schedule II, rats dose-dependently generalized dextromethorphan to the PCP cue. And monkeys, two of three in this study, generalized dextromethorphan to the PCP cue with the third monkey showing partial generalization less than that 80 percent criteria. When another NMDA antagonist ketamine, the Schedule II drug, was used as a training drug in a discrimination study, dextromethorphan dose-dependently produced full generalization to the ketamine cue in rats. And PCP, the Schedule II drug, also produced full generalization to the ketamine cue in rats.

Drug discrimination has also been conducted with sigma-one drugs. And when monkeys were trained to discriminate the sigma-one agonist (+)pentazocine, which is a Schedule IV drug from saline, dextromethorphan produced full generalization to the (+)pentazocine cue.

So let's move now into the human pharmacokinetics

of dextromethorphan so you have an overview of that before we go into the human data. In humans, dextromethorphan is well absorbed after oral ingestion with a Tmax of about 1.7 to 2.5 hours. The onset of effect is rapid, often beginning 15 to 30 minutes after oral ingestion. And the half-life of dextromethorphan is about two and a half hours.

Dextromethorphan converts through O-demethylation to its major metabolite, dextrophan, which we abbreviate here DXO. This is catalyzed by the cytochrome P-450 isozyme 2D6, otherwise known as CYP2D6, following oral administration. And dextrophan, like its parent compound, dextromethorphan, has a high affinity for the NMDA channel site.

So what is the abuse-related human experience and the clinical studies that have been conducted with dextromethorphan? Before I get into this, I think it's useful to explain a little bit about the dose response. So the recommended therapeutic dose of dextromethorphan for the treatment of cough is 10 to 30 milligrams orally every four to eight hours. Abuse of dextromethorphan occurs at doses ranging from around 100 milligrams to greater than 2,000 milligrams orally. And the clinical-abuse-related studies with dextromethorphan have used doses ranging from

10 milligrams to 315 milligrams orally as well as 10 milligram to 240 milligrams subcutaneously.

So when people abuse dextromethorphan there are four plateaux of subjective responses that have been described. And the first plateaux is a dose of about 1.5 to 2.5 milligrams per kilogram, around 100 to 175 milligrams in a 70 kilogram person. And that produces mild intoxication and gastrointestinal symptoms. The second plateau, about 2.5 to 7.5 milligrams per kilogram, which converts to about 175 to 525 milligrams per 70 kilogram person produces lethargy, agitation, ataxia, and tachycardia. The third plateau, 7.5 to 15 milligrams per kilogram, about 500 to 1,000 milligrams per 70 kilogram person, produces frank psychotic symptoms, disorientation, and altered judgment.

And then finally, the fourth plateau, 15 to 30 milligrams per kilogram or greater, which is 1,000 to 1,000 milligrams per 70 kilogram person can produce dissociative states, hyperthermia, and a risk of seizures and aspiration.

Now, there are five human abuse potential studies that have been conducted with dextromethorphan since 1953. Three of these studies evaluated dextromethorphan in terms of whether it produces opioid effects in non-tolerant, non-

dependent opioid abusers. Another study evaluated the alcohol-like effects in detoxified alcoholics and in healthy subjects. And the final study evaluated the abuse-related subjective effects of dextromethorphan in healthy subjects.

So Isbell and Fraser in 1953 did the first study. And they administered dextromethorphan at a dose range of 10 to 100 milligrams orally and subcutaneously to non-tolerant, former morphine abusers. And dextromethorphan did not produce morphine-like subjective responses. However, levorphanol, levomethorphan, and racemethorphan did produce morphine-like effects. And this is to be expected based on what we saw earlier about the pharmacology and how it doesn't bond to mu-opioid receptors.

Dextromethorphan at doses of 60 to 75 milligrams orally and subcutaneously produced adverse events such as dizziness, headache, double vision, nausea, and vomiting.

Jasinski, et al, in 1971 also administered dextromethorphan to opioid abusers at a dose of 120 and 240 milligrams orally as well as 60, 120, and 240 milligrams subcutaneously. And in this population, dextromethorphan did not produce increases on subjective scales for drug liking or euphoria. However, dextromethorphan did produce

increases on subjective scales for sedation and dysphoria. And dextromethorphan was not identified as a barbiturate. Barbiturates run the range across the CSA from II to IV, excuse me, it was identified as a barbiturate, but not as an opioid.

Jasinski then went and did another study in 2000 where they administered dextromethorphan at 180 milligrams orally to opiate abusers and they did not increase the ratings on feel drug, euphoria, or drug liking. However, this dose of dextromethorphan did increase ratings on dislike drug.

Soyka, et al, in 2000 also did a study with dextromethorphan. But they gave it to detoxified alcoholics at a dose of 140 milligrams orally as well as to healthy volunteers. And dextromethorphan in this study increased ratings on the alcohol sensation scale. Alcoholic subjects also had an increase in craving for alcohol following dextromethorphan administration.

And then finally, a study came out just this year from Zawertailo, et al, administration of dextromethorphan at a dose of 140 to 110 and 315 milligrams orally to healthy volunteers increased ratings on both positive subjective scales such as euphoria, high, drug liking, and good effects; as well as negative subjective scales such as

dysphoria, sedation, bad effect, unpleasantness, and dizziness.

Now we talked earlier about dextrorphan. So two studies have evaluated whether dextromethorphan metabolite, dextrorphan, is responsible for the psychoactive effects of dextromethorphan and these two studies used either poor or extensive CYP2D6 metabolizers, remember that's the enzyme that converts dextromethorphan to dextrorphan, or they use quinidine which inhibits 2D6 activity which will then prevent dextromethorphan from being created. And these were very small studies, only n's of six to eight. But these studies suggest that both dextromethorphan and its metabolite, dextrorphan, contribute positive and negative responses to the overall experience following dextromethorphan ingestion.

Let's move now to the human deaths and overdoses that have been reported in the medical literature with dextromethorphan. As Dr. Klein mentioned, in 2005 five teenage males in Washington state, Florida, and Virginia died following ingestion of dextromethorphan with or without other drugs. In each case, the deaths were deemed to be the result of a direct toxic effect of dextromethorphan. And these five deaths led to the publication of a FDA talk paper on dextromethorphan

entitled, "FDA Warns Against Abuse of Dextromethorphan," that came out in May 2005. And this was put out to warn the public about the risks associated with the abuse of Dextromethorphan.

So let's go into these case reports. There were two from Bellingham, Washington, in which two young men who were 17 and 19 years old ingested dextromethorphan and were found dead at home. An autopsy found pulmonary edema, cerebral edema, and frothy foam in major airways. The cause of death was determined to be acute dextromethorphan intoxication in both cases. And both individuals tested positive for cannabinoids. And one tested positive for diphenhydramine.

Now I want to explain a little bit more about what happened. There was a bag with 47 grams of white powder that was found near these two young men who had died. And it had a label on it that said, "Dextromethorphan hydrobromide 100 grams, not for human use." Now the young men had apparently the dextromethorphan from Chemical API, a chemical resale company in Indianapolis that purchased powdered dextromethorphan from India, repackaged the substance, and then resold it over the Internet. And these young men repackaged the dextromethorphan into gelatin capsules which

they intended to sell. Now this is important because this Chemical API will appear in the other case reports as well.

So there was a single case report from Danville, Virginia, in which a 19-year-old young man ingested dextromethorphan and was found unresponsive and later pronounced dead. The only finding upon autopsy was pulmonary edema. And the cause of death again was deemed to be dextromethorphan toxicity. The young man had obtained the dextromethorphan, again, from the Chemical API.

Then the final two case reports are from Cape Coral, Florida. Two 19-year-old men ingested powdered dextromethorphan once again, from the Chemical API source, in addition with Robitussin which contains dextromethorphan and OTC Benadryl containing diphenhydramine. And these two young men were later found dead. Autopsy reports showed that both individuals had heavy, wet, congested lungs. And the cause of death, again, was deemed to be dextromethorphan toxicity.

In addition, there are overdose cases associated with these case reports of death. So in the Washington case report, at least three non-fatal overdoses were linked to the sale of capsules containing powdered dextromethorphan by one of the young men who died. In the

Florida case report, one male youth ingested the same amount of dextromethorphan as well as the diphenhydramine. But he survived this drug ingestion because he became very ill and he vomited and also probably because he weighed 70 pounds more than his friends who died.

So in summary, in these published case reports, all five deaths and all four overdoses associated with these dextromethorphan cases involve the ingestion of illicit, powdered, non-pharmaceutical dextromethorphan with or without the presence of other drugs including pharmaceutical dextromethorphan.

Let's go into the adverse events associated with dextromethorphan. There are CNS-related adverse events with dextromethorphan. And the medical and scientific literature has been reporting on these for over 50 years. And these CNS-related AEs include mood changes, perceptual alterations, inattention, disorientation, aggressive behavior, nausea, restlessness, insomnia, ataxia, slurred speech, and nystagmus.

There are also non-CNS-related adverse events with dextromethorphan. And in a review of medical case reports published through 2008, doses of dextromethorphan greater than two milligrams per kilogram, around 140 milligrams in 70 kilogram person produced tachycardia,

hypertension, and respiratory depression. Severe folate deficiencies have also been reported in dextromethorphan abusers.

And then there's also a unique adverse event, because dextromethorphan is typical found as a hydrobromide salt, bromism is possible in chronic users. And bromism symptoms include memory impairment, drowsiness, tremors and ataxia, skin eruptions and psychiatric symptoms including delirium and psychosis. However, bromism appears to be rare and it requires a very high serum bromide level probably from a very chronic abuser.

So let's go into the summary of the preclinical and clinical data with dextromethorphan that I presented. The preclinical pharmacology shows that dextromethorphan is primarily an NMDA antagonist with no affinity for mu-opioid receptors. Like other scheduled NMDA antagonists dextromethorphan is self-administered by animals. In drug discrimination, dextromethorphan generalizes to scheduled NMDA antagonists and to sigma-one agonists.

And the summary of the clinical pharmacology is that dextromethorphan abuse at supratherapeutic doses produces four plateaux of subjective effects with increases degrees of intoxication. In clinical studies, dextromethorphan does not produce opioid-like effects, but

it does produce abuse-related subjective responses. There are five deaths and four overdoses associated with dextromethorphan that was illicitly obtained. And both CNS and non-CNS AEs are reported with dextromethorphan abuse.

Thank you. Did you want me to take questions or shall I sit down?

DR. KRAMER: I think we'll have the next presenter and then take question.

DR. BONSON: Fine.

DR. KRAMER: Unless there's any pressing clarifications that people want to ask right now. Okay.

DR. CALLAHAN-LYON: Good morning. I'm Priscilla Callahan. I'm in the Division of Nonprescription Clinical Evaluation. And I'm going to discuss the clinical perspective of dextromethorphan.

My presentation will give a brief history. Dextromethorphan is a monograph ingredient including the approved indications. A review of the references that were used to support its inclusion in the monograph, and then the current clinical perspectives including the American College of Chest Physicians guidelines, and a review of the references that were used to support the clinical guidelines and then some conclusions.

My sources of information included the FDA cough

and cold proposed rule, tentative final monograph, and the final rule, and the reference articles that were reviewed by the FDA panel: The American College of Chest Physicians evidence-Based Clinical Guidelines and their published literature references. The primary data for this has not been reviewed by FDA. I also looked for other professional organizational guidelines including American College of Physicians, the American Lung Association, and the American College of Family Medicine. All of these, however, refer to the ACCP guidelines. So that was my primary source.

Dextromethorphan is one of three compounds that was actually tested in research seeking a nonaddictive substitute for codeine. It's been available over the counter as a cough suppressant since 1958 and was included in the original cough and cold monograph proposed rule in 1976. In the final rule in August of 1987, antitussive active ingredients were listed in two categories: Oral, taken by mouth and acting systemically; and topical, which relieve a cough when they're inhaled or applied directly to the chest or the throat or dissolved as a lozenge.

The over-the-counter availability of antitussive include chlophendianol, which has never been marketed in the United States; codeine, which is not available currently, it is behind the counter in some states;

dextromethorphan, which is widely available over the counter; diphenhydramine is listed as an antitussive but is not marketed as a cough medicine; and then camphor and menthol which are the two topical agents are widely available.

The dextromethorphan final rule gives two approved indications: temporary relief of cough due to minor bronchial irritation as may occur with a cold and temporary relief of cough associated with a common cold.

In addition, there are several additional statements that are allowed in the monograph. I've listed them here. These allow the companies to apply additional statements to their package labeling to emphasize certain properties of their products.

The monograph system and the monograph review process involved the review of several studies. And I'm going to present some of them. The first is two studies that were done in the '50s and '60s on dogs and cats. These were done on several different antitussive drugs including dextromethorphan. Both of these showed evidence of cough suppression efficacy for dextromethorphan that was comparable to codeine. And both of the studies showed that the dextromethorphan was less sedating than the codeine.

Dr. Bickerman evaluated the response to treatment

in 15 healthy human subjects after citric acid vapor exposure which was given to induce cough. The dextromethorphan dose of 10 milligrams reduced the number of coughs by about 25 percent over four hours. A codeine dose of 30 milligrams had similar, slightly less reduction in the number of coughs. And the placebo that was administered had no activity.

Dr. Cass in 1954 treated 120 hospitalized human subjects that had persistent cough. In this study he compared three different doses of dextromethorphan with codeine and placebo. They did demonstrate dose response for the dextromethorphan and all the doses of the dextromethorphan and the codeine beat the placebo. The dextromethorphan and the codeine had equal antitussive effects milligram by milligram, but the codeine was noted to have more ill effects.

And Dr. Ralph in 1954 studied dextromethorphan in 183 patients both symptomatic and asymptomatic patients. It is significant, I think, that many of these patients had active tuberculosis. There was no comparator. They had marked moderated improvement in the cough as judged by an observer in 84 percent of the symptomatic subjects. The other interesting part of this study was 20 of these subjects received up to 75 milligrams a day of

dextromethorphan for 30 days with no significant ill effects.

So with this background I want to move now to the current clinical thinking on the use of dextromethorphan. What I'm going to do is briefly describe the clinical evaluation of cough and then focus on the guidelines on dextromethorphan use currently. Cough is one of the most common symptoms for which patients seek medical attention. As everyone knows, cough is irritating for the patient and for those around him. And per the 2003 CDC statistics, acute upper respiratory infection was the most common illness-related diagnosis in emergency department visits. If you look at the leading patient complaints for emergency department visits in 2003, cough is the number four.

The evaluation of cough focuses on the etiology and the duration of the cough in the physician evaluation. Cough is defined as either acute, subacute, or chronic depending upon its duration. It may have many possible etiologies. And patients may cough for more than one reason. While the duration is an important consideration for clinicians, it's noted that the over-the-counter labeling addresses duration for length of treatment, but not for treatment initiation.

Clinical guidelines, before I discuss the

specific guideline that I'm going to go through, I want to discuss guidelines in general. Clinical guidelines are systemically developed statements that are designed to assist the practitioner and the patient in decisions about appropriate health care for specific clinical circumstances. Guidelines are produced under the auspices of a medical specialty associate either private or governmental. They are not individually produced. HHS and specifically AHRQ, has a national guidelines clearinghouse. And to be included the guidelines must meet these criteria: They must produced under this medical specialty association, they must have corroborating documentation available. And guidelines are not FDA documents.

The American College of Chest Physicians, which is a leading professional organization focusing on respiratory diseases, originally published an evidence-based consensus panel report on cough, excuse me, in 1998. This was updated in 2006. The panel had extensive worldwide representation. And they made recommendations based on the quality of evidence looking at the study design and the strength of methodologies. The references are published literature, but the primary data has not been FDA reviewed.

The recommendations were made based on a scale

from strong to negative. They also had inconclusive recommendations in expert opinion only when there was limited clinical data. These recommendations are made based on the diagnosis. And what I've done is picked out the diagnosis for which dextromethorphan was specifically mentioned. In chronic cough due to acute bronchitis, patients with this diagnosis, antitussive agents are occasionally useful and can be offered for short-term symptomatic relief. This gets a weak recommendation. And the antitussive agents that they are referring to are dextromethorphan and codeine.

In patients with the diagnosis of chronic cough due to chronic bronchitis, the central cough suppressant such as codeine and dextromethorphan are recommended for short-term symptomatic relieve. This gets a moderate recommendation. In patients with post-infectious cough that is not due to bacterial sinusitis or early pertussis infection the centrally-acting antitussive agents should be considered when other measures fail. And the other measures that they refer to are the inhaled ipratropium, inhaled steroids, and oral steroids. This gets a moderate recommendation, but it is expert opinion.

In cough due to upper respiratory infections, patients with central cough suppressant such as codeine and

dextromethorphan are noted to have limited efficacy for symptomatic relief. And these are not recommended. They get a negative recommendation from this panel. And in a subset of this group, cough due to upper respiratory infection due to the common cold, again, they do not get a positive recommendation, and the specifically state that over-the-counter combination medications with the exception of the older antihistamine, decongestants are not recommended until randomized controlled trials prove that they are effective cough suppressants.

The ACCP guidelines had three principle studies which were used to give their recommendations for dextromethorphan. The first one done in 1996 was a single-dose, placebo-controlled, double-blind randomized control trial of 451 patients with cough due to upper respiratory infections. The study was done at a pharmaceutical research center and completed over three cold seasons. They measured cough counts. And they did notice a decrease with dextromethorphan compared to placebo of 19 to 36 percent depending on the year. But the only statistically difference was at certain time points along the dosing interval, not for the entire treatment period.

The second study was done in 2000. It was only 43 patients. It was a single-dose, double-blind study,

stratified, randomized and parallel group evaluation of dextromethorphan and placebo for cough associated with an upper respiratory infection. They measured the cough sound pressure, the frequency, and the subjective severity score. Both the dextromethorphan and the placebo had decreases in all these areas but the differences between the two groups was not statistically significant.

The third was a meta-analysis conducted in 2001 with pooled data comparing dextromethorphan with placebo in six studies, total of 710 patients. It was a randomized, double-blind, placebo-controlled, single dose study in adults with upper respiratory infection. All the studies were sponsored by a pharmaceutical company. And the dextromethorphan demonstrated statistically significant difference for the total number of cough bouts, for the efforts, and for the latency, an average of 12 to 17 percent difference. But the individual studies were not powered to show statistically significant differences.

Additionally, there was a Cochrane Review. There was one that was included in the initial ACCP guidelines. But they updated it in 2009 and I went through that. In the Cochrane Review they found 25 trials on medications with acute cough in children and in adults in ambulatory settings, a total of almost 3500 participants, almost 3,000

adults. But the dextromethorphan was only included in three of these trials. And it was the three that I've already discussed.

The conclusion from the Cochrane Review was that there is no good evidence for or against the effectiveness of over-the-counter medications in acute cough. And that many of the studies were of low quality. They were very different from each other. And it made the evaluation of overall efficacy quite difficult.

So in conclusion, cough is a common symptom for which patients seek treatment. The studies using dextromethorphan as treatment for cough do show a modest effect. And the options for over-the-counter therapy are very limited. Practically speaking, dextromethorphan is the only available systemically active, over-the-counter cough medicine.

DR. KRAMER: Thank you, Dr. Bonson. If you could stay up there. And we have questions.

Dr. Cooper.

DR. COOPER: My question is for Dr. Bonson.

DR. BONSON: Yes, sir.

DR. COOPER. In your presentation, I'm trying to get a handle on sort of the issues related to abuse potential. And you presented from human studies

information about both the dissociative effects and the unpleasant effects that were seen. In your review of the case reports that you presented, did you see -- did you find any evidence of what's driving the abuse? Is there a targeted response that these cases were trying to achieve relative to the four plateaux that you described in your presentation?

DR. BONSON: I want to emphasize I did not review case reports about people using dextromethorphan for abuse purposes. There are a myriad out there in the medical literature. So I just reported on a review that described those four plateaux, okay. But my understanding is that the kind of individual who would be likely to abuse dextromethorphan is a person who is interested in hallucinogenic-like drugs. So it has effects that are similar to, but not identical to, 5-HT2 agonists like drugs. So if somebody is interested, for instance, in LSD or psilocybin, which is a 5-HT2 agonist, they may also be interested in experiencing an NMDA antagonist such as dextromethorphan.

Does that answer your question?

DR. COOPER: Yes.

DR. KRAMER: If I could just clarify before you go away, so by what you just said, what some people would

call unpleasant effects because they don't like feeling dissociated from reality, other -- some of these teenagers may be seeking; is that fair to say? Because I think that when you look at a scientific study and they say, well, people wouldn't abuse it because it's unpleasant, you have to decide who is seeking to use it for what.

DR. BONSON: I think you're raising an excellent point that goes back to those experimental studies that were conducted with dextromethorphan. And so in three of the five studies where you had the experimental population being opioid abusers, the people who prefer opioid drugs. And then you give them a drug that is not an opioid, they were, you know, trying to understand the pharmacology of it. Was it like an opioid? The answer was no. But in this population of people who may not have liked hallucinogenic -- if we can, you know, use that term -- like effects, maybe it's not surprising that, you're right, they experience that as dysphoric.

But we don't know that. Those questions were not asked directly. And they didn't have the background experience for that.

DR. KRAMER: Richard Honsinger.

DR. HONSINGER: I use a lot of dextromethorphan in my patients. And often I think my response is placebo.

But sometimes placebo works. On slide -- I'd like to ask Dr. Bonson, on slides 35 and 36, were any of those studies placebo-controlled? And would you give us the results of those studies?

DR. BONSON: Let's see, 35, bear with me. 35, these were placebo-controlled, yes. Yes, I believe they were. I can certainly look up for anybody who has a question about the details and the methodology on any of these studies, I obviously couldn't hold 40 different methodologies in my head, but we can certainly look that up to make sure. But I'm sure that they did, yes.

And what was your question about that, sir?

DR. HONSINGER: Yes, and what were the results of these studies, both 35 and 36?

DR. BONSON: 35 and 36, I think that since I'm speaking off-the-cuff, I'll look them up and tell you after the break.

DR. KRAMER: Okay. The next person is Leslie Walker.

DR. WALKER: I had a question about the pharmacokinetics. From what I can tell, most of these studies are in adults and we know that children and adolescents pharmacokinetics can be different, is there any evidence at all that there -- is there any study at all

that looks at the adolescent pharmacokinetics in any study that shows that this is efficacious in any way?

DR. BONSON: My presentation, as you know, was on the abuse-related pharmacology and pharmacokinetics. So I'm sorry, I don't actually have a full pharmacokinetic repertoire to draw from

DR. WALKER: Even for abuse, what has been looked at with adolescents in the pharmacokinetics?

DR. BONSON: Again, I'm sorry, I was just giving any overview of the pharmacokinetics. And I don't know the differences in different populations based on age.

DR. KRAMER: Okay. Dr. Nelson.

DR. LEWIS NELSON: The description of the patients who died and their post-mortems were described as heavy, wet lungsy, you kind of highlighted that which is kind of a classic description of opioid fatality. Yet, I don't see in detail here whether or not opioids were part of the mix of drugs that these kids had taken. And if there's any explanation as to why dextromethorphan, which isn't an opioid and should not produce an opioid-like death, if you want to relate it to the PCP-ketamine group, would produce a sort of autopsy finding that would be very typical of an opioid.

DR. BONSON: I don't know that they did an

analysis of this Chemical API-sourced illicit dextromethorphan. So they're saying that it was a dextromethorphan toxicity because dextromethorphan was found in their system. They did not report, at least, that there were any opioids on board and that, you know, some of them had cannabinoids, some of them had diphenhydramine. I don't know how to explain this, it's very difficult to know what's happening with an illicit-source drug.

DR. LEWIS NELSON: Yeah, I mean, that's always one of the problems with these forensic reports. In the previous speaker, somebody said that there were reports of people taking 100-fold overdoses and having no problems. But you always have to take those reports with a grain of salt also.

DR. BONSON: Well, yeah, I think that that's what's interesting about that. Because in my response-lie that I gave before I started explaining the human data, we see that the therapeutic dose, 10 to 30 milligrams several times a day is many, many-fold lower than the very high end, up to 2,000 milligrams, that people take for abuse purposes. And they're very few deaths that are reported, right. So I think that that's the interesting distinction is that these five deaths were all associated with an illicit form of dextromethorphan.

DR. LEWIS NELSON: Right. And the people that wrote report are forensic toxicologists --

DR. BONSON: Correct.

DR. LEWIS NELSON: -- who are very well respected, so I assume they would have probably checked for these other relatively commonly available agents. I don't know if that was included in the report. But it just kind of seems like a funny combination of, you know, post-mortem findings with the drugs they suggested they found.

DR. BONSON: Correct.

DR. KRAMER: Could you clarify, Dr. Bonson, whether in those cases, whether the levels of dextromethorphan that were found in the people that died were very high?

DR. BONSON: Again, I'd be happy to look that up if -- I have all the papers with me.

DR. KRAMER: Because that would get to Lewis's question if it was just that it was present, that's one thing. But if they reported very high levels, that would -- that would be other information that we'd like to know.

DR. BONSON: I agree. I'm happy to look that up at the break.

DR. KRAMER: And I have -- I have two questions.

I just want to clarify with Dr. Callahan, based on what you said, I want to make sure that my interpretation is correct, it appears to me that the ACCP guidelines are in direct conflict with the monograph that's approved for OTC labeling because all -- and it's a 125 products on the market and most of them are clearly stating that this should be used for the common cold.

DR. CALLAHAN: It would appear that way.

DR. KRAMER: And the next thing I think would be very important for the committee to understand, and I'm not sure which of the people from FDA would be best suited to answer this, perhaps Ms. Mehler, perhaps Dr. Bonson, it's the issue that someone started to -- someone already raised, the distinction between prescription drugs and scheduled drugs. And in particular, I think it's important for us to understand historically what happened with Robitussin, with codeine cough syrup. I go so far back that I started working in a drug store when I used to have people sign the register for Robitussin with codeine and it was easily accessible behind the counter.

And I understand that there's a very complex series of things that have happened since that product -- first, I'd like you to explain, am I correct that that product is a Schedule V, Robitussin with codeine? And if

so, what the distinction is between federal laws about how that is sold and subsequent decisions by states that are sometimes more restrictive. Because I think there's common misunderstanding that Robitussin with codeine is a prescription drug, period, which I don't think is true. I understand that 18 states have more restrictive requirements than the federal law. And I just think that the committee needs to understand that comparison to make sure that we understand any similarities or differences that might occur if we recommended scheduling for dextromethorphan.

DR. BONSON: I'm going to defer to my legal colleague.

MS. MEHLER: I'm assuming, and Dr. Klein, jump in if I'm wrong or Dr. Ganley, the product you're talking about, the Robitussin with codeine or something with codeine, is a OTC product under the Food Drug and Cosmetic Act; is that correct? So there is a big-old distinction in the Federal Food, Drug, Cosmetic Act between prescription products and over-the-counter products. And it has to do with whether or not the drug can -- whether a patient can self-diagnose and whether or not the drug, and I don't have the statute in front of me so I'm not going to get it exactly right, but whether it's, basically, appropriate to

be available OTC, self-selection, treatment, can you understand the directions.

That determination is completely separate from whether or not a drug meets any of the findings under the Controlled Substances Act for scheduling. All right. So those are two separate federal distinctions, scheduling under the Controlled Substances Act, prescription OTC under the Food, Drug, Cosmetic Act, that is why we see over-the-counter schedule products. And generally, I think we see them all in Schedule V.

And DEA has regulations about how an over-the-counter controlled substance can be sold. And I believe there's another level of requirements about how one gains access to them and the record-keeping required and where, you know, sort of how you get that. Now that's -- then on -- from the federal system we also have all the systems of the states. And they all have their own requirements about how drugs are provided, you know, because they license pharmacists and they license doctors. And they have a whole set of rules. They also schedule substances.

So I think in a given state you can see that despite something being over-the-counter -- allowed to be sold over-the-counter by FDA, a state may have a set of regulations about how that's provided. So that is why I

think you're going to see in different states a different, sort of, scheme as to how you gain access to a product.

DR. KRAMER: But that would indicate that a state could not make a product a prescription product, that could just regulate the sale? The 18 states that regulate Robitussin with codeine more strictly don't do it by making it prescription only; is that correct?

Yes.

DR. HENDELES: In the state of Florida a codeine-containing cough syrup requires a prescription only. But yet, in some states -- I think it's a Schedule V and would be available over-the-counter in some other states.

DR. KRAMER: So therein lies the confusion where the FDA says we make a distinction what's prescription and what's OTC by whether someone can self-diagnose, but it's clear that states can have a more restrictive law as in Florida; is that correct?

DR. HENDELES: Correct. But it can't be less restrictive than the federal law.

DR. KRAMER: Okay. I just want to clarify, the reason I'm pressing this for us to understand is obviously we're talking about options for people who self-medicate to treat cough and it's not a question whether Robitussin with codeine helps cough, it's a matter of abuse potential,

accessibility. And I think, therefore, understanding those two products was important for us. Thank you for --

Other questions?

Yes, Dr. Hernandez.

DR. HERNANDEZ-DIAZ: Yes, I have a question about the potential interaction with diphenhydramine both from a pharmacological point of view, is there any reason to believe that the combination product would have more adverse effects and fatality? And also from a behavioral point of view four of the cases or three of the cases were using diphenhydramine at the same time; is it because it produces more hallucinogenic effects or --

DR. BONSON: To my knowledge --

DR. HERNANDEZ-DIAZ: -- why were they taking these kids diphenhydramine at the same time?

DR. BONSON: People take an amazing amount of things together to see what happens. There are no controlled studies to my knowledge that have investigated whether diphenhydramine potentiates the effects of dextromethorphan. And we're here today to discuss dextromethorphan as a single entity by itself because that's the way the Controlled Substances Act asks us to evaluate a drug. We can't evaluate it as it to other drugs.

DR. KRAMER: Dr. Bonson, could another answer to that question be that these products occur together in many of the over-the-counter products people abuse, there are combinations of cough and cold preparations that contain -- in fact, ACCP says you should use a first-generation antihistamine for cough. So there are combinations with diphenhydramine and dextromethorphan, correct?

DR. BONSON: That is actually very true. And there are many other drugs that are formulated with dextromethorphan. And we know about some of the adverse events that occur from that. But I didn't want to discuss those today because of the reason I just laid out.

DR. KRAMER: Right.

DR. BONSON: But I do want to emphasize that dextromethorphan deaths, where there was diphenhydramine in addition, that was not a legitimate combination over-the-counter product.

DR. KRAMER: Okay. We have two more questions we're going to take and then take a break.

Richard Honsinger.

DR. HONSINGER: Am I right in your analysis that there have been -- there were five deaths and four fatal cases, but all nine of these cases were related to a drug that came from India sold in the bulk and there have been

no cases since that time of 2005 in the last five years?

DR. BONSON: To my knowledge, those five deaths and four overdoses were associated with that illicit form of dextromethorphan and that there are no deaths associated with dextromethorphan that I've seen reports of. Perhaps others know of some?

DR. KRAMER: Excuse me, we were sent a list of deaths for every year. They weren't all single-agent dextromethorphan, but clearly there have been dextromethorphan-associated deaths that the committee was sent in advance.

DR. KLEIN: Yes, the Poison Control Center fatalities are listed in the background packages.

DR. BONSON: Would you like to elaborate on that, Dr. Klein?

DR. KLEIN: Yeah, there have been a number of Poison Control Center incidents which were actually in the original DEA submission to the secretary. And in addition, we have deaths, many of them where dextromethorphan is present in the fatality, not necessarily causative. There have been other issues involving attempted suicides where dextromethorphan was present.

DR. BONSON: Yeah, but I that the emphasis is that single-entity, Dr. Klein, not --

DR. KLEIN: No, those are just the cases that perhaps we'll see they're presenting next, we'll be able to elaborate more on those events.

DR. KRAMER: The committee members received in their packets, dated August 30, an addendum to the background that lists the death by year. And I'd be glad to show it to you.

Okay. We have one more question from Edward Krenzelok.

DR. KRENZELOK: Thank you. I wonder if maybe Ms. Mehler can help us answer this question. I was wondering about scheduling or prescription status of dextromethorphan internationally. I looked about it before the meeting and couldn't find any countries where it was a prescription drug and I just wonder if it is a prescription drug or in some way controlled internationally?

MS. MEHLER: I'm not aware that's it's controlled internationally. I don't know its prescription status internationally, which, again, for us is two separate things. But not necessarily elsewhere so I'm not aware of that.

DR. KRAMER: Did the studies of abuse that were reviewed by FDA that were public reveal an international reports?

MR. MULLINS: It has been banned in a couple of countries, it has.

DR. KLEIN: The World Health Organization will be looking into dextromethorphan abuse. They are planning a future meeting by its expert committee.

DR. KRAMER: Thank you.

Okay. I think we need to go to the break. If you do have additional questions, Dr. Winterstein is on here --

DR. WINTERSTEIN: It was just a response to the international question.

DR. KRAMER: Go ahead.

DR. WINTERSTEIN: It received status in many international countries doesn't mean that one can retrieve something from a shelf. But it simply means that it doesn't require a prescription but it's still handed out by a pharmacist or by pharmacy staff.

DR. KRAMER: As opposed to a grocery store.

DR. WINTERSTEIN: Right.

DR. KRAMER: Before we take our break I need to read you a statement. It's going to be a short break. We have to start again at 10:00. So the committee members are reminded that there should be no discussion of the meeting topic during the break amongst yourselves or with any

member of the audience. And we'll start again at 10:00.

(Recess)

DR. KRAMER: I think we're continuing on with the Office of Surveillance and Epidemiology. If they're here? Tracy Pham?

DR. PHAM: Good morning. My name is Tracy Pham. Today I will provide the analysis for the utilization trends of over-the-counter and prescription dextromethorphan products. The outline of my presentation is as followed. I will describe the national sales data of over-the-counter dextromethorphan products and the out-patient prescription data for dextromethorphan products and cough and cold products.

I will also describe the databases used to obtain the findings for over-the-counter sales data and out-patient prescription data. Finally, I will discuss the limitations of the databases and summarize the presentation.

We begin with the National Over-the-counter sales data. IMS Health, IMS National Sales Perspective database which used to obtain the total sales of the over-the-counter and prescription dextromethorphan products from year 2005 to year 2009. The IMS Health, IMS National Sales perspective measures the volume of prescription and over-

the-counter drug products sold in eaches from manufacturers to retail and non-retail channels of distribution. Throughout the whole presentation eaches are the number of packets, bottles, and vials of a product shipped in a unit.

This figure illustrated the total sales and market-share percentage of over-the-counter and prescription dextromethorphan products from year 2005 to y year 2009. The x-axis shows the years. The y-axis shows the number of bottles sold in eaches in millions. The column breakdowns in each year showed the market-share percentage of over-the-counter and prescription dextromethorphan products. From year 2005 to year 2009, the sales of over-the-counter and prescription dextromethorphan products increased by 19 percent. Approximately 173 million bottles of the whole market were sold in year 2009.

Of these, over-the-counter dextromethorphan products accounted for 96.5 percent of the total market sales with 167 million bottles sold. This amount breaks down to 90 percent of the sales over-the-counter combination dextromethorphan products. 6.5 percent of the sales of over-the-counter single-ingredient dextromethorphan products, prescription combination dextromethorphan products accounted for the remaining 3.5

percent of sales. Prescription single-ingredient dextromethorphan products had no reported sales in year 2009.

We also analyzed the total dollar amount of over-the-counter and prescription dextromethorphan products for year 2009. Approximately 810 million dollars of the whole market were spent on dextromethorphan products in year 2009. Of this amount, 78 percent of the total dollar amount were over-the-counter combination dextromethorphan products, eight percent of the total dollar amount were over-the-counter single ingredient dextromethorphan products. And the remaining 14 percent of the total dollar amount were prescription combination dextromethorphan products.

You just heard the overall sales and dollar amounts of dextromethorphan products. I will now describe the sales of over-the-counter single ingredient dextromethorphan products broken down by dosage form from year 2005 to year 2009. Of the total sales of over-the-counter, single-ingredient dextromethorphan products oral liquid formulations accounted for the majority of sales followed by regular oral-solid formulations and mouth-throat topical formulations which include lozenges or sprays.

In year 2009 86 percent of the total sales of over-the-counter, single-ingredient dextromethorphan products were oral-liquid formulations. 13 percent of the total sales were regular oral-solid formulations. And two percent of the total sales were mouth-oral topical formulations.

In an effort to look at the pediatric use of over-the-counter, single-ingredient dextromethorphan products, we analyzed the sales trends of concentrated oral drops, formulations under oral-liquid formulations. And in year 2009, no sales of concentrated oral-drop formulations were reported.

I will now describe the sales of over-the-counter combination dextromethorphan products broken down by dosage form from year 2005 to year 2009. Of the total sales of over-the-counter combination dextromethorphan products oral-liquid formulation again accounted for the majority of sales followed by regular oral-solid formulations; long-acting, oral-solid formulations; and mouth oral topical formulations. In year 2009 60 percent of the total sales of over-the-counter combination dextromethorphan products were oral-liquid formulations. 32 percent of the total sales were regular, oral-solid formulations. Six percent of the total sales were long-acting, oral-solid

formulations. And .4 percent of the total sales were mouth, oral-topical formulations. In year 2009 concentrated oral drops formulations accounted for .5 percent of oral-liquid formulation market sales.

We also analyzed the sales of over-the-counter combination dextromethorphan products by the top five co-active ingredients from year 2005 to year 2009. In year 2005 pseudoephedrine, as shown by the brown line, was the number one co-active ingredient found in dextromethorphan products followed by acetaminophen, chlorpheniramine, and phenylephrine. Over the years, the sales of dextromethorphan products containing pseudoephedrine decreased while the sales of dextromethorphan products containing other active ingredients all increased.

In year 2009, the number one co-active ingredient found in over-the-counter combination dextromethorphan products was acetaminophen followed by phenylephrine, guaifenesin, chlorpheniramine, and pseudoephedrine.

I will now move on to describe the prescription data for dextromethorphan products. SDI, Vector One: National database was used to obtain estimates of the number of out-patient prescriptions dispensed for dextromethorphan products from year 2000 to year 2009. As shown on the previous slides, the vast majority of

dextromethorphan products were sold as over-the-counter.

From here on, I will discuss out-patient use of dextromethorphan products captured from prescription claims only, which represent a small portion of the overall use of dextromethorphan products. SDI, Vector One: National is a national level projected prescription and patient-centric tracking service which receives over two billion prescription claims per year representing over 160 million unique patients from a sample of approximately 59,000 retail pharmacies in the U.S.

From year 2000 to year 2009, the overall number of dispensed prescriptions for dextromethorphan products decreased by 14 percent. Approximately 7.9 million prescriptions were dispensed for dextromethorphan products in year 2009. Combination dextromethorphan products accounted for 99.9 percent of the total prescription market share. And single-ingredient dextromethorphan products accounted for less than one percent of the total prescription market share.

We also analyzed the prescription market share of combination dextromethorphan products by co-active ingredients from year 2000 to year 2009. During the study period the number of dispensed prescriptions for dextromethorphan products containing phenylephrine and

chlorpheniramine increased while the number of dispensed prescriptions for dextromethorphan products containing other active ingredients all decreased. In year 2009 phenylephrine and chlorpheniramine were the most common ingredients found in prescription dextromethorphan products followed by co-active ingredients pseudoephedrine and carbinoxamine and co-active ingredients pseudoephedrine and brompheniramine.

You just heard the results for prescription dextromethorphan products. I will now describe the prescription data results for dextromethorphan products and their comparators under cough and cold products for year 2000 to year 2009. Comparators include benzonatate, non-analgesic codeine products and non-analgesic hydrocodone products.

From year 2000 to year 2009 the overall prescription market for cough and cold products decreased by 34 percent. The prescription market for codeine-containing products and benzonatate increased by approximately 39 percent and 40 percent respectively while the prescription market for hydrocodone and dextromethorphan-containing products decreased by approximately 24.5 percent and 76 percent respectively.

This graph illustrated the prescription market

share of cough and cold products in year 2009. Approximately 44 percent of prescription share were dispensed for non-analgesic codeine-containing products in year 2009 followed by benzonatate with 31 percent of prescription share, non-analgesic hydrocodone products with 19 percent of prescription share and dextromethorphan products with six percent of prescription share.

We analyzed the prescription market of cough and cold products by the top ten prescribing specialties for year 2009. General practice, family medicine, and osteopathic specialists prescribed the highest proportion of dispensed prescriptions for cough and cold products with 40 percent of dispensed prescription market for cough and cold products in year 2009. Internal medicine specialists follow with 22 percent of dispensed prescriptions market.

We also analyzed the prescription market of cough and cold product by patient age in increment of 10 years for year 2009. The majority of dispensed prescriptions for benzonatate, non-analgesic codeine, and hydrocodone-containing products were dispensed to patient population age 51 to 60 years old. Meanwhile, the majority of dispensed prescriptions for dextromethorphan products were dispensed to patient population age zero to 10 years.

In an effort to look at the use of

dextromethorphan products in the pediatric population age 17 years and younger, we analyze the prescription market for dextromethorphan products for ages zero to 10 years, 11 to 17 years, and 18 years and older for year 2002 to year 2009. Over the years the number of dispensed prescriptions decreased for the older population while it remained relatively steady for the pediatric populations from year 2004 and forward.

You heard the results for dextromethorphan products. I will now discuss the limitations of the databases used to obtain these results. IMS Health, IMS National Sales Perspective only captures approximately 50 percent of all over-the-counter sales. These data do not provide a direct estimate of use, but do provide a national estimate of units sold from the manufacturer to various channels of distribution.

The amount of products purchased by these retail and non-retail channels of distribution may be a possible surrogate for use. If we assume that facility-purchased drugs in quantity reflective of actual patient use. We are unable to determine user demographics, frequency, or amount of over-the-counter products used at the consumer level and concurrent product use.

Internet sales data were not captured. SDI,

Vector One: National only describes out-patient prescription use and captures products only at prescription claims which represent a small portion of the overall use of prescription products. Over-the-counter products sales were not captured.

To summarize, sales of over-the-counter and prescription dextromethorphan increased during the study period. Over-the-counter single-ingredient and combination dextromethorphan products accounted for 6.5 percent and 90 percent of the overall sales respectively. Prescription dextromethorphan products accounted for 3.5 percent of the overall sales. Prescription dextromethorphan products were dispensed less than benzonatate, non-analgesic codeine and hydrocodone-containing products.

Family medicine, general practice, family medicine, and osteopathic specialists were the top prescribers. Patient population aged zero to 10 years old received the majority of dispensed prescriptions for dextromethorphan products. Thank you.

DR. KRAMER: Before we go on to the next speaker, could somebody from the FDA, having heard this kind of presentation, it may be confusing to some of the panel members as to what would require a dextromethorphan product to be required to be prescription as opposed to over-the-

counter. Could somebody clarify that question? My understanding from this presentation is there are some single-agent dextromethorphan prescription products, at least they were described in the presentation we just heard that some of those were single-agent prescription. And so, I think some of us are confused about this. I'll speak for myself.

DR. GOVERNALE: Laura Governale, OSE. Occasionally a prescriber may elect to write a prescription for an over-the-counter product and the parent would take that prescription to the pharmacy and it would be processed as a prescription and captured as a prescription even though the pharmacist would just walk directly to the over-the-counter aisle, pick up that prescription -- pick up that drug product and then just bill it as a prescription. So that's why we would sometimes see -- an over-the-counter product being dispensed as a prescription.

DR. KRAMER: That's helpful to interpret the presentation we heard. It's quantitating the number of prescription products. But it could be just the chance of someone deciding to write it on a prescription pad.

DR. GANLEY: Yeah, this is Charlie Ganley. In the background book there's a page and unfortunately it's not sequentially numbered. It's the orange book. And for

all the approved dextromethorphan prescription products they contain promethazine which is not an OTC product. So if you combine it with a non-OTC ingredient it has to be a prescription.

DR. KRAMER: Thank you. I just got confused when I saw these descriptions of prescriptions for dextromethorphan only. But Dr. Governale's answer clarifies that. Thank you.

Any other questions from the committee about that?

Yes, Janet.

DR. ENGLE: I had a question about slide number five that talks about the total sales and market share for over-the-counter and prescription dextromethorphan products. You indicate that there's been a 19 percent growth. What I'm curious about is what has the whole category done? Because if the entire cold-and-cough category has grown 19 percent, 20 percent, whatever, I mean, that would mean something different to me than if just dextromethorphan grew. So do you know that data?

DR. CALLAHAN-LYON: We didn't look at the data for the whole cough-and-cold market. We only looked at the dextromethorphan products.

DR. KRAMER: Let me just underline that, that's a

very important question given that, for those of us that have looked in the drugstore shelves recently, it's hard to find a cough-and-cold product that doesn't have it in it. So we have in order -- do you have the order? You all put your hands up at the same time. So let's start with Dr. Woody.

DR. WOODY: What's the population growth during that period of time? In other words, what's the -- how does that relate to the growth of the population?

DR. KRAMER: The question is what is the population growth during the time that the use increased by 19 percent.

DR. CALLAHAN-LYON: I'm sorry, I don't have that data available.

DR. KRAMER: Good question.

Next question, Dr. Krenzelok.

DR. KRENZELOK: Was there any correlation with the prevalence of influenza and H1N1 that would account for increased sales during this period of time.

DR. KRAMER: Did you all look at concurrent correlation with H1N1 epidemic?

DR. CALLAHAN-LYON: I'm sorry, we didn't look at the concurrence. But that could be a possible answer for as to why there is an increase in use of cough, I mean,

dextromethorphan products.

DR. KRAMER: Lewis Nelson.

DR. LEWIS NELSON: I just want some clarification too just so I understand, I mean, almost everything we talk about here is single product. But they didn't make up the tiniest fraction of all the dextromethorphan use. So, I guess, just so I understand what the implication is of the decisions we make today, it effects all of the products, I assume. And why are we only talking about single product. I don't know who that's directed at, perhaps Dr. Klein.

DR. KLEIN: Well, any scheduling recommendation would apply to all products, all preparations, all combinations and mixtures of products that contain any quantity of dextromethorphan.

DR. LEWIS NELSON: Right. I guess my question though would be from a practical perspective, maybe, you know, there's different qualities of these single product than there is from the overall group. You know, certainly abuse potential may be adverse effects, you know, effects in overdose, things like that. So I don't know, maybe there's a good reason and that's it. It seems like we should be seeing data about the whole, you know, the 93 percent or 90 percent of the products, not the three percent.

DR. KRAMER: Lewis, my understanding is that we're being asked because DEA asked FDA to do this to make a scientific judgment about the abuse potential of the specific ingredient dextromethorphan. And as Dr. Klein explained, that our decision or recommendation would effect anything that contained it. I didn't interpret everything we received as only describing single-product dextromethorphan. The packet is filled with combinations and the Poison Control reports are combination products as well. Maybe I'm missing something.

DR. LEWIS NELSON: Except, you know, for example on the last speaker, the overdose data and the death data was really focused on, you know, trying to find single-entity dextromethorphan, not the combination products. Because, you know, when you look at the Poison Center data, it's certainly the majority. I'm not saying there's anything wrong with it, I'm just wondering, as each speaker speaks about it they very clearly distinguish the single product from the overall product. And I just wanted to see what the implications of all that were.

DR. KLEIN: Well, again, any scheduling recommendation would effect all of the products.

DR. KRAMER: Lewis, I'm understanding now, you're really saying the way the FDA has chosen to present the

data to us suggest they're trying to tease out the individual. And yet, it has the implication -- there may be other implications with combinations? Okay.

We have a lot of people raise their hands. And how are we doing? Do we have time for this? Let's see, let's just go through.

Warren Bickel.

DR. BICKEL: Hi, given that we know that abuse of drugs seems to be at a higher prevalence among adolescents and young adults, I was wondering if you have information about the age categories of individuals who purchase these products?

DR. CALLAHAN-LYON: I'm sorry, we don't have that information available.

DR. KRAMER: Since they can just take it, nobody knows.

Sharon Stancliff.

DR. STANCLIFF: I'm wondering if the single-product dextromethorphan is found on the same shelf as the combination products or if it's housed differently because it's such a small portion of the market.

DR. KRAMER: Yes, Dr. Hendeles.

DR. HENDELES: It's on the same shelves.

DR. KRAMER: Leslie Walker.

DR. WALKER: Yeah, I had a question, again, thinking about the abuse potential, compared to how much over-the-counter sales there are, how much is actually available on the market and has that changed in the last 10 years? How much is industry-produced and how much are on the shelves? I don't know if anybody has that information.

DR. KRAMER: I'm not sure -- could you clarify what you're asking when you say how much is industry produced --

DR. WALKER: How much are we producing and how much is actually available compared to how much is sold? Because, you know, kids don't tend to buy it, they take it. So I'm curious, are we actually making the right amount for the amount that's sold or is there much more available on the market than actually is sold? Does anybody -- you know, I thought I saw something in the background that talked about how much is actually produced in this country.

DR. KRAMER: How much is -- the presentations that are traditionally presented by the epidemiologists are number of packages actually sold that are leaving points of sale. And you're asking for the total number of packages that are manufactured?

DR. WALKER: Yes, to compare.

DR. KRAMER: That may be a question for later

when we've got the manufacturer presenting.

DR. KLEIN: I don't believe we have a handle on that, but a good amount of the bulk dextromethorphan is important.

DR. KRAMER: I think there's an underlying impression that we got from reading the background packet and seeing some of the websites and testimonials that there's a fair amount of this product that is put into the pockets of teenagers that aren't purchased. So there's a concern there, I think, that you implied, you know, that shoplifting is never going to be captured in these sorts of sales.

All right. Moving on.

DR. CAMILLI: All right. Good morning. My name is Sara Camilli. And I'm a Safety Evaluator in FDA's Office of Surveillance and Epidemiology, Division of Pharmacovigilance II.

In the next 10 minutes I will discuss cases of dextromethorphan abuse in FDA's adverse event reporting system, also known as AERS. First, I will give a brief background on AERS. Second, I will highlight cases of abuse reported for dextromethorphan as an active ingredient. This analysis is included in your background document. Third, I will provide information on additional

abuse cases reported under two brand names Coricidin and Delsym. For over-the-counter products consumers often submit reports under the brand name rather than the active ingredient. Thus, we included this additional analysis for this meeting.

Our first topic, AERS. AERS is an FDA database that captures adverse event report that are submitted voluntarily by healthcare professionals and consumers. AERS includes both U.S. and foreign reports allowing us to perform large-scale safety surveillance. However, there are several limitations. First, less than 10 percent of adverse events are reported to AERS. Second, data cannot be used to determine the incidence of an adverse event. Third, report quality is variable and many lack key information.

Now while I move on to the second topic, the dextromethorphan active ingredient search. These are the cases in your briefing document. We searched AERS for cases received between 2004 and 2008 reporting dextromethorphan as an active ingredient and specific event terms associated with abuse. Among them including abuse, misuse, dependence, and overdose.

This search included both U.S. and foreign reports. We identified 177 cases including 33 that

reported as single-ingredient dextromethorphan product and 17 that reported a combination product of dextromethorphan plus guaifenesin. We initially focused on a subgroup of cases, dextromethorphan only or dextromethorphan plus guaifenesin to minimize the potentially-contributing effects of other active ingredients. Thus, we excluded the remaining 127 cases because the product contained multiple ingredients or the product contained insufficient information to make a case assessment.

This chart shows select characteristics of the AERS cases. The majority of cases reported single ingredient dextromethorphan as opposed to dextromethorphan plus guaifenesin. Median ages were similar for the two products. A slight majority of the patients were male, a similar finding for both product groups. In total, eight deaths were reported. We'll discuss these now.

The deaths included three overdoses and five suicides. The overdose cases were associated with dextromethorphan single-ingredient products. One reported use of multiple drugs and another tested positive for illicit drugs. Five individuals committed suicide, all with dextromethorphan plus guaifenesin; four used multiple drugs; and one died due to a gunshot wound. Overall, a causal drug-event relationship was difficult to establish.

Now I will move on to the last topic, AERS abuse cases reported under the brand names Coricidin and Delsym. As background, there are five Coricidin products that contain dextromethorphan all of which are Coricidin HBP products. They contain varying amounts of dextromethorphan per tablet, 10, 15, or 30 milligrams. Only one of the products, Coricidin HBP Cold and Cough, contains 30 milligrams dextromethorphan per tablet, the highest amount.

Coricidin HBP products contain co-active ingredients which vary and may include an analgesic, antihistamine, expectorant, or combination thereof. Not all Coricidin products contain dextromethorphan.

Delsym contains a single active ingredient dextromethorphan polistirex. Different than other formulations which contain dextromethorphan hydrobromide. Delsym is available as an extended-release suspension and contains the equivalent of 30 milliliters dextromethorphan hydrobromide per five mls suspension.

We searched AERS for U.S. cases received from initial marketing through the end of 2009 that reported the brand names Coricidin or Delsym and abuse event terms, again including abuse, misuse, dependence, or overdose. We excluded accidental pediatric exposures and reports naming Coricidin products that do not contain dextromethorphan.

While we did not search AERS for all brand name products containing dextromethorphan, these results are likely representative of cases involving other dextromethorphan products. We identified 246 Coricidin and 34 Delsym cases of abuse.

Here's a chart containing select characteristics of the Coricidin and Delsym abuse cases. The median age was 16 for the Coricidin group and 30 for the Delsym group. Gender distribution was similar. A greater majority of the Coricidin cases reported abuse as the reason for use. Looking at Delsym, cough was the second most frequent reason for use. Some reports describe individuals drinking Delsym for cough who liked the buzz so they consumed more than initially intended.

Quantity consumed was reported in a limited number of cases and amount varied among the two groups. The meeting quantity of Coricidin consumed was 16 tablets. Equivalent to 480 milligrams dextromethorphan if Coricidin HBP Cold and Cough was consumed. Looking at Delsym, the median quantity of dextromethorphan consumed was nearly four times higher. 300 milliliters is equivalent to 1800 milligrams dextromethorphan hydrobromide.

As there are five different Coricidin HBP products available, we looked at which Coricidin HBP

product was reported most frequently. Coricidin HBP Cold and Cough, the only product with 30 milligrams dextromethorphan per table was associated with 97 percent of the cases that reported a specific Coricidin HBP product. Hospitalization or emergency room visits were reported in 129 of the Coricidin and 16 of the Delsym cases. And together 12 individuals died.

We'll look at the deaths in greater detail now. Deaths were reported in eight Coricidin and four Delsym cases. Individuals in six of the eight Coricidin cases died from other causes than dextromethorphan. The remaining two individuals, a 20-year-old male and a 15-year-old female, died after taking Coricidin with multiple other drugs. The Delsym cases included one case of a 42-year-old male who took Delsym at the recommended dose in combination with thioridazine. Two cases described death after taking higher than labeled amounts of Delsym with other drugs. The final individual committed suicide four days after abusing Delsym.

In conclusion, our review suggests that the use of dextromethorphan has been associated with intentional misuse of products for abuse purposes.

DR. KRAMER: Yes, Dr. Winterstein.

DR. WINTERSTEIN: I understand that these kind of

searches are very difficult to conduct, but I'm curious. What's the market share of Coricidin and Delsym relative to all dextromethorphan products and combination products since you made the statements generalizable. So this issue of generalizability might relate to the distribution of the demographics you showed us. But, of course, for us it's interesting to see what's the overall number of case reports that you're receiving.

DR. CAMILLI: So you're asking about the market share of Coricidin or the overall number of cases that we --

DR. WINTERSTEIN: In your statement about generalizability.

DR. CAMILLI: Well, as you can see we found 246 cases of Coricidin abuse. And that is a large amount compared to all of the cases of dextromethorphan abuse that we found in the AERS system. So it was a large amount. For market share I would have to refer to my FDA colleagues who know a little bit more about the actual use of the products.

DR. KRAMER: Dr. Winterstein, could you clarify whether you were asking about market share for legitimate uses? I mean, are you just saying what percent of the market of cough and cold is this product? Is that what

you're asking?

DR. WINTERSTEIN: Yeah. I'm just trying to get a handle on what's the total number of reports that come into AERS that might be possibly related to dextromethorphan. So we have the search for dextromethorphan presented at the beginning and then we have two selected combination products. But I don't know what the market share is. So if they make 90 percent of the market for dextromethorphan, then this would give us a pretty good idea of what's overall reported if they only make five percent. So it would be nice to have the market share of those two products relative to everything that's being sold that has dextromethorphan in it.

DR. KRAMER: Dr. Woody.

DR. WOODY: Two questions, were you counting suicides as abuse is one question. And then the other is d you have the denominator for the total number of Coricidin and Delsym tablets that are sold? We've heard a denominator like 140 million -- what was the term?

DR. KRAMER: Eaches.

DR. WOODY: Eaches, eaches, 140 and I'm sort of, like, you know, taking the numerator and the denominator. Granted, there's huge underreporting in the AERS system.

DR. CAMILLI: Right.

DR. WOODY: So that's to be taken with a grain of salt. But I'm curious if you had the denominator or an estimated denominator for those two.

DR. CAMILLI: I do not have an estimated denominator for the number of tablets that have been sold.

DR. KRAMER: Dr. Cooper.

DR. COOPER: My question, Dr. Camilli, in trying to understand the sensitivity of the AERS data in understanding the epidemiology of dextromethorphan abuse, two question, one's related to the use of the abuse search term. And has that been useful in understanding signal for abuse of other, for example, prescription opiates, et cetera. And the second question has to do with the sensitivity of the AERS system in picking up signal or adverse events related to other over-the-counter product preparations. So we can understand where this might lie.

DR. CAMILLI: To answer your question about the search, we used a very generalized search to capture as many cases as possible of potential abuse. And then as described in the background packet and from what I talked about a little bit today, we actually did a hands' on review of the cases. So we used a very general abuse search in AERS and then did a hands' on review of those cases.

And you'll have to remind me of your second question.

DR. COOPER: Well, back to the first question, has that strategy been effective in finding other patterns of abuse for other medications?

DR. CAMILLI: I will have to refer to my FDA colleagues for if they can give specific examples. I am not -- do not have any available.

DR. WYETH: This is Jo Wyeth from the Office of Surveillance and Epidemiology. To answer your question, people typically do not report that they were abusing a drug to FDA to our AERS system. So we typically might use crude counts. But at best, it's very rudimentary in trying to get a sense of that, comparing OTC products with prescription.

DR. COOPER: And the second question had to do with whether over-the-counter preparations are often picked up for any adverse events.

DR. WYETH: Say that again, in terms of abuse?

DR. COOPER: How often is there a signal that's picked up from over-the-counter preparation? Is that a way that those adverse events are often reported?

DR. WYETH: When AERS was first established back in 1997 it was not set up to monitor OTC products,

particularly the monographs. And as Dr. Camilli reported, people sometimes report with active ingredient. But a lot of times they're reporting it under the brand name. So it's difficult to try and do signal detection.

And in addition, in 2008 they changed the reporting requirements for OTC products. So we're still kind of learning some of that in terms of how we use AERS for signal detection.

DR. KRAMER: Could you clarify if the change was a requirement that OTC --

DR. WYETH: The reporting requirements --

DR. KRAMER: What was the change?

DR. WYETH: All right. Can somebody from the OTC group, maybe Dr. Schiffernbauer, can you go ahead and respond to that? Joel, on the reporting requirements.

DR. GANLEY: Prior to 2008, I think it was made in 2008, there was no requirement, it was voluntary reporting for any adverse events for monograph-marketed products. Companies still had to keep that information on hand. FDA could go in and inspect.

So in 2008 there was a bill passed, I don't recall the name of it, that required the reporting of adverse events, serious adverse events for dietary supplements and monograph drugs. Okay?

DR. KRAMER: Requirement by the manufacturer to report?

DR. GANLEY: Yes.

DR. KRAMER: Okay. Thanks.

I think we need to go on to the last FDA presentation so that we don't get off schedule.

DR. DORMITZER: Okay. Let's see if I can -- how do I get it to -- there.

Good morning. My name is Cathy Dormitzer. I'm an epidemiologist in the Division of Epidemiology in the Officer of Surveillance and Epidemiology. And today I will provide a brief background on the Drug Abuse Warning Network, the selection of comparator products. I will discuss the methods used to calculate proportions and estimates of drug abuse ratios. I will present the estimates themselves, and the summary and conclusions drawn from these data.

The Drug Abuse Warning Network, DAWN, is a public health surveillance system administered by SAMHSA which is the Substance Abuse Mental Health Services Administration. DAWN data is a nationally representative, multi-stage probability sample of hospitals that have emergency departments. And it collects detailed information on drug-related emergency room visits and provides national

estimates on these visits.

For this analysis national estimates of ED visits for single ingredient dextromethorphan-containing products were compared to single ingredient diphenhydramine and pseudoephedrine products. They include both over-the-counter and prescription products. Single ingredient products were selected for this analysis so that the estimates could be clearly linked to the individual drug product.

These drug products were selected because they are respiratory agents that have CNS activity. They were also selected because they have a large market share and except for codeine products, they are largely over-the-counter products. Now national estimates were also obtained for codeine respiratory agents that fall under the Controlled Substances Act and are listed as C-V agents. These products, however, are not single ingredient, but they provide a comparator that is already scheduled.

Oh, it came out the right color. For this analysis we examine one data element collected in DAWN and that is case type. Case type includes types of cases that are not related to drug misuse and abuse such as suicide attempt, adverse reaction, or accidental ingestion. To understand how DAWN ED visits are related to drug misuse

and abuse SAMHSA developed a case definition designated ALLMA which is All Misuse and Abuse and includes the following case types: overmedication, which is the non-medical use, overuse, and misuse of prescription as well as over-the-counter medications that are not documented as drug abuse in the medical chart; malicious poisoning which is when the patient was administered a drug by another person for malicious purposes such as drug-facilitated sexual assault; and other which includes all drug-related ED visits that could not be assigned to other case types, but by design, most documented drug abuse cases will fall into this category. And ALLMA also includes ED visits where illegal drugs or alcohol were present at the time of the visit.

Okay, so this analysis will provide a proportion of ED visits that were classified as ALLMA to all ED visits to examine how much of the ED visits was related to abuse. national estimates of the number of ALLMA ED visits per 100,000 population by age groups will also be examined. The 12-to-17 age group was selected to examine if this group was higher than the proportion of abuse than the 18-plus population. And children under 12 were not included because use in younger ages are usually accidental ingestion.

Lastly, an abuse ratio, which is the estimate of ALLMA ED visits divided 10,000 bottles which has also been referred to as eaches, and this allows for national estimates of ED visits to be put into the context of drug utilization. So in other words, are the low estimates of ED visits the result of low numbers of events or the result of low drug utilization?

This bar chart summarizes the sales of over-the-counter and prescription single-ingredient dextromethorphan products and the comparators. And as you can see there's approximately 10 million bottles of single-ingredient dextromethorphan products both OTC and prescription products sold each year.

For diphenhydramine, the number of bottles sold is much higher. It was roughly 47 million sold in 2004 and more than 56 million in 2008. And for pseudoephedrine, the number of bottles sold went down. It was 20 million in 2004 and 15 million in 2008. There was the lowest number of use for the codeine C-V respiratory agents. It was 6.6 million bottles in 2004 and more than 8.6 million bottles sold in 2008.

This presents the national estimates of all ED visits that were associated with the single ingredient dextromethorphan product and the comparators. As you can

see, the estimates for dextromethorphan products were 3500 ED visits in 2004 and 3900 visits in 2008. The national estimates for diphenhydramine products were considerably higher, more than 27,000 ED visits in 2004 and more than 35,000 in 2008. The estimates for pseudoephedrine products was more than 5,000 in 2004 and close to 10,000 in 2008. The estimates did rise between 2004 and 2007 but then dropped in 2008. For codeine C-V products there were less than 1,000 visits in 2004 and more than 5,000 in 2008.

Now these are the national estimates for ED visits that were related to all misuse and abuse. So these are the ALLMA ED visits. And the estimates for all four drugs are substantially lower. The ED visits associated with misuse and abuse of dextromethorphan products was 1800 in 2004 and more than 2,000 in 2008. And due to imprecise estimates national estimates for codeine C-V products were suppressed from 2004 through 2007.

And this table presents the number of ALLMA ED visits over all ED visits associated with each drug. And as you can see the ED visits for drug abuse represented well over half of all dextromethorphan ED visits. And the proportion of ED visits associated with diphenhydramine was also close to 50 percent. But this proportion was lower for both pseudoephedrine and for the one year that we have

for codeine products, codeine C-V products.

And because there has been discussion regarding the age at which dextromethorphan has been abused and since most dextromethorphan products are over-the-counter, this is to examine who is misusing and abusing these products. Estimates were obtained for the number per 100,000 population by age group, 12 to 17 years of age and 18-plus years of age. Again, due to imprecise estimates the number of per-100,000 population for the age group 12 to 17 years of age was suppressed for years 2004, six, and seven.

Now this analysis makes the assumption that there is equal exposure for all these projects regardless of age. And because there is such variation and drug utilization, the comparator products are not included in this analysis because it sort of makes the issue confusing. And as you can see, the number of ALLMA ED visits per 100,000 population was higher for the 12-to-17 age group when compared to the 18-plus population.

This slide is a summary of the number of ED visits associated with misuse and abuse, in other words, ALLMA visits, per 10,000 bottles. And there were approximately 1.5 to two abuse ED visits associated with dextromethorphan products per 10,000 bottles. And the abuse ratios were higher for diphenhydramine where it was

closer to three ALLMA ED visits per 10,000 bottles. Before pseudoephedrine and codeine products, the ratios were lower where it was closer to one per 10,000 bottles sold.

Okay. So in summary, the proportion of ED visits associated with misuse and abuse of dextromethorphan was higher than its comparator products. And the number of abuse-related ED visits per 10,000 population was higher for the 12-to-17 year olds. Lastly, the abuse ratios for dextromethorphan were higher than two comparator products, pseudoephedrine and codeine. But the abuse ratios were lower than the ones found for diphenhydramine.

Now, when examining DAWN estimates of abuse-related ED visits, it's very important to keep in mind its limitations. First, only single-ingredient products were examined. Now this was done because the estimates would be clearly linked to these drug products. But generally, it is sold in -- the combination products were excluded. But they have a very large part of the market. And also DAWN only captures abuse that results in an emergency room visit. So if abuse were to result in a fatality or did not result in an ED visit, this data would not capture that.

So DAWN data suggests that the use of dextromethorphan products is associated with misuse and abuse. But these data do not provide information on the

extent of this abuse. Thank you.

DR. KRAMER: Thank you. We had one question left over from the last session.

Dr. Honsinger, do you still have a question?

DR. HONSINGER: It relates to both this topic and the last topic. Looking at the deaths, it appears that -- just to make a point that all of the deaths that we have for the single agent were related with the use of another drug. And the only one you might think might not be related was the older man who died with Mellaril, or Thioridazine, which is a drug that is no longer sold and not well-utilized because of its prolongation of Q.T. eterol and deaths from cardiac arrhythmias.

DR. KRAMER: Okay. Mr. Nelson.

DR. LEWIS NELSON: How do you explain the diphenhydramine data relative to the dextromethorphan data? One would look at this and conclude that we should be discussing that rather than dextromethorphan.

DR. DORMITZER: Well this was an *a priori* analysis. So we picked the drugs before we got the results. There is -- the number of bottles sold for diphenhydramine is much higher. And so I don't really have an explanation. But picked the products because they were repertory agents, they were over-the-counter products, they

do have CNS activity. And those were the results.

DR. KRAMER: Dr. Cooper.

DR. COOPER: Related to that, so I know or understand the reasoning behind including the single ingredient and following up on Dr. Nelson's point last time about the notion of the single ingredient and the small market share. Dr. Pham's data suggested that there's a recent year, 167 million dispensings or using of dextromethorphan in the combination products. So with that, you know, if there's such a small proportion that that would actually suggest that there's up to 32,000 ED visits a year with your rate of two per 10,000 eaches. So that the magnitude of the abuse and the use of ED facilities for abuse might be higher than what you're suggesting here.

DR. DORMITZER: I did look at combination products. But the minute I look at combination products, I have eliminated my comparators because they're all in the combinations. So I did look at that and the abuse ratios were lower. But whether you could attribute the abuse to dextromethorphan or for one of the other products that was in the combination, I couldn't do that. So that's why I didn't look at -- I did look at it, but -- and they were lower, but with a combination product, you don't know why

they're there.

DR. KRAMER: Mr. Mullins.

MR. MULLINS: Yes, I want to go back and address Dr. Bickel's question because I do think it speaks to the whole issue of epidemiology and abuse potential. The U.S. Substance Use and Mental Health Services Administration commissioned a study in 2006 to do a profile on the users and abusers of cough medicine, dextromethorphan. They found that the abusers were between 12 and 25. And 3.1 million reported -- young people report that they used the drug in the past. Close to one million reported they had used it in the past year. So those were the numbers on that.

DR. DORMITZER: Yes. And now they're reporting on cough syrup, but you're right. A national survey on drug use and health and monitoring the future both provide question on cough syrup.

MR. MULLINS: But I think the active ingredient that most young people or the users are trying to locate is dextromethorphan.

DR. DORMITZER: Probably.

MR. MULLINS: Well, it was voted number one. There's surveys. What happens on the Internet is they survey each other. And one site and they rank these

hallucinogenics. And dextromethorphan was rated number one as far as accessibility and safety and proclivity for getting high and euphoria.

DR. KRAMER: Could I just talk to the committee? We have five people who have questions. And it's 11:00 o'clock. We're supposed to go on to the sponsor presentation. Do people have questions fairly quick? Let's try a couple and see if we can --

Lewis Nelson, try to be succinct.

DR. LEWIS NELSON: Nothing's ever quick. Well, actually, the other Dr. Nelson and I were on the same wavelength on this question. But I'll try to explain maybe, and you can just tell me if this is right or not about the reason that diphenhydramine seems to be so prevalent, you know, because my practice in emergency at the Poison Center, I don't think we see very much diphenhydramine abuse. I mean, it certainly doesn't seem to rank nearly as high as the abuse of dextromethorphan would.

Perhaps this is a limitation of the way DAWN is collected. You didn't really comment about the limitation in terms of how DAWN case finds, you know, because there's not necessarily somebody who comes in and says, "Hi, I'm here because I'm abusing diphenhydramine," it's both a

mention in the chart as having used or maybe once ever used or been on this drug and coming in for perhaps an unrelated reason and then that reason has to be characterized by somebody as one of those various categories that you create, not you create, that was created that you cite. So both case finding and categorization could be problems because in your ALLMA you include overmedication as the same as abuse and others the same as abuse and it really kind of meshes those things up a little bit too much perhaps because overmedication could mean a lot of things. And it could be interpreted in a lot of ways besides, "Hi, I'm here because I just overdosed intentionally to abuse diphenhydramine."

So there's a lot fuzziness in the data.

DR. DORMITZER: DAWN basically collects drug-related emergency room visits. So was the ED visit related to the drug.

DR. LEWIS NELSON: That's the newest way DAWN works.

DR. DORMITZER: Yes.

DR. LEWIS NELSON: But it hasn't worked that way in some of the data that you have.

DR. DORMITZER: No, no, no, no. I only used the new DAWN.

DR. LEWIS NELSON: Because even then it requires the categorization, again, it's just the fuzziness of the categories could make abuse look, you know, meshed, kind of, meshed up with overmedication. I'm sure malicious poisoning is probably a tiny group.

DR. DORMITZER: Very, very, very small.

DR. LEWIS NELSON: But overmedication is vague and other is just a huge, you know, garbage pail of people.

DR. DORMITZER: Yes.

DR. KRAMER: Okay. I think we're going to -- we have quite a bit of time for discussion this afternoon. And we've got four other people on the list. And we need to add Dr. Hernandez-Diaz, oh, she's on there. We have four other people on the list, but we're going to, if you don't mind, unless it's pressing that you feel you must ask it right now, we'll postpone it until after lunch. Okay.

All right. Next we have the sponsor presentation. And I need to read a statement about this. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation. For this reason, FDA encourages all

participants, including the sponsor's non-employee presenters to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interests in the sponsor including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

DR. SUYDAM: Good morning, and thank you for including us in this very important discussion. My name is Linda Suydam. And I'm President of the Consumer Healthcare Products Association. CHPA is the national trade association representing the leading manufacturers of over-the-counter medicines.

We're here today speaking on behalf of all of our members that make over-the-counter cough and cold medicines containing dextromethorphan. These companies account for more than 90 percent of the OTC market and represent the leading brand name and private label over-the-counter medicines. I look forward to providing you with our

expertise regarding dextromethorphan along with a summary of our efforts to address the abuse.

I spent 21 years of my career at the Food and Drug Administration. And I know the importance of ensuring that medicines available to the public are safe. So let me start by first saying that any misuse of our products is of concern to me and to the industry that I represent. This industry and the companies that you see on this slide have proactively taken the lead to address dextromethorphan abuse and are here today because of their commitment to this issue and to ensuring that all families use these products safely and effectively.

And while we take dextromethorphan abuse very seriously, we feel that scheduling of this ingredient is not warranted. Instead, more effective interventions, which I will discuss later in the presentation, should be employed to address OTC dextromethorphan abuse. Further, any decision to restrict dextromethorphan should be made in the context of both its risk and its benefit.

To put this benefit in perspective, I want to point out that cough is one of the most common symptoms from which people suffer. As you will hear in today's presentations, cough carries a burden for both the individual and society, everything from interrupting the

individual patient's sleep to being a very rapid way to spread viruses among the population. Because of the widespread prevalence of cough and it's a fact on both the individual and public health, it's important for people to have over-the-counter access to a safe and effective medicine to self-treat quickly because most Americans self-medicate when they have a cough. In fact, a nation-wide survey in 2007 of more than 3,000 adults found that two-thirds chose to self-medicate with an over-the-counter medicine when they develop a cough. And while cough is very prevalent, there are very few OTC treatments that options available.

Dextromethorphan is the most common cough suppressant used in the United States in over-the-counter medicines today. Nearly 90 percent of cough suppressants contain dextromethorphan. And consumers rely on its OTC availability and have done so for more than 50 years. In fact, more than 10 times as many OTC medicines with dextromethorphan are sold than are prescription medicines with dextromethorphan. And more than one in three households use dextromethorphan-containing OTC medicines each year. That's nearly 40 million households.

There is good reason for this widespread use of OTC dextromethorphan. And you'll hear more today about

cough and the benefits of self-treating cough as well as the pharmacology of dextromethorphan.

As I stated earlier, we do not believe scheduling of dextromethorphan is warranted. We base this position on research and data which we will detail in our presentation today. Some of the key points you will hear are, first, the abuse of dextromethorphan is relatively limited, particularly in the context of its widespread availability, and it is consistently flat. Secondly, we see that about five percent of teens report abusing dextromethorphan in a given year. And most use is limited to a few times because they report that they're not getting the high that they seek. But they are getting the negative effects including vomiting and blurred vision.

Next, dextromethorphan is not an entry-level drug of choice. Research shows that most who abuse dextromethorphan are already abusing marijuana and alcohol. And in many instances, are using a cadre of drugs including prescription drugs and ecstasy. Fourth, since the data clearly show that there continues to be a rapid increase of scheduled prescription drug abuse, we believe that scheduling dextromethorphan will have only a limited effect on the ingredient's abuse and at a great cost.

What has been proven to be the most effective

solution to reducing substance abuse are research-based interventions that address the key risk factors leading to the abuse. This along with targeted age restrictions, we believe, is a much better and much more effective approach than scheduling. And lastly, access to over-the-counter medicines has a significant individual and public health benefit. And that benefit would be jeopardized by scheduling.

While we do not believe that dextromethorphan should be scheduled, we are concerned about its abuse. And we do believe that reducing its abuse should be a top priority. That is why CHPA and the manufacturers of medicine containing dextromethorphan have taken a leadership role in fighting its abuse. We took this lead on this issue seven years ago when an overall trend for teens looking inside the medicine cabinet to get high became apparent.

Since that time we've been evolving our programming based on available data. And as you can see from this slide, have created and implemented a comprehensive abuse mitigation plan to address cough medicine abuse. This plan focuses on four research-based goals that are targeted the key risk factors leading to abuse. They are increasing parental awareness of behavior

and the risk and importantly encouraging that parental behavior, increasing the teen's perception of risk, increasing social disapproval, and limiting multiple access points through targeted interventions.

In addition, our program includes tools and interventions developed with leading experts and assessments to measure our progress and ultimately our impact. This chart is also available in CHPA's briefing materials on page 51. And I will be outlining this program for you in detail later in the presentation.

While targeted education is the most effective strategy to reduce abuse, CHPA and our member companies also believe that there are steps beyond and in support of education that potentially can have some positive effect on abuse. This intervention includes focusing on places where we know teens are accessing the medicines which include their home, their friend's homes, at retail stores, and through the Internet.

We are actively working with members of Congress to pass federal legislation that would mandate all retailers ban sales of dextromethorphan to teens under the age of 18. Additionally, we have been advocating for a federal bill to restrict the sale of bulk dextromethorphan, the active pharmaceutical ingredient to anyone other than

and FDA-listed entity. Unfortunately, there are no quick fixes to the drug abuse problem in this country. We need targeted approaches that will stand the test of time. It is reasonable to assume that scheduling would reduce access and therefore reduce abuse. However, scheduling alone addresses only one element contributing to the abuse of cough medicine. We are proposing a holistic approach involving multiple intervention points which includes limiting access, but also, more importantly includes implementing the strategies which have been proven to reduce abuse.

What scheduling would do is put a burden on millions of consumers who rely on these medicines to treat their coughs by requiring them to visit and pay to see a doctor and then to take an additional trip to the pharmacy. It also would negatively impact on our already over-stressed healthcare system. In fact, if only 10 percent of those currently treating cough with over-the-counter dextromethorphan went to see a doctor, that would result in nearly four million additional doctor visits each year.

Additionally, we know that teens are abusing prescription drugs at twice the rate of the abuse of over-the-counter cough medicine. Today we'll outline what needs to be considered when weighing the question of scheduling.

We are honored to be joined with leading experts in their field to provide their detailed analysis of this issue. First, Dr. Peter Dicpinigaitis, a professor of clinical medicine at the Albert Einstein College of Medicine and Director of the Montefiore Cough Center in New York and a world-renown cough expert will discuss the impact of cough and the individual and public health need for over-the-counter dextromethorphan. Dr. Charles Schuster, former director of the National Institute of Drug Abuse and President of CRS Associates, will review dextromethorphan in the context of scheduling a drug under the Controlled Substances Act.

Lastly, Steve Pasierb, President of the Partnership for Drug-Free America will talk about the effective solutions in addressing teen cough medicine abuse. As you may know, the partnership is one of the country's leading voices in addressing substance abuse and is also renown for its researched-based national public education programs. I look forward to providing further remarks regarding our proposed abuse mitigation plan and our recommendations for addressing dextromethorphan abuse at the conclusion of these presentations.

We are also pleased to have other experts with us today to answer your questions as you will see from the

slide in front of you. Thank you again for your time. And now I would like to turn the lectern over to Dr. Dicpinigaitis.

DR. DICPINIGAITIS: Good morning. Thank you for giving me the opportunity to speak to you today. CHPA is compensating me for my time and my expenses to be here. In addition to working as a pulmonologist intensivist, I'm also the founder and the director of the Montefiore Cough Center, one of the few centers in the world specifically dedicated to the management of cough. So as its director, I treat people with cough and I conduct cough-related research. Every day I see the very real burden that cough has on the individual patient. And perhaps even more importantly I can appreciate the public health impact of cough, something that might not always be considered.

Today I'd like to briefly review the prevalence and burden of cough, the antitussive effect of dextromethorphan and the health benefits that dextromethorphan OTC offers to both the individual and the public in terms of providing the ability to self-treat cough. As we heard, cough is very prevalent in the general population. It's one of the most common symptoms from which people suffer. In fact, surveys show that more than 40 percent of adults in the United States, this corresponds

to over 90 million people, report that they suffer from cough in a given year.

In this recent survey of more than 1,000 adults, cough was reported as more prevalent than other very common conditions such as heartburn, severe headaches, and rash or hives. In addition to being very common, cough can be a very distressing symptom, it causes a high level of general discomfort and conditions that people report as disruptive and burdensome. Most notably in the general population, sleep deprivation and hoarseness were related as the most bothersome. And as confirmed in quality-of-life studies in acute cough sufferers, urinary incontinence is a particularly troubling problem in women.

In fact, two studies that use validated quality-of-life questionnaires measured the negative of effects of these symptoms on people's lives. One study using the cough-specific quality-of-life questionnaire, abbreviated CQLQ, in people with acute cough, the other using the Wisconsin Upper Respiratory Symptoms Survey, abbreviated WURSS, in cold sufferers. As we can see, sleep deprivation ranked in the top three in terms of being the most bothersome in both studies. It was rated higher than most other cold symptoms such as headache, body ache, and plugged or runny nose. Only hoarseness and the general

signs of feeling rundown and lacking energy were ranked higher. And I can tell you from clinical experience that cough is not only bothersome to the individual patient, but to spouses, significant others, family members, and co-workers.

There are only three non-prescription therapies for oral ingestion approved in the United States for the symptomatic treatment of acute cough due to the common cold. And it's important to remember that there's no specific treatment for the underlying cause of the common cold. There's just symptomatic therapy. Before I describe dextromethorphan's mechanism of action in cough, I'd like to briefly discuss the other treatments. Diphenhydramine is a first-generation-sedating antihistamine. The mechanism by which diphenhydramine suppresses cough remains unclear. We know very little about chlophedianol's pharmacology. There's been no research published on the pharmacology of this agent since the early 1960s.

Dextromethorphan is a centrally-acting antitussive like codeine, but it does not interact with opioid receptors. It targets the pathophysiologic pathway of cough in the medullary synapses of the vagal afferent nerves. Coughing is initiated when the sensory nerve endings of vagal afferent nerves in the larynx, trachea,

and large bronchi are stimulated. These afferent impulses are integrated into a cough response in the medulla and are then transmitted to the larynx and the expiratory musculature. This then generates the expiratory event of cough.

Two excitatory transmitter systems, glutamate and neurokinins have been identified in the vagal afferent nerves that regulate cough in animals and humans. Dextromethorphan interacts with various receptors implicated in the cough response including the sigma-one and the NMDA receptor and it inhibits glutomenergic transmission thereby suppressing the cough response in the medullary synapses of the vagal afferent nerves.

Consistent with the pharmacological action of dextromethorphan as an antitussive, multiple studies have confirmed the ability of dextromethorphan to suppress cough in animals as well as in both induced and natural cough in humans. Dextromethorphan has unequivocally been demonstrated to cause a dose-dependent reduction of cough in multiple animal models. And multiple studies of induced cough in humans have confirmed dextromethorphan’s ability to inhibit cough.

To date, the scientific community has been unable to develop robust antitussive models to measure drug

efficacy in acute cough and common cold patients. But despite methodological shortcomings and challenges, there are in fact studies supporting the efficacy of dextromethorphan in acute cough due to common cold. By far, the largest evaluation of dextromethorphan is a meta-analysis of randomized, placebo-controlled trials involving more than 700 patients. This patient-level meta-analysis demonstrated a statistically significant antitussive effect of dextromethorphan versus placebo using the object of endpoint of automated cough counting.

There are benefits on both an individual and a public health level to have people self-treat their cough. And there are potential disadvantages of dextromethorphan OTC where no longer available. As we heard, most Americans self-medicate when they have a cough and when they do so they primarily choose OTC medications that contain dextromethorphan.

So what are the potential implications of dextromethorphan no longer being available as an OTC product? There are several possible outcomes. Patients may seek out alternative over-the-counter products. But as I showed you, there are only two other oral OTC medications available, diphenhydramine and chlophendianol. My personal opinion is that these agents cannot fill the role that

dextromethorphan currently plays as the most commonly used OTC antitussive. Another potential problem is that people will simply not treat their coughs. This will result in additional morbidity to the individual and, as I'll discuss shortly, may have public health implications as well. And finally, rather than self-treating their cough, some patients will go to their healthcare provider's office for treatment. This will not only increase the strain on our healthcare system, but may lead to an increased number of prescriptions for other medicines including opiates and antibiotics.

In my opinion, when more people consult physicians for their cough, more narcotic cough suppressants may be prescribed, in particular codeine and hydrocodone. Studies show that even at present, nearly six-and-a-half million prescriptions are written each year for codeine-containing cough suppressants. In addition to the undesirable side effect of sedation at antitussive doses, increased prescribing would result in more of these narcotics being available in home medicine cabinets. Furthermore, we know that while the situation, especially in children, is improving, antibiotics for viral upper respiratory tract infections continue to be prescribed on a large scale. In its 2006 report, the agency for healthcare

research and quality concluded that it is still a major problem.

And if people decide not to treat their cough, there's a potential public health consideration. According to the CDC and university researchers, coughing and sneezing are the main ways that airborne viruses spread from person to person. In fact, in a study that specifically looked at influenza transmission, it was estimated that approximately 20,000 viruses are expelled in just one tussive blast. Coughing propels a jet of air a distance of three to six feet from the mouth, and respiratory droplets contained therein carry viruses up to three feet. As a result, treating cough in a timely fashion may be important in preventing spread of virus to others.

In conclusion, cough is one of the most common symptoms effecting the general population of the United States. For many, cough is not merely a trivial annoyance but a significant burden causing substantial morbidity and negative impact on quality of life. Furthermore, the deleterious effect of cough transcends the individual. It can adversely affect family members, co-workers, and the person's community as well. Preserving consumer's access to over-the-counter dextromethorphan for self-treatment not

only provides important health benefit to the individual but also to the general public.

And now I'd like to turn the presentation over to Dr. Schuster.

DR. SCHUSTER: Good morning, and thank you for giving me the opportunity to share with you my analysis of the data and my conclusions regarding the nature and extent of the abuse of dextromethorphan. CHPA is compensating me for my time and expenses to be here today.

I spent 50 years working in the field of drug abuse research and policy. Much of my research has been in developing methods to assess the abuse liability of psychoactive agents. Most recently, my research has been in detecting the diversion and abuse of newly marketed medications. While serving as the director of the National Institute on Drug Abuse, I was part of the process to schedule drugs under the CSA or the Controlled Substances Act. For more than 30 years, I have served on the WHO expert committee on drug dependence. And I was also a member of the FDA drug abuse advisory committee for eight years.

I'd like to start my presentation by clearly stating that after carefully reviewing and analyzing a wide variety of scientific evidence and government databases on

dextromethorphan, I do not recommend that it be controlled under the CSA. I base this recommendation on data that demonstrates that its limited abuse potential and low level of actual abuse, especially considering its widespread availability and use covering more than 50 years here in the United States.

However, while the level of dextromethorphan abuse is limited in this country, I want to make it clear that I am concerned about it. And I do believe that it must be addressed. But I'm also equally firm in my belief that we need to apply the tools that are most likely to address the problem and least likely to cause new problems. This includes further taxing our already over-stressed healthcare system.

As I mentioned, I analyzed a wide variety of scientific evidence and government databases and this assessment is in line with how we determine whether a medication should be scheduled under the Controlled Substances Act. It includes analyzing dextromethorphan's pharmacology in animal and human abuse liability studies, assessing government databases to review patterns in levels of abuse, and the significance of the outcome of that abuse, and finally, assessing the benefits and risks to public health of both the abuse and of scheduling.

So with that as an overview, let's start with dextromethorphan's pharmacology. As you have already heard in the very excellent review of the pharmacology by Dr. Bonson from the FDA, dextromethorphan may be related structurally to an opioid, but it is not an opioid, which as you know, is class of drugs that are controlled in the CSA, but unfortunately, frequently abused by teenagers and adults as well.

Dextromethorphan is the d-isomer of levomethorphan and like many d-isomers of opioids, it is not active with the mu-opioid receptor which is assisting mediating the addicting properties of all opioids. Dextromethorphan, therefore, does not produce opioid-like effects. Dextromethorphan and it's active metabolite, dextrorphan are both low-to-moderate affinity NMDA receptor antagonists as is the case for ketamine, phencyclidine, and memantine. Memantine is FDA-approved for Alzheimer's disease and is not controlled in the CSA. As is reviewed in the FDA's briefing materials, there are a number of other binding sites in the brain which may, at high doses, be responsible for the mixed effects of DXM.

And at high doses, there are mixed effects. In those who experience euphoria, for example, most also report high levels of dysphoria. At the doses required to

produce CNS effects that drug abusers are seeking, intense nausea can also occur. That was listed as gastrointestinal effects on the first slide that was shown by the FDA. At the doses required -- sorry.

At the doses required to produce the CNS effects, this nausea may very well deter some individuals at least from pursuing this as a drug of abuse. As many members of the committee know because they are active researchers in this area, there are two procedures that were described by the FDA presenter, Dr. Bonson, that are used to evaluate the abuse potential in animal studies. These are drug self-administration studies and drug discrimination studies.

When we analyze the pre-clinical studies using these methods, we see, in my opinion, mixed results regarding the abuse-potential of dextromethorphan. In my experience, when we see these types of mixed results, it's usually because drugs have weak reinforcing effects and therefore, relatively lower abuse potential. In animal self-administration most of the animals, but not all self-administer dextromethorphan but only across a limited dose range. In other animal studies, dextromethorphan has been shown not to be self-administered.

In drug discrimination studies, some of which

have been carried out by Dr. Woods and his colleagues, it has been shown that dextromethorphan can substitute for ketamine and phencyclidine. This is similar to other NMDA antagonists such as non-controlled memantine which also substitutes for ketamine and phencyclidine in drug discrimination studies and is self-administered by all the monkeys in which it was tested.

The point is that animal studies are very important predictors but are not definitive predicting actual abuse in the real world. In the human abuse potential studies that, again, were reviewed by the FDA, we see that it takes very high doses well above the maximum therapeutic dose of dextromethorphan to produce psychoactive effects. Here in early work by Dr. Jasinski, we see on the vertical axis scores for MBG of the euphoria scale of the Addiction Research Center Inventory, a validated measure of abuse potential. The horizontal scale shows dose.

As we can see, morphine, shown in pink, produces significant dose-related responses in euphoria. In contrast, dextromethorphan shown in yellow and white lines did not produce increases in measures for euphoria. I want to make a comment about the nature of the people who participated in this study. I have had communication with

Dr. Jasinski about this very important point. Yes, it is true, these were heroin abusers and they were in treatment at the Addiction Research Center in Lexington, Kentucky, for their heroin problem. However, Dr. Jasinski informed me that these were poly-drug abusers, frequently abusing high quantities of alcohol other sedative agents such as barbiturates as well as stimulant drugs and amphetamine or cocaine. I think this is important because these are individuals who enjoy the effects of a wide variety of drugs.

In contrast, dextromethorphan, shown in the yellow and white lines, did not produce increases in measures for euphoria. However, we do see a significant dose-dependent response for both dysphoria and sedation. Dextromethorphan separates from placebo only at eight times the maximum therapeutic dose. In addition, new data, again referred to in the FDA presentation by Dr. Ziratayo (ph), that was published this year, demonstrated that negative effects of dextromethorphan increased with dose in tandem with the effects sought by the abuser.

We know about these negative effects not only from clinical studies, but also from Internet monitoring and focus groups. Users describe these negative effects including nausea, blurred vision, disorientation, and

overall a dysphoric feeling. Yes, there are some teenagers that will want to get off their natural feeling and take any drug to produce that. However, this is a very small minority of the kids who are abusing drugs. Again, I believe that this is one of the reasons why dextromethorphan is not favored as a drug of abuse.

Withdrawal and tolerance are also two primary markers of physical dependence. These do not appear to be factors in the abuse of dextromethorphan. Although there are sporadic case reports, I found no pre-clinical or clinical studies of physical dependency withdrawal following the repeated administration of dextromethorphan. Taken together with the human abuse liability studies, to me these studies suggest that dextromethorphan has a low dependence potential compared to classic drugs of abuse.

Now since dextromethorphan has been widely used and widely available over the last 50 years, we have extensive experience with its real-world use. In addition, in the last five years, national drug databases such as the National Survey on Drug Use and Health or NSDUH and Monitoring the Future, a study conducted at the University of Michigan, they have begun to track over-the-counter cough and cold medications. I'd like to point out that these national surveys lump all of the over-the-counter

cough and medicine together including many products that do not contain dextromethorphan. So this may result in an overestimation of the abuse of dextromethorphan.

From these surveys, we know who is abusing cough medicines and the extent of this abuse. This is important because this helps us target interventions. While the numbers from the two databases may differ, the trends made a strikingly consistent picture. First, NSDUH shows that abuse rates for all OTC cough and cold medicines are very low in the population as a whole. 0.7 percent of those 12 and older have abused at one time or more in the past year to get high to use the wording of the NSDUH survey.

We know from NSDUH that the abuse of dextromethorphan is at its highest prevalence amongst 12 to 17 year olds. As seen on the yellow bars, just under two percent of the teens in this age group report abuse of OTC cough and cold products in the past year. This declines to one-and-a-half percent of young adults and then drops significantly at older age groups.

Given dextromethorphan's widespread availability and use in more than one in three homes, this level of abuse is, in my opinion, low. The peak of cough and cold medicine abuse in the 12-to-17-year group contrasts with the peak use of classic substances of abuse such as

marijuana and prescription pain relievers seen here in pink and blue. With these two comparators, non-medical use occurs most frequently in the 18-to-25 year age range. Importantly, they also occur at a much higher prevalence level when compared to dextromethorphan.

Regarding the level of abuse, we see a low level of abuse when we look specifically at cough and cold medicine abuse among high school teenagers through the Monitoring the Future survey. Over the four year that this question has been asked, we see a modest downward trend in the eighth and twelfth graders and a very slight increase in tenth graders. But it is relatively stable over this time period. I want to stress the fact that overall more than 95 percent of teens have not abused cough and cold medicines in the last year.

Of the five percent who have, many of those teens were probably experimenting, just trying it a few times. As we saw in the clinical findings, I believe that frequently unsustained trial use speaks to two things, first, dextromethorphan does not produce a very good high; and secondly, the fact that there are unwanted effects such as nausea, disorientation, and so forth. Let me clear, however, I am very concerned about teens abusing dextromethorphan especially those who are abusing it

persistently because these persistent users have a problem, not just with dextromethorphan, but with drug abuse overall. I would venture to say that in my opinion, these are children who also have significant emotional, social, and educational problems as well.

We know from analyzing the data and from focus groups that most of the teens, particularly those who abuse cough and cold medicines persistently, are poly-drug abusers. Those who abuse other substances are far more likely to also abuse cough and cold products than those teens who do not. For instance, those who smoked marijuana were seven times more likely to also use products containing cough and cold medicines. Those who abuse OxyContin are 15 times more likely to abuse cough and cold products compared to their peers who do not.

Qualitative data from focus groups conducted by the Partnership for Drug-Free America show these abusers start with alcohol and marijuana and then try dextromethorphan.

Now let’s move on to the significance of dextromethorphan abuse. And we can get a reasonable analysis of the significance by looking at databases that capture the consequences of abuse starting with data coming from emergency room departments. As you have heard, the

Drug Abuse Warning Network, or DAWN, tracks drug-related emergency department visits. Here on the y-axis we see the rate of emergency department visits. In yellow are those which include a mention of non-medical use of dextromethorphan per 100,000 people. I'm choosing to look at cases termed non-medical use even though it is a broader term that includes cases beyond abuse because it's difficult as we discussed to determine what an abuse case is through emergency department reporting systems.

In addition, I use this category because it's a category frequently referenced by the Drug Enforcement Agency and the FDA. While there is variation over the five-year period starting in 2004, the five-year average, the blue dot, resulted in non-medical use of dextromethorphan being mentioned in just over two and a half visits per 100,000 people. For comparison, when we look at emergency department visits for codeine-containing medicines, seen here in gray, versus dextromethorphan, seen here in yellow, the rates are very similar. This is despite the fact that there are more than five times as many dextromethorphan-containing medicines sold as there are codeine-containing medicines.

For further context, when you look at the rates of emergency department visits for non-medical use of

hydrocodone-containing products in pink to provide an example from our current epidemic of prescription opioid abuse, you can see that the trend upward and the strikingly higher level of abuse of this controlled substance. To me, this provides further substantiations of the low level of abuse of dextromethorphan especially considering the fact that this product present in more than one in three household in the United States.

Poison control centers are another source of information to assess outcomes of dextromethorphan abuse and use. These nationwide centers record calls of actual or suspected contact with any substance. A subgroup of these are intentional exposures, those that include suicide, abuse, and misuse. From 2005 through 2008, we see there is a slight increase after the first year of the period which then remains flat across the remaining years.

Importantly, data from poison control centers show that fatalities were rarely reported for dextromethorphan, 32 or 0.06 percent of intentional dextromethorphan exposures resulted in death, 22 were suicides, three coded as misuse, and the remaining seven were coded as abuse. Of the seven abuse cases, four involved more than one drug including cocaine, morphine, oxycodone, and alprezalon (phonetic).

In looking at the FDA analysis of the AERS database, there was a crude count of 102 fatalities listed in FDA's table one. After applying the FDA's case criteria, 94 fatalities were excluded. Of the remaining eight fatalities, five were completed suicide, two were overdose, and one included preferred terms of multiple drug overdose, drug abuse, and drug dependence.

Another measure of public health significance of a drug is to look at the number of admissions that drug abuse and dependence treatment centers since this is a means to assess whether a substance being abused frequently enough to produce addiction and the need for an individual to enter treatment. The treatment episode dataset, or TEDS, categorizes admissions by the substance of abuse. It combines all OTCs, all OTCs in one category.

Here we see prescription opioids in blue and over-the-counter drugs in yellow which, believe me, are there even though you can barely see them. OTC medicines are at the very bottom of the graph of which dextromethorphan was just a part. They accounted for less than one percent of all TEDS' admissions in the 10-year period between 1998 and 2008. Since it's so hard to see the OTCs on this graph, I've redone it. The number of treatment admissions for the prescription opioids is shown

on blue on the left axis using the standard scale on the previous graph. The number of treatment admissions of all OTC medications, that is any medicine available without a prescription is shown on the red axis using a scale that has been expanded 20-fold in order to be visible.

Even if we assume that all of the OTC cases were actually admissions for treating dextromethorphan abuse, the number of admissions is low. You can see that the entire scale, the red axis, is just above zero on the left axis. For context, OTC admissions never exceeded 1100 admissions per year. And there is no increasing trend over this time period. In contrast, non-heroin opioids increased from about 16,000 to over 90,000 admissions in this 10-year period.

So what does all of this mean when it comes to weighing the benefit and risk to public health? Before I conclude, I want to reiterate the consistent picture all of these outcome sources paint. Admissions to drug treatment centers from all over-the-counter medications of which dextromethorphan is only a part, were low it the 10-year period from 1998 to 2008. DAWN emergency department rates are low and ended at their five-year average which is shown in blue. Intentional exposures from the American Association of Poison Control Centers are marginally up

from the first year, but then flat for the rest of the period and death is very rare. Finally, the number of dextromethorphan abuse-related fatalities in AERS are also very rare.

Compared to most substances of abuse by every metric, dextromethorphan is a remarkably safe ingredient. Its therapeutic index is very high. The risk of fatal overdose is much less with dextromethorphan, with many other prescription and OTC products and typically involves ingestion of multiple substances. However, for those who are abusing these medicines, we have a well-defined profile of the abuser that allows us to appropriately target and tailor interventions to limit its abuse.

When considering scheduling, in addition to analyzing the risk to public health, it's important to look at more than just the potential risks of the abuse of dextromethorphan. We also need to consider what the risks of scheduling it are. And there is a potential negative public health impact of scheduling dextromethorphan. As we heard earlier, scheduling would limit access for people who have legitimate need to relieve their cough. And this would potentially impact both the individual and public health.

I am particularly concerned for the likely

possibility that if patients go to doctors for the treatment of cough, they will be prescribed codeine or perhaps even hydrocodone and opioids with significantly greater abuse potential and toxicity.

In conclusion, after looking at the pharmacology of the ingredient, the scientific data, epidemiology, emergency room visits, intentional exposures from poison centers and treatment center data, I do not recommend scheduling dextromethorphan. The rise in prescription drug abuse teaches us that scheduling a drug isn't a guarantee of preventing its diversion and abuse. I ultimately base my recommendation on five points. Yes, I believe there is -- notice my hoarseness -- there is a need for this substance. Scheduling dextromethorphan may also bring with it some unintended consequences including reduced access to people who need it and negatively impacting public health.

There is not physical dependence on this drug. Third, with dextromethorphan I believe we see a consistently low prevalence of abuse. Fourth, there is very low morbidity and mortality when the drug is abused. Now, I'm not attempting to minimize the problem of dextromethorphan abuse. I am simply trying to put it in proper perspective. Finally, I believe the solution to addressing this abuse is with more targeted approaches

which can mitigate risk while maintaining availability and the benefits of this product.

I'd now like to turn the presentation over to Steven Pasierb, the President of the Partnership for a Drug-Free America.

Steven.

MR. PASIERB: Good morning. I want to thank you for having me here today and the opportunity to talk to you about this very important issue. I've actually worked in the addiction prevention and education field for over 20 years. And I've served in the role of the President of the Partnership for a Drug-Free America for nearly a decade. While the Partnership does receive annual grants from CHPA, I am not being reimbursed for my time or expenses here today. I'm actually here to put the behavior of intentional abuse of OTC cough medicine into perspective. We've talked around that a lot today.

Since the Partnership started 24 years ago, we've been dedicated to conducting research and understanding why young people use drugs. Because we know from research and from experience that it's only when the underlying attitudes and beliefs are changed that it's possible to change behavior. We've also learned that the most affective interventions are focused less on what a specific

substance is an more on changing the risk in social disapproval attitudes among both the non-users as well as those currently abusing the substance or said another way, we need to focus less on the myriad substances being abused and more on the behavior of abuse.

Today I'd like to share with you some of our latest research on cough medicine abusers and also our recommendations for addressing the issue. When the Partnership began working with the Consumer Health Care Products Association seven years ago, we really looked at the issue, we were concerned about what was happening. And we were seeing an overall change in the drug abuse landscape in America. We were seeing increases in teen abuse of synthetic drugs like ecstasy, but also prescription pain killers and sedatives while also hearing reports of kids abusing cough medicine to get high.

We conducted the first national quantitative study on cough medicine abuse prevalence among teens. And we were concerned in that study that roughly five percent of teens reported abusing cough medicine in the past year. Most importantly, we at the Partnership and other experts at the time believed that this problem was poised to grow significantly worse. Here at the bottom of the slide you see a quote from the National Drug Intelligence Center

Bulletin, and the piece I've pulled out is, "Dextromethorphan abuse among adolescent most likely will increase," and that was back in 2004.

The data we had on cough medicine abuse indicated really the same confluence of factors that we were seeing drive up teen abuse of other drugs, drugs like ecstasy and inhalants. And those factors were a lack of parental awareness, either of the behavior or the risks of that behavior. We know that this simply was not on parents' radar screens. And unfortunately, if they did know, they were not concerned because they'd say it was just medicine.

We also saw a very low perception of risk among teens. Our first data in 2004 showed a risk level of only about 41 percent. And social disapproval attitudes among teens were not even apparent. This was essential in America hidden behavior. We knew that teens had various access points for the product, in their own home, on store shelves, from the Internet, and from friend's homes. The good news, fortunately, over that seven-year period is the abuse of dextromethorphan has remained consistently flat. We believe this is due to a combination of factors including the significant prevention efforts that have been mounted over the past seven years. But in short, we do believe that those prevention efforts, to date, on cough

medicine abuse, have worked, but more importantly that we can do more.

At the Partnership we have extensive experience with the challenges of substance abuse and efforts to both prevent and intervene. Our experience supports a cognitive model of abuse behavior consistent with the work of others. We understand that the behavior of abuse is rooted in individual's knowledge, their perceptions, and beliefs about the substance being abused. Thus, to modify the behavior, one needs to understand the abuser's perceptions of the abused substance and then design interventions to modify those perceptions. While the ultimate result will be change in behavior, this can really only be accomplished through a staged, systematic approach.

Until we launched our efforts with CHPA, frankly, the prevention field really didn't know much about the prevalence of cough medicine abuse. And there was also minimal insight into both the behavior and even less into those who were abusing the product. To help understand who these kids are, we rely on a combination of quantitative national research that we conduct every year, the PATS study, and qualitative learning that we do on an on-going basis. The most recent qualitative learning conducted around the country this past summer.

First, I'd like to talk about the qualitative research, how it was conducted, and what it indicates about the behavior. This summer we conducted a series of qualitative studies comprised of young people who had abused or were currently abusing over-the-counter cough medicines. And I can tell you it's actual a tough study to recruit for because the prevalence is so low. We require geographic diversity, group diversity, and we conducted multiple sessions. Now because as I just mentioned, the only way to change drug abuse behavior is to first change attitudes and perceptions, we needed to learn about what motivates teens to choose cough medicine as something that they want to add to the list of things they abuse.

And then what are their perceptions of the product, what are their social disapproval levels of the behavior. So our questions in the study focused on those factors. What we heard in nine out of nine focus groups is that over-the-counter cough medicine is a lousy high. And teens and young adults know it. The majority said when they did it, it was unpleasant. Some even thought that it went on too long and in desperation they finally decided to sleep it off rather than continuing experiencing the high.

Many of the teens we talked to had in their first experience with over-the-counter cough medicine, thrown up

or temporary lost vision or locomotive ability. And none of them viewed that as a positive outcome. So it's not surprising, as we've saw in the data presented by Dr. Schuster, that most of the teens in this study tried cough medicine and they only did it a few times before abandoning it.

The teens in our research really told us the exact same things we see in the data from Dr. Schuster. Teens who were abusing over-the-counter cough medicines were more likely to be abusing other drugs including prescription opioids and ecstasy. In all of our groups, most reported that they had already been drinking alcohol and using marijuana and then added over-the-counter cough medicines. Teens also told us as they looked out at the drug landscape that they regarded cough medicine users as losers.

Users who we talked to regard over-the-counter cough medicine really as a poor substitute for other drugs including alcohol, marijuana, ecstasy, shrooms or mushrooms, and LSD. OTC cough medicine consistently ranked very low on their list of drug of choice. And then one of the most interesting things from the study which I think is very important is an insight from that qualitative research that there is a substantial confusion among cough medicine

abusers between over-the-counter cough medicine and prescription cough medicine with codeine and of course without dextromethorphan. Even when we directed to very specifically talk about OTC cough medicine, they persisted in confusing them by commenting on what they saw as a much more pleasurable high from prescription cough syrup.

They had a knowledge base, a language, a lure if you will, about prescription cough syrup with codeine that they simply didn't have around the over-the-counter product. This confusion at the consumer level lead us to believe that cough medicine abuse prevalence levels reported in Monitoring the Future as well as in the Partnership's own national research may actually overstate the prevalence of over-the-counter cough medicine and ignore the abuse of prescription cough syrup.

We're actually going to be changing our questionnaire going forward and we're right now in discussions with Dr. Lloyd Johnston who's the principal investigator of the Monitoring the Future study about making changes to his study so that we can more accurately reflect this. But in total, the qualitative and quantitative research leads us to some fundamental strategic insights, each of which we believe has implications for prevention programming. The first insight

is that we need to capitalize on what the teens themselves call that lousy high and what the teens call that loser image of cough medicine abusers and make that a key element of the prevention effort. These are powerful concepts that de-motivate users and a reason why most teenagers who try these medications only abuse them a few times before quitting. And I'll speak a little bit more about that in a moment.

The second insight, both from qualitative and quantitative data is that for those teens reporting more frequent abuse of cough medicine, that's about half of the five percent total, are mostly teens who are simultaneously abusing multiple drugs of which dextromethorphan is at the very bottom of their list. What this tells us at the Partnership and given what was know about drug abuse and prevention, is that these heavy, poly-substance abusers will find substance to abuse whether those substances are legal, illicit, prescribed, or over-the-counter witness their familiarity with and ready access to the prescription cough syrup which they were far more eager to include on their menu of drugs of abuse than they were OTC cough medicine.

As a result, our suggested approach brings together proven prevention strategies to reduce drug abuse

with findings from all this recent research. And actually, it represents a significant ratcheting up of the teen-specific efforts to date. Research from the last 35 years tells us that teen drug use can be best affected with active parental involvement, increasing youth perception of risk, and increasing youth perception of social disapproval.

Let me spend a moment explaining how each of these strategies affect substance abuse, how we know this to be true, and our recommendation for integrating these principles into reducing cough medicine abuse. First, why are parents so important? Well, parents have been a focal point of efforts at the Partnership for decades because what may come to a surprise to many parents is they truly can have an impact on teen decisions to use drugs. In fact, quantitative national research consistently shows, year in, year out, that teens who report learning about the risks of drugs at home from parents who are caring adult, are 50 percent less likely to abuse drugs.

And parents can also address the supply side of this issue by restricting access to medicines in their own home. So any component of addressing cough medicine abuse needs to include an emphasis on motivating and mobilizing parents. Secondly, we know that when risk perception of a

drug goes up, use goes down. It is a very elegant and straightforward scenario. As you can see from this chart on the screen, substances with a lower perception of risk have a higher prevalence of use. For example, in 2009 the perception of risk among tenth graders for marijuana was only about 20 percent, while use was among one of the highest, right around 27 percent. Compare that to heroin, which in 2009 had one of the highest perceptions of risk at 72 percent and one of the lowest rates at just under one percent. Heroin also has one of the highest levels of social disapproval. So you see kind of the two poles of the scenario.

This relationship between actual usage levels and those perceptions, the attitudes, the beliefs is more deeply illustrated in this chart. And this is an example that focuses on marijuana. When you look at the chart, two things become readily apparent. The first is that perceptions regarding availability of marijuana don't seem to impact whether teens abuse. Availability remains flat, essentially for the period of time. The second fact, and really of crucial importance is that inverse relationship between risk perceptions and actual usage levels, the data show time and again over time that the perception of risk increases, when that happens abuse rates decrease. And

unfortunately, the inverse is also true as you see in the latter part of this graph.

But this body of research really gives us a roadmap for prevention including reducing cough medicine abuse. We've actually provided too additional case studies in the appendix of your briefing book. They're in appendix three. And they both look at perception of risk social, disapproval and usage. One of those goes specific to the issue of inhalant abuse, sniffing household products to get high. I think it has many parallels to addressing dextromethorphan-abuse behavior. Here we have a readily available household product abused primarily by teens and a significant increase in prevalence level in the 1990s.

Now while availability of inhalants remained universal, they were everywhere, targeted research-based public education was employed which helped increase eighth graders perception of risk by 20 percent between 1995 and 2001. Over that same period, abuse of inhalants decreased 29 percent by eighth graders, the grade level at which inhalant abuse is most prevalent. In the study report of Monitoring the Future, the principal investigator, Dr. Lloyd Johnston, specifically pointed to the public education efforts as having contributed to this progress. And he talks about the turn- around in inhaled abuse and

beliefs corresponds exactly with the anti-inhalant ad campaign. And we are inclined to credit much of the improvement to inhalant abuse to that intervention. That's what happens when you really target those risks and social disapproval attitudes.

But based on this extensive experience and also our work today on cough medicine abuse, we're able to make some informed recommendations on how to move forward. First, we know enough about the abuser to reach him or her with very highly targeted messaging. We can effectively leverage those insights we got out of the research and continue to make progress, both changing attitudes and reducing abuse. We live in an age where it's possible to highly target teens and young adults in the same digital, online, and social media that they use every day in their lives.

And therefore, we can do that without risk being educative to the other 95 percent of young people who do not abuse cough medicine. So because prevalence remains so low, we do not recommend a major national scale outreach effort. Rather, we recommend that highly targeted, aggressive and pervasive online and digital targeting both those most at risk and those already engaged in the behavior. The goal of that campaign should be three

things, first, to diminish any perceptions that there are benefits from cough medicine abuse; second, to increase perceptions of social disapproval of the behavior; and third, reduce intentions to abuse cough medicine among at-risk teens and those experimental users. More than half of these younger sensation-seeking teens who might try cough medicine as a cheap and available alternative to alcohol or marijuana can be dissuaded form initiation once they hear from their peers and realize how unpleasant and how pathetic the behavior is.

Secondly, it remains essential to continue to enlist parents in this effort by talking with their teens and safeguarding medicines in their own home, parents can have a significant impact in reducing teen abuse of cold and cough medicines. By giving parents persuasive information about all the risk factors related to substance abuse, we can spur them to action before their children experiment with cough medicine or any of those substances which it appears precede cough medicine. The Partnership also believes there is value in restricting availability of over-the-counter cough medicine at retail to teens under 18. And we've actually advocated in Congress on behalf of those bills to make that restriction.

So in conclusion, we believe that the programs

put in place by CHPA, those that we have done, and those by other organizations are working and have helped stabilize the prevalence of cough medicine abuse. Nearly four decades of experience in learning from the Monitoring the Future study has proven that when you do research-based targeted prevention efforts, they can work to decrease the prevalence of abuse especially among teenagers.

And while we can effectively impact OTC cough medicine abuse, in my view, I think ultimately we would all do well to put this abuse in context, and that is the abuse of all medicines both over-the-counter and prescription. We hope that the FDA, federal agencies, and industry can one day come together in a public-private partnership to educate parents, healthcare officials, healthcare practitioners, and the entire general public on both the short-term and long-term risks of medicine abuse. When we do that, we're going to be making real headway against all of those charts that we saw on all of the different substances. But on all fronts, the Partnership for a Drug-Free America stands ready to work with FDA to continue working with CHPA and all other stakeholders on taking on this issue and contributing in any way we can.

Thank you for your time. I'll turn it over to Dr. Suydam.

DR. SUYDAM: Thank you. As you've heard today, CHPA and the presenters before you have a tremendous amount of expertise and knowledge in the pharmacology of dextromethorphan, its abuse prevalence, and in developing effective, targeted strategies toward preventing and reducing cough medicine abuse. We just heard from the president of the Partnership of a Drug-Free America that the most effective way to reduce substance abuse is through targeted interventions. I'd like to spend a few moments talking about CHPA's educational and legislative efforts to address dextromethorphan abuse and importantly what our plan is moving forward.

But first let me say I'm very proud of the fact that we have been proactive and aggressive in our approach to prevent cough medicine abuse. This timeline which I know is very busy chronicles many of our efforts and represents the work we have been doing over the past seven years. You have a copy of this timeline in your hand outs as well in appendix one of the briefing book. I don't have to go through all our programs today, but I encourage you to pay particular attention to the 12 pages of appendix two in your briefing book that summarizes our efforts to date.

As you heard earlier and as you can see from this timeline, we took the lead on this issue in 2003 when an

overall trend toward teens looking inside the medicine to get high -- medicine cabinet to get high became apparent. Because of our concern, we contracted the Partnership for Drug-Free America and immediately encouraged national monitoring of this behavior along with research to better understand the level of awareness about cough medicine abuse.

We began developing resources to educate parents and caregivers on the issue. Based on what we learned from the research, we focused our initial outreach primarily to parents and to key influencers of teens like healthcare professionals, teachers, counselors, law enforcement officials, and community leaders. We notified government agencies including the FDA and the DEA of our plans to address this issue. We also began exploring legislative tools to help reduce access to teens.

Up to now, most of our programming has been targeted to parents because drug abuse experts including the DEA and the Partnership initially cautioned us against reaching out directly to teens out of concern for over exposing otherwise uninformed teens about the potential for the use of this ingredient. This advice was based on the low prevalence of abuse and the lack of knowledge about the abuse behavior. In fact, we really know much about this

behavior or the abuser. While we heeded this advice in our effort to not inadvertently do more harm than good, we did develop some individual tools for teens and have improved upon these over the years.

Just recently the partners conducted research in understanding the abuse behavior and attitudes and perceptions of the teens who were and were not abusing cough medicine. Thus, we now feel prepared and confident in moving forward with targeted interventions to change perceptions and attitudes about cough medicine abuse. While our program has evolved and is still growing, we have developed a comprehensive abuse mitigation plan to address dextromethorphan abuse.

We created this entire framework based on the specific factors identified by the Partnership for Drug-Free America that were just presented by Steve Pasierb. The elements of the plan are increasing parental awareness of abuse behavior and the risks from the abuse. And importantly, enlisting their involvement in addressing the issue because we know that kids whose parents discuss the risks of drug abuse with them have half the chance of being involved in drugs. Increasing the perception of risk among teens, because 35 years of drug abuse prevention research proves that perception of risk has a significant impact on

levels of abuse increasing social disapproval of the abuse behavior as teens are less prone to abuse drugs that carry a social stigma. And finally, limiting the multiple access points to dextromethorphan-containing medicines by targeting where we know teens and some young adults are getting the medicines, from their home, their friends' homes, retail, and from the Internet.

Each of the evidence-based goals of our program is linked to specific tools to carry them out and tied to specific assessments to measure their success. The assessments are based on measuring the number of people we reach and the changes in their attitudes and behavior with our ultimate goal to reduce abuse in teens by one-third in five years from five percent to three-and-a-half percent.

We know that we first need to change attitudes and perceptions before impacting abuse behaviors. We believe that the elements of our plan will lead to this overall reduction. So let me take you through our plan. As I do, please bear in mind that many of the elements of this plan have been underway for some time. Our first goal is to raise awareness of the behavior and risks among parents and caregivers and importantly to get them talking to their kids about the risks.

Our preliminary research of parents of teens

found that parents didn't have the knowledge of the abuse. They didn't think it was dangerous. And not surprisingly, they were absolutely adamant that this was not behavior in which their own children were engaged. To leverage this important role parents play in their teens' decisions about drugs, we have been utilizing a wide variety of tools to educate parents about this issue and to encourage them and to be involved in preventing abuse in their homes.

We conducted a national survey to get a baseline to assess their awareness and the effectiveness of our programs by measuring the increase in conversations that parents report having with their kids about cough medicine abuse as well as the reverse, what teens report their parents are telling them oftentimes that's different. Regarding parent-teen conversations which we all know are so important in keeping teens drug-free, 42 percent of parents reported talking to their teens about the dangers of abusing OTC cough medicine. Our goal is to increase this percentage almost 50 percent to 60 percent of parents by 2013.

While we do not have a baseline on teen-reported conversations with parents, we will work with the partnership as they monitor this particular aspect. To meet these expectations, we will continue with the tested

and proven elements of our current efforts including our extensive programming, consumer engagements, media outreach, advertisements, town hall meetings, community tool kits, and our comprehensive Websites and partnerships. We developed our programs and materials with leading substance abuse and prevention experts. And we've continued to add new programming and partners each year to widen our reach and evolve our programming as new data has become available.

While we don't have time to discuss all of our programs for parents and caregivers, I'd like to highlight just a few examples of our outreach as well as the resources we have created to raise awareness about this issue. Unfortunately, in the FDA review of our programming and resources that was provided to you in your briefing book, it was terribly incomplete. The review did not mention the content-rich material we have developed over the past seven years including our number one resource where we steer all our consumers, stopmedicineabuse.org.

We originally created this Website in 2007 in order to provide consumers with a memorable URL that communicated a very simple and strong message, stop medicine abuse. The Website highlighted the risks and warning signs and provided resources and materials for

parents to learn more about cough medicine abuse. In 2009, we improved the site with engaging, in-depth information and features about cough medicine abuse and concrete steps that parents can take to help prevent their teen's abuse. Stopmedicineabuse.org also provides access to all of our programs and resources for our various audiences, including parents, caregivers, educators, healthcare professionals, retailers, and even students.

The site even includes information on prescription drug abuse in recognition of the fact that the research points to an overall behavior of teens looking to medicine in general to get high. We also have an active educational partnership with WebMD. As you may know WebMD is the number one resource for health information. WebMD reaches 82.1 million monthly unique visitors which is one of two U.S. adults including three of four U.S. women. In just over a year we have received more than 650,000 individual visitors to our content on the WebMD site.

Our collaborative destination includes original features about abuse, the risks and the warnings, common slang terms, and videos of one teen's history with drug abuse -- with medicine abuse. It also provides parents with information and practical tips about how to detect abuse and what to do to prevent the abuse or address it if

it exists.

We also leverage our partnership with parents through our award-winning Five Moms campaign. We started the Five Moms stopping cough medicine abuse campaign three years ago. It features five real-life mothers who represent a cross-section of America and have experience dealing with this issue in their own homes or in their professional or volunteer work. The purpose of this grassroots online campaign is to get parents involved in our cause of raising awareness of OTC cough medicine abuse and to reach out to other parents with solid, clear information about abuse and its risks.

The messages of Five Moms are straight-forward, cough medicine abuse is real and can touch any family. And parents can take some simple steps to prevent this type of substance abuse in their own homes. Since this program is launched it has reached nearly 35 million parents and is still growing. Many of our materials have been adapted for Spanish-speaking audiences and in fact one of our moms is a Latina who provides messaging directly in Spanish. And to help parents recognize which products contained dextromethorphan our industry voluntarily developed and printed an education icon on their products containing dextromethorphan. The stopmedicineabuse icon instructs

parents to visit our stopmedicineabuse.org Website that I just discussed.

While the heart of our work has so far been focused on parents, we have done some initial work directly targeted at teens on increasing their perception of risk which is our second goal because you have to change attitudes in order to impact behavioral changes. Because the Partnership, through its PATS survey monitors this attitude, we will use its research as our measurement tool. We are very encouraged already from the research of the Partnership for Drug-Free America that shows that teen perception of risk has increased from 41 percent in 2004 up to 47 percent in 2009. We plan to increase our teen-directed outreach substantially. And our goal is to drive this number to 60 percent in the next three years.

Increasing perception of risk is very important as you've heard from Steve Pasierb because it is a key influencer of actual abuse. Research shows that perception of risk in the 50 to 60 percent range have a significant impact on the abuse itself. Some of the tools that are already underway to reach teens through our outreach program with D.A.R.E. America that have directly reached more than one million students and a program with the National Association of School Nurses that just launched

this year is already estimated to have reached almost one-and-a-half million teens. Additionally, with the Partnership for Drug-Free America, we developed an online tool called DXMstories.com specifically to intercept teens and young adults who were searching the Internet for information on how to get high from cough medicine. This site provides information on the health risks of dextromethorphan abuse through real-life testimonials from teens who have abused cough medicine and from their parents and also from those who have not. Because of the information we gained from the qualitative research conducted by the Partnership we are ready to move forward with a more aggressive campaign to influence attitudes directly. We will do this by increasing their perceptions of risk and increasing the social disapproval of abusing cough medicine which we know are the most effective drug prevention strategies.

Increasing social disapproval, therefore, is our third goal. Since this initiative is new and involves information not yet studied, we do not have a baseline yet for attitudes toward social approval. However, we plan to get this baseline next year from both the Partnership and Monitoring the Future surveys and then we'll determine a goal to increase social disapproval by 2013. In the

meantime, now that we understand the abuser and the abuse behavior, we are confident that we can move forward with the campaign to reach out to teens and young adults directly and more proactively than we have in the past. The Partnership has extensive experience with these types of campaigns and we are already partnering with them to develop key components of this initiative.

We already have key insights that demonstrate that unlike other substance of abuse, we have an advantage towards success with dextromethorphan. First, the drug pretty much unsells itself. As we heard from Dr. Schuster's presentation as well as the Partnership's qualitative research, dextromethorphan is a lousy high and those who try getting high with it don't like it and don't continue abusing it. Secondly, abusing dextromethorphan is not viewed by others as cool. And third, dextromethorphan abuse is not a social activity unlike alcohol, drinking alcohol or taking ecstasy. We will use these powerful insights in developing our new programming and believe they will have a significant impact on both current abusers and at-risk teenagers.

Specifically, our outreach to teens and young adults will include both the continuation of what we've already been doing, including our programs in the schools

and in the communities through CADCA AND D.A.R.E. and the school nurses, along with an enhanced and expanded digital platform that will target those who are looking for information about getting high on all drugs. Today's highly specialized web landscape makes it possible to truly target abusers and at-risk teens. Working with the Partnership and other experts, we will design a digital media campaign that will include a new Website to update our current DXMstories and focused on a wider more mature audience and videos created by teens and young adults explaining vividly how sickening abusing over-the-counter cough medicine actually is.

The videos will highlight what happens from abuse such as experiencing nausea, vomiting, blurred vision, and becoming physically impaired. These videos will have a viral functionality to share the stories and the videos themselves. In addition, we will include a major marketing component to this initiative including digital advertising search and social media. We have begun development of this initiative and plan to roll out all these elements early next year.

Because the highest prevalence of abuse is among teens, our final goal is to reduce availability of dextromethorphan to teens through legislative initiatives

as well as encouraging parental monitoring of medicine cabinets. This goal is centered on limiting the multiple access points where we know abusers are getting the ingredient in their homes, in their friends' homes, at retail, and now to a lesser extent on the Internet.

First, after surveillance, identify a problem with bulk dextromethorphan even before the incidents that were cited by the FDA. CHPA took a leadership role in addressing the unique problem of bulk dextromethorphan. Since 2005 we have been urging Congress to prohibit the sale of bulk, unfinished dextromethorphan to anyone not registered with the FDA. And to address access at retail for the last three years, our industry has also been vigorously advocating for a federal age restriction on sales to teens under the age of 18.

Our bulk bill has passed the House of Representatives three times. And we have an age-restriction bill currently pending in the Senate. We encourage both FDA and the DEA to lend their full support to these bills. But because we also know a key access point for cough medicines, all medicines in fact, is right in the medicine cabinet. We need to be vigilant about encouraging parents and caregivers to monitor the medicines in their homes. Our baseline reports that 31 percent of

parents say they monitor OTC cough medicine in their home. We plan to increase this number to 60 percent in three years.

As a result of all the efforts I've just presented, we believe that scheduling of dextromethorphan under the Controlled Substance Act is not warranted. We are confident that the solutions we discussed today will be more effective than scheduling. This conclusion is based on a number of very important factors including dextromethorphan's benefits to public health, a low and flat prevalence of reported abuse from national governmental-sponsored surveys, a limited level of morbidity and mortality based on emergency room visits and treatment center data, and very importantly, more than 35 years of research that tell us research-based interventions are the most effective ways to address substance abuse.

Based on the overwhelming research in this area and advice and support from drug prevention experts, we are confident that the interventions outlined in our abuse mitigation plan are the right and logical approaches and will lead us to a one-third reduction in the abuse of over-the-counter cough medicine. Thus, instead of scheduling, CHPA is committed to continuing to expand our on-going research-based educational interventions urging Congress to

pass legislation for a national age restriction on OTC medicines containing dextromethorphan to prohibit the sale to those under the age of 18 as well as prohibiting the sale of the unfinished bulk dextromethorphan to any party not registered with the FDA, encouraging involvement of national drug abuse surveillance to better reflect issues related to cough medicine abuse, and lastly, supporting medicine abuse as part of the national drug policy agenda.

We thank you for your time and attention to this important matter. And we would be happy to take any questions.

DR. KRAMER: Thank you. I'd just like to talk to the committee about the time. We're supposed to break at 12:30 for lunch. Actually, just a show of hands of how many people have questions for the sponsor?

Okay. I think we're going to have to -- I hate to say this -- we're going to have to postpone the questions to the sponsor until after lunch with one exception, I'm very concerned about something that might be confusing to the committee or even potentially misleading. And that is the repeated reference to the fact that if dextromethorphan were scheduled that it would limit access to legitimate users by requiring them to see a physician to get a prescription. And I think that is very misleading

because it is not synonymous that once something is scheduled that you need a prescription. If this were scheduled, presumably it would be Schedule V, it would not require a prescription even in those states that require a prescription for Robitussin with codeine. There is no indication that this is a widespread, as you yourself have said, widespread subject of abuse such that states would require a prescription.

So could you please clarify that?

DR. SUYDAM: Well, in 18 states, regardless of what the product is, if a product is Schedule V, it is automatically considered prescription. So every product that is scheduled in Schedule V in those 18 states would require a prescription.

DR. KRAMER: Could FDA verify that those 18 states that require prescriptions for Robitussin with codeine also require it for all Schedule V products; is the legal group able to comment on that? I think that's an important -- we just need to understand if we're talking about the implications of scheduling, what the impact to legitimate users would be in those 18 states.

DR. KLEIN: It would not be a result of immediate scheduling under the Controlled Substances Act. The Schedule V doesn't have a prescription requirement.

DR. KRAMER: But I think the speaker is stating that in those 18 states the legislation the state's enacted required that federally-designated Schedule V would require a prescription in that state. It' a question we really need to understand. And maybe we could postpone the answer until after lunch if you want to --

DR. THROCKMORTON: I doubt that we'll be able to get the details. Each of the 18 states may well have specific statutes that differ or something. It'd be unlikely we'd be able to give you a blanket answer to the impact in the 18 states. It's likely they differ slightly.

DR. KRAMER: Even a single state.

DR. SUYDAM: My understanding is that and from experience we've had working in states that when it is Schedule five in those 18 states, it requires a prescription.

DR. KRAMER: But that's different than -- I think we need to know whether the legislation in those states states it that way or if you're experiences driven by Robitussin with codeine -- or codeine-containing products.

DR. SUYDAM: No, our experience is driven by a lot of other issues. And I think Robitussin, by the way, with codeine has not been on the market since 1991. But there are codeine products that are in fact in the

states --

DR. KRAMER: Or Glycoglycaline (ph). Okay.

DR. SUYDAM: -- required by the 18 states to have a prescription. The other thing that Schedule V does is requires that you must access it through a pharmacist which means not only can you not get it at the local grocery store where many people or convenience store, and for people in rural areas where you have significant lack of pharmacies that are open 24 hours a day, you are in fact limited to a pharmacy -- pharmacist interaction, so only when the pharmacist is available to give you that product.

DR. KRAMER: One more thing, if you could look up for after lunch, in your packet on page 18 of 78 in the CHPA briefing packet, you list the number of pharmacies in the U.S. versus the number of retail outlets to the point that you just raised. But those statistics were from 1995. And from my community we're at most intersections there's now three major chain drug stores because once there's one, the other two major chains have to compete at the same intersection. I'd like to know if this number is in any way changed. And I suspect it has changed.

DR. SUYDAM: We can certainly look that up --

DR. KRAMER: Okay. That would be useful.

DR. SUYDAM: with our colleagues at the National

Association of Chain Drug Stores.

DR. KRAMER: Okay. So we'll adjourn for lunch and we have to be back at 1:30 to convene for the open public hearing.

(Whereupon, at 12:33 p.m., a luncheon recess was taken.)

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

(1:31 p.m.)

DR. KRAMER: While everyone's taking their seat, we have had a discussion about balancing being able to ask the questions the panel has of CHPA and yet not wanting to delay the speakers in the open public hearing. And we've made a little compromise, we understand that the speakers in the open public hearing have stated to FDA that they want to hear the morning presentations by sponsors and FDA fully. So what we thought we would do, if it's acceptable to everyone, is take 15 minutes of the session to ask the questions that are pressing of CHPA so that everyone can hear the answers. And then we'll start with the official presentations.

How many presenters?

MS. FERGUSON: There's six total.

DR. KRAMER: We have six presenters in the open public hearing. Is there anyone affected, in the open public hearing that cannot handle that change in schedule?

It's a 15 minute delay. Okay. That will open -- actually we'll just start with this.

MS. FERGUSON: Yeah.

DR. KRAMER: Okay. So for panel members who have questions of CHPA, I'm sorry, I forgot, Dr. Suydam has some answers to the questions we asked before lunch.

DR. SUYDAM: I do. You wanted updated pharmacy data. And from SK&A Market Research firm 2010, the total number of chain and independent pharmacies in this country is now 48,098 which is less than the 55,000 that was in our '95 estimate. And that really is a result of the number of independent pharmacies that have gone out of business over the last 10 years.

DR. KRAMER: Okay.

DR. SUYDAM: The other question you asked was about the percent increase of the growth of the overall over-the-counter cough-cold category. And the numbers we have from 2006 to 2009, the entire sales volume of the category grew 18 percent. As you saw, the FDA figure said 22 percent volume increase in dextromethorphan sales, but that was from 2005 to 2009. So those numbers are fairly, pretty much the same.

DR. KRAMER: Okay. All right. Panel members with questions. We didn't write down everyone who just raised their hands at the end, so you'll have to -- I think I saw -- Almut Winterstein first. And Elaine Morrato. And Allen.

DR. WINTERSTEIN: I have two -- I actually have several questions, but I'll reduce it to two in the interest of time. And I apologize in advance for

mispronouncing your name, Dr. Dicpinigaitis.

DR. SUYDAM: Dr. Dicpinigaitis, yes.

DR. WINTERSTEIN: Could you comment on the ACCP guidelines that were presented to us by the FDA and in particular to the issue related to upper respiratory -- acute upper respiratory tract infections and the negative recommendation for antitussives or dextromethorphan in particular?

And then secondly, kind of try to sketch or describe the population for us that you would think would actually benefit from dextromethorphan in general.

DR. DICPINIGAITIS: Thank you. So the ACCP guidelines were similar to many other guidelines that have published to guide clinicians. And the charge of the committee was to make clinical recommendations based on what was available in the published literature. And as we've already alluded to, there's been major problems with conducting good human cough research mainly because even to this day, for example, we don't have a well-validated commercially available cough counter, for example.

So even now, although we're getting better at it, human cough research is very difficult to do. So the guidelines committee was limited to making the recommendations based on what was in the published

literature. So based on what they found, they did feel comfortable making a positive recommendation for cough due to chronic bronchitis and post-infectious cough for dextromethorphan they just felt that the data in the literature was insufficient to put forth a recommendation for the use of dextromethorphan.

DR. WINTERSTEIN: It seemed to me that there was a negative recommendation. I'm not sure I recall what kind of grade that was, but negative recommendation to me usually suggests that there was evidence against.

DR. DICPINIGAITIS: No, but the wording was negative based on absence of data. And they recommended that good, adequate trials be performed to actually answer the question.

DR. WINTERSTEIN: So who would you characterize would benefit from dextromethorphan then?

DR. DICPINIGAITIS: Well, I use dextromethorphan in my practice. And I deal with chronic, severe olfactory cough. And I do see benefit there. But I see a lot of benefit in acute cough as well. So I think dextromethorphan can be an effective antitussive in a variety of different coughs including cough due to common cold.

DR. KRAMER: So could you just clarify on your

answer, I just want to make sure I understand, so you're saying that although the ACCP said that because there isn't evidence of effectiveness in the common cold, it shouldn't be used, you're saying that because there's not evidence of effectiveness that you're recommending that people use it according to the monograph?

DR. DICPINIGAITIS: My opinion would be that absence of evidence is not evidence of absence of an effect. And, you know, I have to lean on my 20 years of experience using it and I find it an effective antitussive in certain patients.

DR. KRAMER: But you don't -- you generally, in your practice are treating chronic cough.

DR. DICPINIGAITIS: Right. Since I'm the cough guy, a lot of my colleagues and friends come to me with questions. So, you know.

DR. KRAMER: Okay. And the evidence that you have for the common cold?

DR. DICPINIGAITIS: What I do is based on clinical experience and extrapolation from the very solid evidence that I think is there in the database for animals and human-induced cough models, has convinced me that dextromethorphan is undoubtedly an antitussive.

DR. KRAMER: Okay. Next, on the list --

DR. WINTERSTEIN: I had second question, do I get it?

DR. KRAMER: I'm sorry, go ahead. I'm sorry.

DR. WINTERSTEIN: The other question I have is related to the plan for outreach to parents and so forth to reduce the abuse potential. And I was wondering, and I know that this is probably a very difficult question to answer, could you quantify the interventions you are planning in terms of resources that are attached to the staff members funds, whatever, what is the plan altogether?

DR. SUYDAM: First of all, let me say, this is not something we're planning to do. This is something we've been doing for seven years. We've invested resources, significant resources of both the CHPA and significant dollars in the number of programs that we have done already.

I think that our current plan is to get -- we know that from the past we've reached more than a half billion impressions. Impressions are the way advertisers capture who has seen the material. And that's direct contact, it's publications, and it's media impressions. The current program, we expect to add another 50 million parents and caregivers impressions every year for a minimum of the next three years. And we think that plus the way to

reach the goals is to have a comprehensive program which is what we have now in place. And the dollars are in the millions that we have spent already. And we will spend more.

DR. KRAMER: Okay. The next person on the list is Mary Ellen Olbrisch.

DR. OLBRISCH: You're proposing to make an age restriction on who can purchase this. But I take it you're not planning to put this product out of reach? You want the consumer to be able to get it off the shelf just as they do now?

DR. SUYDAM: That's correct. We are proposing that you cannot buy it if you're 18. What would happen, you would be -- they would scan it, and they would ask you for an ID if you looked like you were under 35.

DR. OLBRISCH: Have you considered investing more in anti-shoplifting technology since that seems to be a method by which a lot of teens are acquiring this product?

DR. SUYDAM: Actually, that isn't necessarily true. The data don't show that cough medicine is any more significantly stolen than any other product in the drug store.

DR. KRAMER: Next on the list is Elaine Morrato.

DR. MORRATO: Yes, it's actually a follow-up

question with regard to the legislation. So I agree in terms of your goals of limiting access to teens. I was wondering if you could give us an assessment, if you will, on the likelihood of the legislation that's being proposed of actually passing by 2012 on being restrict access to dextromethorphan and its bulk unfinished form has been advocating, as you mentioned, since 2005. It's passed the house three times in 2006, seven, and nine.

DR. SUYDAM: Yep.

DR. MORRATO: And it's still, I guess, with the House. and then for the second piece of legislation in terms of restricting access since we've been talking to underage teenagers, what do you view is the Congressional outlook of that given the fact that it seems to be, I guess, sitting within the Senate judiciary committee? And the reason why I ask this is I would guess that maybe a democratic administration would be more open to some of these things than maybe a republican, and if we haven't seen passage in the last couple of years what gives more confidence in the future?

And then for the restricting access to age, you mention also that there's voluntary efforts occurring at retailers right now. And perhaps you could give us, if you have any information on the percentage of sales that are

covered by those voluntary retailers.

DR. SUYDAM: Okay. Let me answer the first part. I obviously I'm not going to be giving you an exact answer about whether I think this can pass or not. I think it can pass. I think we have a good chance to have to have it passed.

The Senate has obviously been engaged with a lot of other activities in the last year like healthcare reform and finance reform and Supreme Court nominations and they seem to be somewhat paralyzed by their polarization of the parties. But we think this is a bill, if we get additional support, I mean, we're putting a lot of people on the ground in Congress to speak about this, all of our companies are using their people to go in and speak to various congressmen and senators about it. And if we get support from the FDA and the DEA, I think we will have a better chance of getting this bill passed in the next -- in this Congress because I think that's key is to get it passed this year.

DR. MORRATO: And on the question about how many voluntary retailer --

DR. SUYDAM: We know that many of the major chains, the chain drug stores have implemented voluntary, I know three of the major chains have introduced voluntary

age restrictions. So that's a fairly large number of specific drug stores when you're talking about Walgreens and CVS and RiteAid. But you're not picking up all of the convenience stores, the big box stores, those kinds of places were, you know, we can in fact make a big difference if we have that in place.

DR. MORRATO: So are there any efforts by CHPA to try and expand more voluntary participation given leverage with those outlets?

DR. SUYDAM: We have encouraged the chains to move forward with voluntary age restrictions. It's a little more difficult with the independent, but we have worked with them as well.

DR. KRAMER: Okay. Moving on, Lewis Nelson.

DR. LEWIS NELSON: Just two questions, one for Mr. Pasierb, is that how you say that, sorry. On slides 57 and 61 you give these key abuse reduction strategies which include parental involvement, perception of risk, and social disapproval which all do make sense, but I guess, that's all been done for things like the prescription opioids, right, and it seems like the abuse of those substances is continuing to rise.

MR. PASIERB: Actually, prescription opioids have a very low perception of risk. Most teenagers do not

believe them to be addictive in the research, most parents actually reflect that they're relieved. So when you look at the opioid category, you have low perception of risk, you have low social disapproval. We have high media noise, but that has not translated down into shaping those behaviors among kids.

DR. LEWIS NELSON: Right. And actually, that's what I'm asking. In other words, we've tried to instill those things into people.

MR. PASIERB: I don't think we have. I don't think we have as a nation, I really don't. We talk about individual drugs, but we haven't really talked about it. And we have done some things, the Office of National Drug Control Policy started and then stopped. So I don't think we're anywhere near there. That's why actually the last part of my presentation was that really needs to be our focus. We need to wake the whole country up.

DR. LEWIS NELSON: Okay. And just to correlate that for Dr. Suydam is --since you've been doing this work with PDFA and other groups since 2003, including some of this type of work, do you have any data to support that it's actually working?

DR. SUYDAM: Well, I think there are a number of points. One is, you know, our program has evolved over

time. We started with parents in a relatively small way and have continued to expand that particularly with our Five Moms program and our stop medicine abuse program. What we do know, and I think it's very clear, that there were a lot of people who thought this problem would explode. And it hasn't. And even Lloyd Johnston from Monitoring the Future actually commended us for our prevention programs in 2008 because it appears -- slide on -- as he said, it appears that attempts to discourage the misuse have proven somewhat successful.

So we think we've made a difference. We also know that we have had an impact in that generally the abuse numbers are flat, but they're trended down in two of the three age groups, we know that the perception of risk is increasing, and we know that parental awareness is increased.

So every year we have more programs, more data, and it's more sophisticated. And we think we are having a direct impact.

DR. KRAMER: I think we're going to have to interrupt our questions. We still have people on the list. We will get to you after the open public hearing. We really need to move on so that we don't inconvenience the speakers.

So first, I'd like to read a statement from the FDA. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation. For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, with its direct competitors.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in

their consideration of the issues before them. That said, in many instances, and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chair. And thank you for your cooperation.

Am I correct that at the end of the designated time the microphone will shut off?

MS. FERGUSON: Yes.

DR. KRAMER: And how long does each person have?

MS. FERGUSON: The first four have 10 minutes.

DR. KRAMER: All right. So the first speaker is John Coleman.

MR. COLEMAN: Good afternoon. My name is John Coleman. And I'm President of Prescription Drug Research Center in Fairfax, Virginia. In terms of my potential conflicts of interest, I have worked, I have provided consulting services in the past for two companies, Novartis and Johnson and Johnson who are makers and distributors of dextromethorphan products. However, I'm here today, my appearance here today is at my own initiative and my own expense.

I would like to, if I could, recap some of the findings from the materials that were distributed before the meeting as well as the presentations from this morning. First of all, the abuse of unfinished pure dextromethorphan occurs and it can be fatal. And we heard a very comprehensive and excellent detailed description of that from Dr. Bonson this morning and one of the things she did not mention, but I will, is that the company, Chemical API in Indianapolis was quickly and summarily put out of business by the FDA Office of Criminal Investigations. It conducted an excellent investigation, identified the owners of the company, prosecuted them for introducing mislabeled drugs in interstate commerce. And they are now in custody doing time in a federal penitentiary. So I think that that was a commendable action.

The second point I would like to make is that the abuse of finished dextromethorphan products is indeed a phenomenon that affects mostly teens and young adults. And we heard this from several presenters this morning. And the third I'd like to make is that the Adverse Events Reporting System and the National Poison Data System both show that abuse outcomes are mostly minor to moderate.

In 2008, for example, the published information from the National Poison Data Center indicated that there

were about 52,000 exposures reported for dextromethorphan, approximately 24,000 of those were, excuse me, people under the age of six, persons under the age of six. So they're really not necessarily abuse cases per se. Of the remaining cases, those that had reported outcomes, most fell into the categories of minor to moderate. There was only one reported death in 2008 from dextromethorphan according to the National Poison Data System.

Now while the OTC sales of dextromethorphan products increased 19 percent as you heard from the presenters this morning between 2005 and 2009 the DAWN emergency department visits for dextromethorphan during the period of '05 to '08 increased only five percent. So we don't have a direct correlation here between the increased sales of dextromethorphan and the increased emergency department mentions.

Now the ratios of mentions of dextromethorphan to sales volumes are low the abuse is not widespread but concentrated among young people and young adults and is consistent with ratios and levels that are observed with other non-scheduled drugs.

Now in terms of recommendations that I would recommend would be that first of all, improved public and private educational programs designed to deter or prevent

dextromethorphan abuse. We've already seen wonderful presentations of these types of educational programs. We know that they work. We suggest and recommend that they be expanded.

The second would be to prohibit commerce in unfinished dextromethorphan except for bona fide pharmaceutical purposes. The third would be required age verification for retail sales of dextromethorphan finished products. Now these three recommendations should reduce or eliminate most dextromethorphan abuse without restricting access to an effective safe medication that has been used responsibly by millions of persons each year.

Now we heard a little bit about the pending legislation, let me go into a little bit more of that in detail. There are two bills, one's in the House and one is in the Senate. The first would prohibit commerce in unfinished dextromethorphan except among persons registered to engage in the practice of pharmacy, pharmaceutical production or manufacture or distribution of drug ingredients. That's the House bill.

The second would be to prohibit retail and Internet sales of finished dextromethorphan products to individuals under 18 years of age. That's in the Senate bill. The third would provide federal grants for

community-wide educational strategies to prevent the abuse of prescription drugs as well as non-prescription drugs including dextromethorphan.

Now the House bill was passed by the House on 3/31/09. It's been referred to the Senate Committee on Health, Education, Labor, and Pensions. And the Senate bill has been referred on 6/25/09 to the Senate Committee on the Judiciary.

Lastly, I'd like to say that the FDA and the DEA cannot lobby Congress on behalf of legislation. It's a violation of the law. However, this advisory committee is free to urge passage of these bills as part of its recommendations. And I would so urge and so recommend and advise.

Thank you all very much.

DR. KRAMER: Thank you.

The next speaker is Zak Zarbock.

DR. ZARBOCK: Good afternoon. I have no financial sponsorships to disclose. And I am here on my own dime. As mentioned, I am a physician, a pediatrician currently practicing in the state of Utah. I completed my medical training at the Ohio State University and then my pediatric residency at the University of Utah in Primary Children's Medical Center in Salt Lake City.

Today I hope to provide the perspective of a community pediatrician with regards to both the potential misuse and abuse of dextromethorphan in young children and adolescents. As we now know, the dangers of dextromethorphan when used inappropriately are well-documented and potentially life threatening. Further, the use of dextromethorphan in children has been questioned in multiple clinical trials and shown to provide little benefit for the relief of symptoms when compared to placebo.

We are also well aware that both the recreational use and accidental misuse of products containing dextromethorphan are a significant public health risk. In the pediatric community in the state of Utah, this has been and continues to be a very concerning trend to my colleagues and me. We see firsthand the dangers and potential harm imposed on our patients as well as confusion among parents concerned about what to give their children.

While many over-the-counter products containing dextromethorphan continue to have confusing and misleading labels and while they’re easy access to adolescents for recreational abuse is not better controlled, we are not safe.

Recently in our community, like many areas of the

country, several products containing dextromethorphan were moved behind the counters. This was an effort to curb both theft and abuse as an increasing number of teens in our area abusing these medications and putting themselves at significant risk for the perilous side effects. Personally, I have the unfortunate opportunity of caring for a 16-year-old male in the pediatric ICU at Primary Children's Medical Center who was the victim of Robo-tripping gone awry.

Thankfully for this young man he survived but there are many others who have not. This and other experiences have sparked my interest in helping to eliminate risk and providing safe alternatives for our youth. This problem continues in our state as local poison control agencies are fielding hundreds of calls with regards to dextromethorphan. In the state of Utah last year the Poison Control Center received approximately 200 calls relating to intentional abuse of dextromethorphan. This number is certainly not representative of the overall problem because most instances of abuse likely go unreported.

However, possibly a larger problem is encompassed in the 750 calls for unintentional misuse of dextromethorphan including many by parents who accidentally

overdose children because labels are not consistent and can be misleading.

So the question remains as to how we fix the problems at hand. With regards to the abuse potential, in my opinion requiring prescriptions for these medications would put an unnecessary burden on the healthcare society. While their efficacy in children is debatable, products containing dextromethorphan when given at recommended doses have relatively few side effects and don't merit this sort of regulation. Instead I would also vote for a minimum age requirement to purchase products containing dextromethorphan.

I would propose at a minimum age 18 or possibly higher given that it has been reported that nearly six percent of twelfth graders still admit to abusing cough medicine to get high within the past year. Alternatively, these products could be placed behind the counter. However, as has been discussed, this may not always be feasible in many grocery stores and smaller pharmacies. Limiting the number of items containing dextromethorphan that can be purchased at any one time may also help cut down on abuse.

With regards to the use of dextromethorphan in young children, this is another problem that has been

addressed in the past but certainly merits additional attention. As mentioned previously, Poison Control Centers in Utah received nearly four times the number calls for misuse in young children. We need to do more to ensure their safety. Labels continue to be confusing as some read, "Consult a doctor for use in children between the ages of four and six," leaving parents to guess a dose in the wee hours of the night.

Several others already eliminate the guesswork by stating, "Do not use in children under the age of six." Given the potential for harm and the lack of clinical -- of efficacy in children, there is no good reason to put our children in harm's way. We need to standardize the age of use to at least six years of age and make labels consistent. This regulation will mirror what has already been done in other countries including Great Britain, Canada, Australia, and others.

This proposed regulation is possibly even more important for the multi-symptom products containing several active ingredients. In an attempt to help calm a coughing child in the middle of the night, tired parents often reach for whatever is available in the cupboard as long as it is different than what they've already been given. They will try another product and by so doing put their child at risk

of excessive amounts of previously-dosed ingredients. These products should call out that there are several active ingredients that should not be combined with other cough, cold, allergy, and flu medications.

Some have also argued that imposing further age restrictions on cough and cold medicines will create more problems by giving parents fewer options and encouraging them to use small doses of adult medications. We as healthcare providers need to provide solutions. In a recent study, Dr. Ian Paul at Penn State University clinically showed that the administration of buckwheat honey was superior to dextromethorphan in children two to 18 years of age in the reduction of coughs associated with upper respiratory tract infections. His research has also shown no clinically significant benefit with dextromethorphan in children in two randomized placebo-controlled trials in 2004 and 2007.

I have taken this research personally a step further by creating a buckwheat honey cough syrup that is now available in thousands of grocery stores and pharmacies including every Walgreens across the country. The product is called ZarBee's Children's Cough Syrup. And it is one of a few safe alternatives that will allow parents to use an effective remedy without putting their children's health

in jeopardy. I feel the FDA would do well to provide information to parents about safe alternatives and to clearly standardize restrictions in labels to eliminate any confusion.

In conclusion, we as healthcare providers, law makers, and parents need to provide safe alternatives for our patients and our children suffering through symptoms related to irritating coughs, colds, and flu. We need to better regulate the availability of potentially harmful products from the hands of our youth by increasing the age of purchase and where possible restricting their access for potential theft.

And we also need to standardize labels that increase the age of use to at least six years of age without any ambiguity so caregivers have no question about how to safely dose medications for the young children. Thank you.

DR. KRAMER: Thank you.

The next speaker is Becky Dyer.

MS. DYER: Good afternoon. My name is Becky Dyer. I'm one of the Five Moms from the Five Moms Campaign. The Consumer Healthcare Products Association does compensate me for my expenses. But they do not compensate me for my time.

Obviously I'm in law enforcement. I'm from Hutchinson, Kansas, and a pretty small community of about 45,000 people. I'm also a D.A.R.E. officer and a patrol officer. I'm a little nervous. You guys are a little bit different than my usual crowd of, you know, a community of 1,000 and maybe 20 people show up for PTO meeting, but I appreciate the opportunity to be here.

I know you've already been briefed on the Five Moms Campaign. It's something I'm very passionate about, something I've taken very personable to continue on. I kind of stand up here and hold many different hats, the obvious law enforcement. I am a mom to a six-year-old son. And I have a big responsibility within my community on educating kids about the dangers of drugs, making good choices through the D.A.R.E. that has enabled me to be in our schools to talk to the kids about the dangers of drug abuse.

Recently D.A.R.E. has added a supplemental program on safe medicine use and that was a great opportunity to kind of touch on this topic that we're here today for with the kids. And I was really surprised at the stories that were told to me in class on the practices at home when it comes to medicines. We had great conversations with the kids and obvious that there's a lack

of education within the homes of any kind of medicine, prescription or over-the-counter.

Through the Five Moms Campaign it has enabled me to reach out to parents which is very hard to do as law enforcement, as an educator when it comes to substance abuse. The Five Moms Campaign was launched in May 2007. It has myself included and four other moms from all over the country. We all have different jobs, but we all have the same passion of sharing this information with parents whether that is through the Internet, through media outlets, through word of mouth, sitting, you know, having coffee on a Sunday morning, you know, talking to our friends about the dangers of cough medicine abuse and what we can do to educate our parents, our friends, our grandparents, and kids about the abuse itself.

And it's funny when I became involved with the Five Moms Campaign, right around that time we had a young person overdose on a product in my community and that was the first time I had ever heard of this type of abuse. So I thought to myself I'm in law enforcement, I'm an educator, if I don't know about this, think about all the parents out there that don't know as well. So when I heard about the campaign I was very excited to get involved because I knew there was a lot more people out there that

were kind of ignorant to this type of abuse.

The Five Moms I believe has been very successful. We've had a lot of media outreach. Our Website, stopmedicineabuse.org, has been also successful. And it's been very simple goal of ours to stop this type of medicine abuse. We have a lot of shared conversations online. We've reached over 35 million people through Internet, through our interviews we've done on television, through newspaper. And then we've taken what we've learned and what we've experienced and have talked to other families, other parents, and we take them back to our own communities. We talk in our churches. I'm on the radio at least five, six times a year, especially right around cold and cough season because I want to get this information out there to the people that I serve in my community.

And I, you know, get a lot of phone calls that come back. And there's just a lot of people out there that really want to hear about this. They have no idea. I also sponsored a town hall meeting which was pretty successful. We had about 60 people come. And once again, hearing, you know, the questions that the parents had, the educators, the doctors that were there just made me realize even more that education is what we have to continue about any kind of drug abuse and specifically, I think, cough medicine

abuse because I think the parents out there don't see it as a problem and the kids out there don't see it as a danger.

So through our campaign we have definitely, I think, made a difference. And we hope to continue that difference so that maybe we're not here in five years still talking about this because I think it's possible.

Our mission with the Five Moms Campaign has been very simple when it comes to our message and that is to encourage parents to educate themselves about the problem, what kind of signs to look for, talk to their friends about it, and talk to their kids. And that is what seems to not happen in a lot of things when it comes to parenting, especially with what I deal with on a daily basis at my job. Talk to your kids about the dangers of any drug abuse and what we're here to talk about today.

Through the Five Moms, we can also provide educational materials through -- to schools, to different community groups, and give them the signs of what to look for within their own homes, how to make their own homes safe, how to safeguard their medicine cabinets, and have those important conversations with their own kids. So we've been very successful with that.

My other that I guess I have on today is that I'm a mom. My son has autism and some other health issues.

And boy, when he has a cold or cough, I think we've all experienced that before with your kid hacking in the bedroom at 11:00 o'clock at night and needing to provide them relief, I mean, we've all -- I've used it, I certainly feel safe to give it to my son. And you know, I hope that continues.

One quick story is my son's on a handful of different medications for various reasons. And one time I told him I didn't feel good. And he said, "Mommy, just take my medicine." And he's six. And I took that opportunity to explain to him about how medicines work and the dangers of sharing. So that is another message that we as a whole need to get out there to all of our schools and our kids is that sharing medicines is not safe or abusing them in great quantities. So I took that opportunity as a young, you know, my young little kid to start there. And that's another thing I really push with my parents is that, you know, you're never too -- they're never too young to start educating them about safe medicine use because medicines work as long as we use them safely.

Through law enforcement we deal with a lot of different topics. Seatbelt usage, you know, wrecks are, in my community, are up this time of year for some reason and we have a lot of fatality accidents. So what do we do? We

go out into the schools, we educate them about the dangers of texting while driving, wearing your seatbelts, that's all through education. Drinking and driving, same thing, it's all about education. And I feel, as a nation with this problem that we're seeing is that we haven't done enough. With the campaign that we have, other programs that are out there, I think if we kind of add our resources together, you know, I think this can be accomplished.

I don't want to see this product removed from the shelves as a consumer. As a law enforcement officer, I want to go out there, encourage other officers, other educators, other people like yourselves to go out into your own communities and talk about this because I think education is really where it's at. And I think we're doing a good job so far.

I'm about running out of time. I didn't think I'd talk even five minutes, but here I go. So another aspect of why I wanted to be here today is that healthcare costs are rising, health insurance is rising. As a single mom, my deductible that I just found out a couple weeks ago is going to be $5,000 out of pocket what my county is offering. Or the option is higher premiums. So for me, taking my child to the physician for a $90 doctor call to get a prescription for something I could buy off of a shelf

is just not practical. And I think you're going to see that, not just what I'm saying but all around the country on what we're facing in years to come when it comes to healthcare.

So that's another point I kind of wanted to address as a single parent working, you know, paycheck to paycheck. And I think I probably represent a lot of people out there.

So thank you for your time and I think I'm done.

DR. KRAMER: Thank you.

The next speaker is Kevin Nicholson.

MR. NICHOLSON: Good afternoon. I'm Kevin Nicholson, Vice-President and Government Affairs and Public Policy for the National Association of Chain Drug Stores. I have no financial relationships to disclose.

NACDS represents 140 companies, traditional drug stores, supermarkets, and mass merchants with pharmacies from regional chains with four stores to national companies. Our members fill nearly 2.6 billion prescriptions annually which is more than 72 percent of annual prescriptions in the United States. I thank you for the opportunity to share our perspectives on the abuse potential of dextromethorphan and public health benefits and risks of this ingredient as a cough suppressant. NACDS

is committed to pursuing effective strategies to help prevent the abuse of both prescription and over-the-counter medications and the devastating effects of such abuse on people's lives and on society. With an emphasis on the pursuit of effective strategies, we do not believe it would be appropriate dextromethorphan under the federal Controlled Substances Act.

Scheduling dextromethorphan is not warranted and could lead to substantial negative impacts upon consumers. We believe more effective alternatives to scheduling exist. As we have heard today, dextromethorphan is the most common ingredient in over-the-counter cough medicines in the United States. It was approved by FDA in the 1950s to replace codeine in cough syrups to prevent codeine abuse. When used in therapeutic doses, dextromethorphan produces very few side effects and has a decades-long history of safety and efficacy.

Although dextromethorphan is an inherently safe substance, there are incidence of individuals taking massive doses such as 25 times or more of the recommended dose to receive, excuse me, to achieve hallucinogenic and similar effects. This abuse of dextromethorphan is not widespread among all age groups. It is concentrated primarily among teenagers. And this concentration makes

possible a targeted approach and strategic approach to preventing abuse.

To address this, for example, we have supported federal legislation that would prohibit the sale of dextromethorphan to minors. In fact, a number of our member companies already have policies that impose age restrictions on the purchase of dextromethorphan. It is also important to note that abuse of prescription and non-prescription medications commonly found in the home -- found in home medicine cabinets is a problem somewhat unique to the current generation of teenagers.

We expect the abuse of these products by teenagers to wane over time both as a result of the successes from educational and similar efforts to reduce abuse and as the novelty abusing these products diminishes. NACDS has worked with entities ranging from the White House Office of National Drug Control Policy to the Drug Enforcement Administration to help raise awareness of the scourge of medication abuse particularly among young people.

Unlike most controlled substances, withdrawal, tolerance, and physical dependence are not issues with dextromethorphan. This is consistent with research among substance abusers which shows little recurring abuse of

dextromethorphan. We are unaware of any reports of dextromethorphan products being illegally diverted from the supply chain for abuse purposes.

We are aware, however, of reports of isolated incidences of teens purchasing unfinished, bulk dextromethorphan as a drug for abuse. Because unfinished dextromethorphan can pose a greater risk given unknown doses and an ability to take extremely excessive amounts, NACDS has supported legislation before Congress to make the illicit distribution of unfinished dextromethorphan illegal.

We believe that the federal legislation we have supporting affecting both dextromethorphan products and unfinished dextromethorphan powder are more effective alternatives to scheduling dextromethorphan as a controlled substance.

Since teens are the primary abusers of dextromethorphan, policy initiatives should focus on how best to address teen abuse in the most effective and least disruptive manner possible. Scheduling dextromethorphan would cause unnecessary increases in healthcare costs. Dextromethorphan is consumers number one choice to treat cough. Depriving consumers of the option to self-medicate with dextromethorphan would have substantial public health

consequences because cough and cold are extremely prevalent in the U.S. population affecting the average adult two to four times per year.

Cough poses a significant health burden on individuals who would like seek alternative treatments. Most consumers rely on self-care to treat these relatively low risk, but potentially disruptive health conditions. If dextromethorphan were to become a controlled substance, consumers would likely respond in one of three ways, one, consult a practitioner to obtain a prescription medicine; two, choose another OTC medicine such as diphenhydramine or codeine; or three, leave their condition untreated.

Forcing consumers to seek a practitioner to obtain a prescription would dramatically raise healthcare costs. These increased costs would arise from increased administrative burdens for scheduling visits, conducting consultations, and handling additional prescriptions. A side cost would arise from the increase in physician visits as patients would also expect to receive prescriptions for antibiotics to treat their conditions which are ineffective against viral infections.

All of this would lead to unnecessary higher costs to healthcare payers in both the public and private sectors. Moreover, consumers would endure the additional

costs of physician office visits and time away from work to accommodate the office visits. Consumers without a primary care provider would have the burden of seeking one out, but would more likely end up in the emergency room adding to healthcare costs.

For consumers who pursue another OTC cough suppressant, there really is no practical alternative. The only other FDA-approved over-the-counter cough suppressant available in the U.S. is diphenhydramine which causes drowsiness. Diphenhydramine is commonly used as an over-the-counter sleeping pill. This somnolescent effect renders diphenhydramine an unsuitable alternative.

In many states, codeine is available without a prescription in limited quantities. A greater number of consumers turn to codeine whether OTC or prescription would likely lead to a greater abuse of codeine a substance that is well known for being potentially addictive and for which abuse already commonly occurs. People who suffer from cough and cold condition untreated are less likely to be less productive at work and less likely to endure a reduced quality of life as well as experience related negative impacts on work and private activities.

I would like to add that we discourage a behind-the-counter or a Schedule V requirement for

dextromethorphan. Due to space limitations, such a provision would severely limit product variety and consumer access as space is already limited to accommodate pseudoephedrine products.

Theft of dextromethorphan products has not been a major problem for our members. A better approach to prevent abuse would be an age restriction. We believe that it would not be appropriate to subject dextromethorphan to scheduling under the Controlled Substances Act it is not an addictive substance. Its abuse is limited to a teenage subculture. And such abuse is dissimilar from the types of abuse we find related to Schedule I through V controlled substances.

Its abuse appears to be a related to peer pressure and novelty as opposed to physical addiction. There's insufficient evidence that the abuse or potential abuse of dextromethorphan constitutes a public health and social problem warranting scheduling. However, potential impacts from scheduling would affect most consumers in a significantly negative manner both individually and at the macroeconomic level.

We thank you for the opportunity to share our views on the legitimate uses of dextromethorphan and the impacts of potential scheduling changes on this cough

suppressant medication. We urge the committee to recommend against the scheduling of dextromethorphan as a controlled substance. Thank you.

DR. KRAMER: Thank you.

The speaker is Bob D'Alessandro.

MR. D'ALESSANDRO: Thank you. Good afternoon. I appreciate the opportunity to speak before you. I was so afraid that you would shut the mic off after five minutes that my comments will be very brief.

As you said, my name is Bob D'Alessandro. I'm the founder and the president of the Center for Applied Prevention. I traveled here today at my own personal expense. I first became aware of dextromethorphan abuse in 1988 while I was working for Governor Roy Romer to design a statewide community-based drug abuse prevention program for the state of Colorado. I was an invited speaker at the first FDA advisory committee hearing on dextromethorphan abuse in 1990. I was also an invited speaker at a state level FDA advisory committee meeting on DXM abuse in Harrisburg, Pennsylvania, in 1991.

Since 1988 I have served through the Center for Applied Prevention and through another substance abuse prevention organization of which I was the executive director as a consultant and an advisor to several

pharmaceutical companies specific to their role in preventing DXM abuse. I served in a similar capacity to CHPA several years back when they were conducting a retroactive study of Poison Control Center data through the test database and in the early development of their DXM prevention program. And I was an unpaid advisor on a couple of occasion to PDFA the Partnership for a Drug-Free America both on a prevention of DXM abuse and many, many years ago on the issue of inhalant abuse.

Since 2009, the Center for Applied Prevention has been operating a DXM call center providing information, referral, and technical assistance to callers specific to the issue of DXM abuse through a grant provided by the Pfizer Pharmaceutical company. Over the past decade, I have spoken to literally hundreds of DXM abusers personally, to parents, law enforcement officers, educators, and community drug prevention advocates regarding the issue of DXM abuse. This experience validates most of what has been presented here today regarding the prevalence and characteristics of DXM abuse and its abusers.

Why am I here? I mentioned that I came here at my own personal expense. And I think I came here for myself. I've spent the last 35 years trying to bridge the

gap between research and science regarding the issue of drug abuse and its prevention and the application of such research and science at the local, state, and national level.

Obviously, I'm near the end of my career not at the beginning. I question whether I've made the best use of my time as prevention of substance abuse today as it was 35 years ago is driven not by science but by other factors including politics and ideology. I'm here today because I see an opportunity to change this trend for the better. And to make a lasting impact on how we address substance abuse problems from here forward.

I believe that the program described by Mr. Pasierb will have a direct positive effect on preventing DXM abuse among adolescents. I also believe that scheduling DXM will have little, if any, impact on the problem. You may ask yourselves, why not do both and just hedge our bets. It's a good question, but I believe that there are unintended consequences of such an action. By addressing DXM abuse as a supply problem, you perpetuate the myth that the product is the problem and that by limiting supply you can solve the problem.

Such messages also unintentionally diminish the important role played by parents, educators, community

organizations, and those that involve youth directly in positive pro-social activities. Closing, I believe, the comprehensive program described by Mr. Pasierb and Ms. Suydam is a model of the best practices to date in addresses abuse of pharmaceutical products and that the metrics it will provide through its careful monitoring and evaluation will prove to be a significant demonstration for addressing all substance abuse issues in the future.

Thank you, and I appreciate your time.

DR. KRAMER: Thank you.

And our last speaker is Robert Sosnowski.

MR. SOSNOWSKI: Hello. Thanks for having me this afternoon. I'm here -- the only conflict of interest I would say at this point in time is I was a founder and CEO of a company called DexGen Pharmaceuticals. We launched a single-agent dextromethorphan product in the early 2000 range. It currently is not available in the United States. I do still hold intellectual property and some patents on the combination use of dextromethorphan and other NMDA receptor antagonists with methylators for the treatment of home-assisting related diseases.

Let me start. My name is Bob Sisnowski. I was founder and CEO of a small pharmaceutical company in New Jersey called DexGen Pharmaceuticals. In 2001, the company

launched their first product, dexalone. It was the first single-agent dextromethorphan hydrobromide, gel cap, 30 milligram available in the United States. Our company's marketing plan was to focus on special needs populations, specifically oncology patients with metastatic cancer cough and elderly patients on multiple drug therapies.

We felt the need for a single-agent, easy-to-swallow product was quite evident in these types of populations. We soon learned about legitimate off-label uses by physicians who cited certain studies regarding the efficacy of using dextromethorphan as an NMDA receptor antagonist as an adjunct to opioid pain medication to reduce tolerance and increase efficacy for treatment of peripheral neuropathies and its use in supportive care to reduce CNS toxicities in high-dose methotrexate therapy in pediatric leukemia patients.

We also quickly learned about the abuse of dextromethorphan especially by children and young adults. Soon after our products launched, we received a phone call from someone who purported to be an owner of several Pickwick stores on the west coast. The gentleman wanted to know how much product could he buy for $10,000. He said he could wire the money overnight. We informed him that we do not sell direct and that he could place an order with his

wholesaler via Cardinal, McKesson, AmerisourceBergen. His ignorance of the standard operating procedures regarding the procurement of OTC and effical pharmaceutical products made us very weary and we began to do some research.

That research led us to understand the illicit demand for dextromethorphan on certain Internet cites including aerowit, DXM, dextroverse, I would encourage you all to look at these, which focused exclusively on robo-tripping, a term named after dextromethorphan product, Robitussin. These cites claimed to promote safe, recreational use of dextromethorphan and provided tips such as how to extract dex from combination products and how to avoid overdosing on dex. These cites also claimed to be doing a public service by advising users not use Coricidin HBP because of the potential that chlorpheniramine maleate, an ingredient in combination products, can cause death when abused.

When our research indicated that these cites were specifically mentioning our product's name, dexalone, we became very concerned and immediately adjusted our marketing to safeguard against potential dangerous abuse. These marketing safeguards included the following: we actively promoted keeping dexalone behind the pharmacy counter, we felt abusers would be less likely to purchase

dexalone if they had to ask a pharmacist for it; we promoted dexalone to physicians as an effical OTC, a term we use to try and differentiate the product and made physicians, pharmacists, and consumers aware that its use should be monitored.

We developed an ethical OTC information pattern provided to physicians so that pharmacists could see the physician had prescribed dexalone for a specific reason to benefit a specific patient. We specifically designed what some would call dull and unappealing packaging which worked for us and the precautions we hoped to promote. We ran mass e-mail and FAX campaigns advising pharmacists to stock dexalone behind the counter to avoid potential abuse. And we did this several years before it was required for products containing pseudoephedrine, a move we wholeheartedly endorse and applaud.

Our market research indicates that at least 80 percent of our business was generated by physician prescriptions. And we're extremely proud of that. Our product was available via the Internet pharmacies such as drugstore.com. We had no way of determining where those sales came from. However, as a credit card was required for purchase, our hope was that minor children would not be able to get it. In 2003, as part of a financial decision

we licensed the product to another company who marketed it until 2008. Dexalone is no longer available in the United States, but we recently reclaimed our marketing rights to it.

We now explain the possibility of relaunching dexalone. If we do decide to do that, we would again market the product in the same responsible manner --

DR. KRAMER: Could we turn the speaker on for a second because we have one speaker not coming? Just hear the end.

MR. SOSNOWSKI: -- if we decide to do that, we would again market the product in the same responsible manner and promote that pharmacies keep it behind the counter and sell it based on physician recommendation. At DexGen, we wholeheartedly believe that the companies -- the product's efficacy and safety when used properly and under a physician's care, that it was safe and effective. A single-agent dex product is free of alcohol, antihistamine, lactose, and is safe for a wide variety of patients.

In 2001, the *Journal of the American Pharmaceutical Association* chose dexalone as one of the top OTC products launched that year for its safety, efficacy, and convenience.

I'm here today as a former manufacturer who has

first-hand knowledge of, as well as a professional stake in you decision, to encourage the advisory panel to consider the serious abuse potential of dextromethorphan and the danger it does present to our children. If you're not ready to require making it a prescription product, please consider requiring the same regulations for its purchase as you did for products containing pseudoephedrine.

I'd like to applaud the organizations that are here today for informing the community about the dangers of dex abuse especially the Partnership for a Drug-Free America.

In conclusion, I just want to share a short story with you. When I was leaving last night to come here, my 16-year-old son asked me why I was going to Baltimore. I told him I was going to speak to the FDA about dextromethorphan abuse. I said to him, I said, "Do the kids in your high school abuse dextromethorphan?" He said no. I said you mean no one ever talks about, like, robo-tripping or, you know, things like that in your high school.

He said, "Oh, yeah, dad, lots of kids suck down cough medicine to get high." So for Kenny and all the kids in his high school and the kids across the country, I just ask the panel to limit kids' access to dextromethorphan.

Thanks.

DR. KRAMER: Thank you very much.

Okay. The open public hearing portion of this meeting has now concluded. And we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

So what we're going to do is before we get to the actual questions, we're going to try to address the remaining questions.

Dr. Suydam, you stood like you were --

DR. SUYDAM: I have one other thing to show you which is about the 18 states that have prescription requirements when its Schedule V.

DR. KRAMER: Okay. Did the FDA do any research or are you comfortable with our depending on CHPA to give us the information? Okay.

DR. SUYDAM: Well, what I have are three states, obviously we couldn't look up all the state statutes. But we have three states that we will define. And if I can put a slide on, we don't have it?

Okay. It was on. If you see, the California, the first one is California which says -- and I'm sorry,

but I can't read it from here.

DR. KRAMER: I can read it, you want me to read it? Except as provided in Section 11159 or when dispensed directly to an ultimate user by a practitioner other than a pharmacist or pharmacy no controlled substance classified in Schedule III, IV, or V may be dispensed without a prescription meeting the requirements of this chapter.

DR. SUYDAM: So that's California.

DR. KRAMER: Okay.

DR. SUYDAM: No controlled substance, III, IV, V can be dispensed without a prescription. Colorado, I think has the same thing in their statute you can all maybe read that yourself. And Hawaii, that's the same thing as well.

DR. KRAMER: So do we know whether those are representative of all 18 exceptions? I mean, there could be 15 that just specify specific drugs or is -- do we --

DR. SUYDAM: They're illustrative of the 18. I can't tell you that they are all by statute, some are by regulation. But we can in fact get you -- it's jut going to take us more time.

DR. KRAMER: Frankly, I'll just speak on my own opinion. I think that asking us make this recommendation without the understanding of the implications of access to legitimate users is really difficult. I feel that I would

like to know exactly what the situation is so that I can make a responsible decision. So I hear you, thank you for getting this. It would be nice to have the other 15. But short of that, maybe the FDA can advise us at to what they'd like us to do in that regard.

DR. THROCKMORTON: I guess I'd say we understand that the impact of the scientific opinions that we're looking for from you is going to have an impact on access. And so we understand that you are going to want to understand what your decision-making would lead to. So It's important to understand -- I understand where you're coming from. Having said that, each of the states are free to exercise their own choices here. And it'd be difficult for us to try to interpret each one of them for you.

So I guess to turn this around, what I'd ask you to do is to begin by helping us understand the science as is presented. Where you see that as being impacted by the various legislative things, whether state or local or national, comment on those. But to focus particularly on what you understand to be the science around the abuse liability of the dextromethorphan.

DR. KRAMER: So we can understand the science. But if there was absolutely no downside to the access to legitimate users of creating it in Schedule V, that would

prevent any future bulk distribution, I recognize that this one manufacturer is out of business. I'd like to understand from FDA if there are any other bulk manufacturers that produce DXM.

But if it was absolutely, you know, if it created no difficulty for legitimate users to access the drug, then it's harder to understand -- we've heard most of the arguments mounted by CHPA and speakers on their behalf, have talked about the impact on legitimate users and the cost of accessing physicians for a prescription. And then talked about the quantitative aspects of how many people use this. And frankly, when you're considering a possible side effect of death, the quantitation is not the issue. The issue is can you avoid it with minimal implications to legitimate users. And it's hard to get that answer without the information. But we can make our recommendations. And maybe we'll effect future states that consider what they're going to do after this.

Any other committee members want to comments in this regard? Okay. So we have questions left over -- hang on a minute -- we'll first take the questions that were directed to people who had questions for CHPA since it's the most recent one. And we still have four from the morning, left from FDA.

Leslie Hendeles.

DR. HENDELES: Thank you. I don't remember which member made the statement that scheduling doesn't work. And I'd like them to indicate what the evidence of that is.

DR. SUYDAM: I'm not sure that any of us said that scheduling wouldn't work. But I think we all said it had limitations. And I'd like ask Mr. Pasierb to perhaps speak to that issue.

MR. PASIERB: While I didn't cover that in my presentation, clearly the drugs that we do deal with, both the prescription and the illicit street drugs that we're dealing with with kids all represent being scheduled medications. So from my standpoint, from a child's standpoint, the scheduling doesn't have a deterrent impact. Whether or not it has an availability impact is outside of my area of expertise.

But clearly we're dealing with prescription opioids, prescription sedatives, prescription tranquilizers, prescription other things which kids are abusing as part of this overall medicine abuse behavior and all of them have the scheduling as a common quality.

DR. KRAMER: Do you have any other questions?

Warren Bickel.

DR. BICKEL: I have a question for Dr. Suydam.

So we know overall that the prevalence of addiction is correlated with or inversely correlated with socioeconomic status and educational attainment. I was wondering if you could address how your educational programs will specifically target those with lower educational attainment and lower socioeconomic status.

DR. SUYDAM: Our programs are multi-faceted and as you heard from Becky Dyer of the Five Moms program, it's a word-of-mouth program that goes out to the schools, the local communities, deals with the individuals in those communities and we have, in addition to that, worked with the D.A.R.E. program which is in all the schools. Home-to-homeroom is one of the programs that I didn't mention. It's with the school nurses. And that's in all of the schools. We think in the first year we've already reached one-and-a-half million students. We have done brochures, on-line articles, a nurses' office poster, and much more.

And I think those programs, because it the multi-faceted nature of all the programs, we're reaching people at all levels of our society.

DR. KRAMER: Leslie Walker.

DR. WALKER: I had a question and I'll give a little context for it. There was a high-use of marijuana in the '80s and a little past that. And then there was a

big dip in what kids thought the risk was. And there was a decrease in the use of marijuana for a while. And part of that was because of the huge national addressing in education and all kinds of input to kids that age that this was something that was actually a risk.

But when that move meant lost funding, went away, the increase in marijuana use began again. So my question is, I heard three years, somewhere around three years you were interested in putting money into the educational process, which I think if it's done with other methods to help change behavior can be very effective. But as long as the drug is available, it would need to be -- there would need to be the same kind of a push toward that because of generational forgetting. The kids that are being educated now are not the same kids 10 years from now. And it would be bad for us to keep coming back every decade to have to deal with this if you don't put things in place for a while.

DR. SUYDAM: We understand that completely and I'm sorry if I gave the perception that we were going to end this program in three years. What I said was we were setting goals for a three-year attainment that we could then repeat and talk to whomever about what our goals were. This program, we understand, is an on-going program. At

three years we will be -- we will have been at this for 10 years. And we intend to and know that you have to keep after this issue, as you said, every generation of new kids coming into that 12-to-17 age group has to be educated about the issue and needs to hear from their parents. And the parents of those children because there's new parents every generation too, they need to be educated as well.

So it is an on-going effort that we think will continue.

DR. WALKER: Just an added question, just a side, with the education, usually, education while important doesn't tend to change behavior, are you doing any research to try to move beyond that as the years go on?

DR. SUYDAM: Well, I think we see this as a multi-pronged effort, more than just education. But interventions in a lot of different ways. We are obviously doing the research including testing messages, making sure we understand the issue continuing with the qualitative research because that's so useful to understand why teens abuse programs -- abuse drugs and why we can get them to understand what's going on. So we think the better profile we have of the abuser, the more likely we are to be able to target those interventions.

DR. KRAMER: I also had some questions, the first

one, I guess Dr. Suydam, you could answer. I'm confused about the recommendation to restrict the sales to teens under 18 years of age in a setting where as you mentioned, the number of retail outlets, not pharmacies now, is very large. And I'm trying to imagine someone coming into a 24-hour pharmacy or 7-11 and picking something off the shelf and bringing it to the clerk and the clerk being likely to ask that person for an ID. I mean, it was a huge effort to get people to ask for IDs for cigarettes and for alcohol. I mean, is this realistic that if this had a age limit that it could be enforced in a setting where it's freely available wherever you might go?

DR. SUYDAM: Well, certainly, we believe it has to be a national program to be effective. There have to penalties for not doing it. And we know that the cigarette testing has actually worked. And it did take time to get the convenience stores and the local mom and pop stores to recognize the importance of doing age restrictions.

But we think that it gives us one more tool to actually make sure that parents know that their kids can't go to the local store to buy it. And we will be, obviously, encouraging surveillance of those retail establishments.

DR. KRAMER: Then the other thing is a

combination comment and question, some of the things that Steven Pasierb commented on when he was describing the focus groups that were done, I think you made a comment that it was hard to recruit to these focus groups. And you made the comment that it was hard to recruit because the abuse was not that common. But there's an alternative hypothesis which is hard to recruit because of the kinds of teenagers specifically that abuse these sorts of drugs would not be volunteering for your focus groups. If it's a disaffected child that is seeking to have psychic alterations, not opioid-type dependence, but escape and whatever drives people towards hallucinogens, is it realistic that -- you may have just selected out those people that find those sorts of things objectionable and had a self-fulfilling prophecy in your focus groups which albeit it's a focus group, but it's qualitative and it could have been very much affected by selection bias.

MR. PASIERB: We didn't do just a general population recruit. We went to addiction treatment centers, into educational settings and other places to try to find kids who had either presented with these problems or otherwise to try to dampen that very effect. And very specifically in the groups that we did in Los Angeles, we recruited for the five-time user, so not just the kid who

had used it most, but going out and finding the kids who had used it on multiple occasions.

So we were able to populate the focus groups with kids who had direct experience abusing DXM and direct experience with poly-drug abuse. So it took the time and effort to do that in reaching out to the Karens and the others in the treatment community to be able to populate those groups. That's again why we went to multiple cities as well.

DR. KRAMER: Also, I could see why the Partnership for Drug-Free America wouldn't prioritize this type of abuse because of the huge amount with other types of products as the top, number one, national campaign for you to focus on. But I'm still having a hard time understanding why even a small level of abuse is not of concern.

MR. PASIERB: That is not my statement at all, the small level of use is absolutely a problem and why we've been on this for the last seven years. My purpose is saying that when I have a 95 percent non-usage level, and I use national television, national radio, and I talk to 310 million Americans, I actually have the risk of introducing more kids to the potential of the behavior and how to engage in the behavior.

So much like the advice very early on, we have a five percent behavior we can target that five percent very heavily. Let's not broadcast out to all the world that there's this thing called robo-tripping and here's how you do it and here's what the products are and here's where you go to get it. In fact, we heard that in some of our qualitative research, kids saying, "The reason I did it is I just happened to be sitting in the living room and the news was on. And there was a story about it. And I said that's great. I went to my computer. I looked it up," probably ended up at aerowit and that's why he started doing it.

So we do, in the prevention field, while you would normally think that you want to tell the whole world and cry from every tower, we do never want to be educative on this. It's one of the struggles we had with ecstasy abuse. It was only when ecstasy moved out of the club scene into the mainstream that we really went after ecstasy on a national scale.

DR X: So that would argue against a widespread educational approach?

MR. PASIERB: On dextromethorphan, yes, a targeted approach on dextromethorphan, a widespread on marijuana, widespread on alcohol where you have much more

prevalent use.

DR. KRAMER: Okay. Dr. Winterstein.

DR. WINTERSTEIN: Follow up on this because now I'm confused, didn't you talk about how important it is to increase the perception of risk for those medications? I mean, that was one of your number one strategies.

MR. PASIERB: Yes, perception of risk among the kids who are likely to be in the behavior, not all 100 percent of society. We know that we can target online in the same spaces where those kids are, the kids who are most at-risk, at-risk sensation-seeking teens who may be seeking this kind of high, current users, and chronic users.

So there are places that we can go in the online, digital and social media space to find these kids and talk directly to them without talking to the majority -- I mean, we have 35 million families in America with kids who are in this target audience, the last thing we want to do is try to build risk, if you will, where the thought has never occurred because the downside of that is being educative.

DR. WINTERSTEIN: So any of your effort would focus on a select group of at-risk children?

MR. PASIERB: At-risk, high sensation-seeking teens, current users, and those chronic, poly-drug abuse users even though we know we're not going to be as

effective with the multiple poly-substance abuse users as we are with the other two groups.

DR. WINTERSTEIN: If I remember those data correctly, there were like four or five percent of children who have tried those out, right?

MR. PASIERB: Uh-huh.

DR. WINTERSTEIN: That's a pretty large group to me, you know.

MR. PASIERB: Absolutely, but the tools you have in prevention, particularly around media communication, are gross tools. They're talking to the country. So when you put an ad on television you reach far more people than you intend to reach on a niche behavior. So you want to go to where they are. You want to find where they are and you want to talk to them in a persuasive teen-to-teen voice and not put an ad on a FOX television show where you may have 40 million teens or whatever the numbers may be, watching that message and then you risk being educative.

It's one of the things we constantly deal with in this field although NDCP deals with in the field as well as the folks at Monitoring the Future. In fact, Monitoring the Future, as an example, did not want to ad the cough medicine questions to the study because they constantly worry about the study being educative.

If the study goes into schools and starts asking kids so what about cough medicine abuse, they say to themselves yeah, what about cough medicine abuse and they want to try it. So that's always what we deal with in this field is not to do more harm than good, our version of that approach.

DR. KRAMER: Marilyn Eichner.

MS. EICHNER: My question is to the industry, you've looked at risk perception, but have you looked at that in marketing? Your major marketing is to pediatrics. So there's a number of drugs and you take a 12-year-old and you have a pediatric cough medication in the cabinet, which, since 2007 there's no new data that shows that it even helps in pediatric cough, so I'm assuming that the people that it helps the most are adults above the age of 18. You have a 12-year-old looking at a children's cough medication and automatically they think that that's a safe high.

And when you talk about a lousy high or, you know, a -- forget the term that was used -- but abusers look at -- they look at a safe high and it's easier to get that, it's easier to get that children's medication for 12 and 13 year old and not be suspicious and your large retail stores, when someone goes up to the counter with an over-

the-counter children's cough medication, they're not going to question the DXM that's in that or question it being bought. I don't know how you're going to differentiate between both.

DR. SUYDAM: Well, let me talk to this a little bit. First of all, I think it's really important that we educate parents about protecting their medicine cabinets. We know that the issues with medication misuse and abuse are multi-faceted. We know, for example, that a large number of the adverse events under six are because of the fact that medicines are not protected in the home and that the curious toddler can get in and drink the cough medicine or take whatever is there.

So we are, number one, asking parents to first of all protect their medicine cabinet. That's one of the most important things they can do. And we can obviously talk to parents about the importance of teaching their family that medicines are effective because they have active ingredients that can cause problems if taken beyond the normal dose. So those are messages that we've been trying to get across in our parent's campaign. And I think we have successfully gotten them across.

Let me just mention on the pediatric issue because I spoke before an FDA committee on pediatric cough-

cold products three years ago. And we committed at the time to do pediatric research and we have done and started doing all of the pediatric research that we promised. Consistent with our commitment we started and did the PK studies on two to 17-year-olds. And they were completed for all eight ingredients that we were talking about at the time including DXM.

With DXM we have a method's development program that has been completed for a study that will look at the efficacy of dextromethorphan in six to 11-year-olds. We're taking these in pieces. That first efficacy study will be underway shortly. We will then follow that with a confirmatory efficacy study in next year's, so we'll have one in this winter season, 2010-2011, a confirmatory study in 2011-2012. And we have continued with our active safety surveillance program through the Rocky Mountain Poison Center.

So the method was the first -- well, the first step was the PK data, got that for all eight ingredients. The second step is method's development and we've started that program for dextromethorphan and are also working on pseudoephedrine and intend to move through the other ingredients as well.

DR. KRAMER: Are those controlled studies?

DR. SUYDAM: Yes, they are.

DR. KRAMER: Against -- dextromethorphan will be compared with what?

DR. SUYDAM: I don't know the --

DR. KRAMER: The vehicle?

DR. SUYDAM: The vehicle, yeah.

DR. KRAMER: Thanks.

Elaine Morrato.

DR. MORRATO: Thank you. I wanted to get back to the points that Mr. Pasierb was making in terms of the -- I completely understand the perspective of needing to balance targeted education to those that are at risk. But I'm also concerned with the narrowness of the education plan that you've outlined that's just focusing on on-line media as the primary vehicle for delivering the message.

I guess part comment, part question that I think there's opportunity to be a bit more creative in that there's other avenues that you don't have to nationally go to FOX News to advertise. I don't familiar with the Montana Meth Project?

DR. SUYDAM: Yes.

DR. MORRATO: Okay. I live in the state of Colorado. It started in Montana. It's now, I believe, in eight or nine states. Those ads run very graphically, very

visually on TV shows that my teens watch. It's not on FOX News. And I believe that the way a message is delivered is as important as where it's being delivered. And if you're truly trying to inoculate teens against wanting to do something, it's how you deliver it. You're not just educating them on how to do it. But to your goal that you said which are largely to make it unattractive, to make it uncool, et cetera.

So have you looked at other media besides just online?

DR. SUYDAM: We have already, as I keep reminding people, this is a program that we started in 2003 and have continued to grow and evolve all of our efforts including the DXM stories that we had online when the child whose looking to figure out how to get high tries to find information online and the DXM stories pop up, slide on.

But in addition that, we have had educational resources that are available to those without Internet. And we have done this through a number of community organizations. The Community Anti-Drug Coalitions of America have 5,000 community organizations throughout the country. We have done town hall meetings with them. We developed a tool kit with them that can be used in those 5,000 communities that they are active in. We have spoken

to all of their national meetings in the last five years. and we have given them the resources that they need to take back to their communities.

As I mentioned earlier, the National Association of School Nurses is a group that is now working on this issue within the schools. And the school nurses tend to be people who know what's going on in their schools. They see the problem children first. And then we mentioned our programs with D.A.R.E. America and the Partnership. We've done conferences, we've done town halls. We've done PSAs with the Partnership and with others. We've done advertising campaigns. And we have the educational icon to alert parents to the issue which we think is incredibly important.

So the new digital program is just the new piece to the program that's being added this year. The other parts of the program will continue as they have gone on in the past.

DR. MORRATO: But in terms of the -- which I find very appealing and I agree, is the teen-to-teen directed peer influenced, oriented messaging, these brochures and town halls are very good, I'm sure, in terms of reaching out with parents and with adults that are interacting with the teens. But is there any other activity that's really

promoting teen-to-teen? Besides the on-line content?

DR. SUYDAM: Well, I think CADCA is an organization that actually has student volunteers who work within their program to do student-to-student messaging. So we would welcome any ideas that you might have to expand our programs because we're always working to make them better.

DR. KRAMER: If I could ask Dr. Suydam one more question.

I was struck, in reviewing your background packet, that very early on you pointed out that you wanted to have an evidence-based strategy. And you commented that the evidence suggests that -- you listed the factors that correlate with abuse. And two of the things you talked about, and we've talked about today, perception of safety and ready access. And the first thing that occurred to me when I read perception of safety is having it on the grocery store shelf easily bought by anyone suggests that this doesn't need control, number one.

And I'm really questioning the strategy for, depending on legislation to require restriction to those under 18, depends on the legislation being passed and then depends on every single clerk in every of those 750,000 retail outlets, every grocery store, every 7-11 actually

complying. And I think it strikes me as a little unrealistic having watched what happened with more dangerous tobacco and alcohol issues.

So I'm struggling with whether everything is hinging on -- and the ready access is obvious -- if everything is hinging on these few states that have maybe unintentionally created a problem by making everything that's in Class V prescription. If we look at the other states, making this drug a scheduled product would make it behind the counter, accessible to legitimate users and in most communities, 24 hours a day because pharmacies are frequently 24 hours now.

DR. SUYDAM: Well, I mean, first of all, you'd be going from 700,000 outlets to 55,000.

DR. KRAMER: If I could finish, I think we have to separate out the elephant in the room which is there would be a huge impact on retail sales of these products, on the sales volume. The question is whether the medical legitimate use would be a significant problem because we do know that dextromethorphan is in a very large number of products. The question is whether every time a product with dextromethorphan is purchased it's because the patient is seeking a cough suppression product or whether they're seeking something to treat their cold.

And so I just want to challenge the assumption that the only way to limit access or that your approach to limiting access would be effective or more effective than the obvious which is to make it Schedule V.

DR. SUYDAM: Well, I think that age restrictions is in fact just one part of a comprehensive program. We believe it's a tool that you need to give parents. You need to tell parents your child can't go to the local 7-11 and buy this product. So it's one more tool that we have given you. In the meantime, I mean, whether the product is Schedule V or not, if a parent does not protect their medicine cabinet, their child will still have access to it, whether it's scheduled or not.

So I think the important thing is to have a multi-faceted program with parental awareness being prime and number one because we know parents can have an impact and to give them the tools they need to do that by having the right way to talk to your kids, to know what to say, what to look for in terms of the abuse and to know that you child can't go and buy it in the local store.

DR. KRAMER: Looking at all the Websites we were given to look at in the background packets from all the people that submitted them, I was really struck that the predominant profile of the abusers described were 12-to-17

year-olds not getting it from their medicine cabinet at home, but getting it from other sources. And I'm -- I just had a little afternoon, after lunch lapse there about the main point that I wanted to make, it will come back to me.

Somebody else want to say something here?

Yes.

DR. KOSTEN: I was suggesting that you should try to be a governor of Arizona in particular, I think.

DR. KRAMER: Yes, Dr. Woody.

DR. WOODY: Could somebody go over the pros and cons of sort of behind-the-counter versus as it is sold now, sort of on the shelves as we saw pictures on the shelf and then the last speaker talked about behind the counter. And I'm not clear about the pros and cons of one or another.

DR. KRAMER: Was that question directed to Dr. Suydam?

DR. WOODY: Yes

DR. SUYDAM: Well, behind the counter would in fact be just another solution to one piece of the problem which is access. I think you saw from the chart that Mr. Pasierb showed that when accessibility to marijuana stayed the same, the only change you had was when you increased perception of risk and then the use dropped off.

So we really need to focus on how do you specifically address the issue. What would happen if behind the counter, it depends on how you would make it behind the counter. Pseudoephedrine went behind the counter because the Combat Meth Act was passed in 2006. That was a federal piece of legislation. It would be very different placing it behind the counter also has limitations because you can't get it unless the pharmacy is open. And there are lots of places where pharmacies are not easily accessible. And when the parents wants it late in the evening when their child starts coughing, literally, there are in this country having lived in New Mexico myself, I know there a lot of places where you don't have pharmacies.

DR. WOODY: But 7-11s have -- I mean, the 7-11 that I go into has a bullet-proof case around it with the guy there and I believe that's where the cigarettes are.

DR. SUYDAM: Cigarettes and alcohol.

DR. WOODY: Yeah. So don't many of the -- I don't know what the general framework is.

DR. SUYDAM: No, the only place you have a medication behind the counter would be in a pharmacy.

DR. KRAMER: That may be related to the fact that some of the legislation has said that has to be handled by

a pharmacist and the registry that's required has to be in the control of a pharmacist.

Did you have any other questions. Dr. Woody?

Dr. Hendeles.

DR. HENDELES: I just want to comment on what happened with pseudoephedrine when that Combat law was passed. It actually removed that behind the counter and only in pharmacies. The law doesn't say it has to be in a pharmacy, but no non-pharmacy is willing to deal with it. And what happens if you happen to get a cold on the way home from this meeting or you're going to get on a plane and you want something? The only thing available, like, in the airports is phenylephrine which is inactivated in the gut and not any different than placebo.

So this Combat law removed it from patients who actually would benefit from it and doesn't effectively remove it from people who want to make meth because you can go into store after store and buy 120 tablets. And there's no connection, there's no registry connects them. And you can buy all -- you just have to go to different stores. So it didn't really accomplish what congress intended.

DR. KRAMER: Although I thought we saw some data that showed that pseudoephedrine abuse has decreased since -- I saw some graphs with it going down.

DR. HENDELES: It was just in one state where they required it to be a prescription I believe it was Oregon.

DR. SUYDAM: I think the data on pseudoephedrine shows, which we follow very carefully, is that there are a number of states in the middle of the country who have extreme meth problems. And those states, obviously, you know, wanted the Combat Meth law. And those labs came down the first year. So from 2006 to 2007 meth labs, which is really what you're worrying about from pseudoephedrine came down.

Now in those states meth cooks are smarter than the law. And they figured out how to get the product again. And so those numbers are up again, extreme -- there's a big drop, big up.

DR. KRAMER: If I could, since I recall what it was I wanted to ask, ask again, I was addressing your statement about open space and ready access. And I was curious what evidence that we have given that this is affecting 95 percent of these teenagers in this age group, 12-to-17, and we still have a very high percentage of parents who are unaware of this sort of use, what evidence do we have that these programs are doing anything other than targeting the 95 percent of parents or the 95 percent

of kids that are unlikely to abuse, how do we have information to know whether this disaffected group likely in households where parents are less likely to be aware, are actually being affected?

DR. SUYDAM: You know, to that, specifically I don't have any data, slide on. But I do know that we have made a difference in two of the categorizations that we think are important. One is the perception of risk, which is a teen's perception of risk. And that's gone from 40 to 47 percent. And the percentage of parents talking to their teens about cough medicine abuse has gone up significantly.

So we think we are making a difference. But I don't know. I think that what we do know about the five percent is there's two-and-a-half percent of that five who are the experimenters, the kids who are thrill-seeking, looking to do something new and try something. And usually those are the kids who only use it one to four or five times and stop. Then you have the other two-and-half percent who are teens and young adults who are poly-drug abusers who continue to use DXM as part of their armamentarium of drugs.

And they specifically, in the qualitative research that the Partnership did, said we use this when we can't buy our cocaine or something else.

DR. KRAMER: I realize the open public hearing is limited by only those that can afford to travel here and speak, but it probably should be noted in the public record that we did receive written statements from parents of children who abuse this and were cyclically dependent, multiple uses and had very, very disturbing stories in term so of the impact on individual teenagers and their families. So I think we should note that and also the American Academy of Pediatrics expressed a similar view, so have that be in the public record.

Okay. We had questions from Lewis Nelson.

DR. LEWIS NELSON: I originally had another question, but that last slide you just showed, could you put that back up one second? Because this comes down to a lot of the problems that I keep seem to be struggling with here which is, I mean, I know you're suggesting that 42 and 47 percent is dramatically improved over a three-year period. I mean, if you go with that trajectory, it's going to take us forever to get to, you know, to, you know, any significant number.

But, A, I've asked this question before Judy did as well, but there's no data that actually says that you made that happen, right?

And also, the bottom, I'm kind of -- I understand

this is an issue, but we now have 60 percent of parents talking to their kids about something that we don't think we should be educating kids about because it's too dangerous to talk about it, right? So I don't whether we're trying to get people to talk about it or not trying to get people to talk about it.

MR. PASIERB: We are using the mass media efforts to parents because parents are both the -- when they have the drug talk with their kid they need to include cough medicine in it. So that is why we reach parents with print advertising, television advertising, all of these different programs because when parents have the drug talk, they tend to talk to their kids about cocaine and heroin, first of all, and not things like marijuana, dextromethorphan, the stuff which are actually more readily available to their kids. So we do use a lot of mass advertising.

We cannot say that we are the sole cause of those increases of number. But in absence of any other messenger in society, talking about these issues to the public, some change has occurred. So, you know, it's not a competitive space, if you will. It's not our messages versus somebody else's messages versus somebody else's and how caused this. We see an increase in these activities, absent of any other influences.

The reason we're targeting teens is, again, if I go to the most targeted teen broadcast media, *Glamour Girl* on the CW network and I put on a commercial specifically about dextromethorphan abuse and how dangerous that is, we know that a certain of those kids will then try it. And that's what we're trying to do. If this behavior were a 15 or a 20 percent behavior, we're talking about tens of, you know, big, big numbers, we would make judgment that now we need to go on broadcast television, now we need to go out in big ways.

So for example, our plan will probably use MTV.com and not MTV. It'll probably use these different ways to really get at the kids without risking talking to the kids of those 35 million in America. And it will have a degree of impact. It is no infallible. But it can definitely cause that. And then as we go forward, the point that was raised earlier, you've got to keep that message going long-term. And you've got to continue to modify it long-term because the kids change. Not only do they age into the cohort, they become very different kids.

DR. KRAMER: Okay. We have three more questions of CHPA. Richard -- I'm sorry, Sharon Stancliff.

DR. STANCLIFF: I'll wait. That's okay. I was going to make a comment.

DR. KRAMER: Okay. Richard Denisco.

DR. DENISCO: It's not really a question, it's more a comment. We're discussing a lot of what-ifs and what-might-bes and what if congress does this and what if congress does that. As a federal employee we're forbidden to lobby or contact congress with anything like that. We are able to be called to testify and you better go when you're called because they do have disciplinary powers, but we're discussing a lot of what-ifs whereas in the final analysis, we're going to have to vote on what exists today.

So I would really like to hear, Madam Chairman, the discussion of my colleagues on the issues.

DR. KRAMER: Thank you.

Did you have a comment?

DR. STANCLIFF: After you pointed out who we're missing at this program including parents, I think we're also missing some of the people that are directly taking care of the kids that are in that 2.5 percent that we talk about. So in my sort of finding out a little bit more, I talked to someone who runs a drop-in center for runaway kids. The biggest behavioral problem they see compared to the opiates, compared to the cocaine is the use of DXM that kids go down to the store, pick up, put in their pocket without paying for it, and come back and it's like, wow,

there's a bunch of kids that look like they're on PCP in here.

And I realize it's a small population, but I'm also just kind of concerned to see them, well, they're only 2.5. We're talking about a drug that can kill people. They're smoking marijuana all day and there's not been one fatality from marijuana in 2008. Harm Reduction Coalition is not an agency that deals with marijuana, by the way. But we're talking about a drug that has killed people.

Now this doesn't mean that I'm recommending scheduling it, but I want to bring it back to that small, but important population that I wish could be a little bit better represented here.

DR. KRAMER: Two more, Rodney Mullins.

MR. MULLINS: Yes, I think we all need to think back 10 years to when we were in high school so that we can reframe this -- so we can reframe this discussion from the perspective of a young person. And some of the things I'm hearing today I think we're not quite thinking like the demographic profile of the user or the abuser of this particular medication.

And I had three questions, quick questions. But I want to go into the campaign. And then I had a question for Dr. Schuster and Dr. Suydam.

As far as the campaign, I'm very concerned about the campaign because if this committee does not take corrective action to schedule dextromethorphan then we will rely upon this educational campaign. So we will be entrusting the pharmaceutical manufacturers to safeguard the health of American families as it relates to dextromethorphan. So I have a question for Dr. Suydam. And my question is young people are very savvy, so I think that if you have a Website that says stopmedicineabuse.org, I don't quite think they're going to go to that. And even -- and then on the other one, DXMstories, I don't think they're -- the WebMD demographic is not kids. Obviously, I know you're targeting the parents.

But I think -- the thing I'm worried about and I'm concerned about is the campaign that you're launching because if we don't take corrective action to schedule DXM, then we will be relying on your aptitude and marketability and having done dozens of campaigns to young people, I'm concerned about your approach because I don't hear anything about outbound relationships with the -- or outbound marketing such as, you know, what are you going to do about youtube. There's probably 1,000 videos with young people robo-tripping. They videotape themselves taking the drug.

DR. SUYDAM: Yes.

MR. MULLINS: There's probably about 20 to 30,000 Websites that prescribe dosing where they tell each other how to take the drug. And they give a lot of miseducation. So I wonder how many staff people that you have that will be going on forums that will be aggressively outreaching in an effort to address those issues because it seems like your approach is passive.

DR. SUYDAM: Not at all.

MR. MULLINS: And I don't if it's connecting with young people because just the titles themselves, that's not the way they operate.

DR. SUYDAM: Well, first of all, I'm obviously not communicating effectively if you haven't gotten the idea that this is a proactive program. This is certainly not passive under any circumstances.

MR. MULLINS: Well, you haven't talked about what you're twittering, what forums you're --

DR. SUYDAM: I can tell you about a lot of the programs we're doing. Stopmedicineabuse is designed for parents. It's not for kids. That's what the icon is for, parents.

MR. MULLINS: No, I understand that, yeah.

DR. SUYDAM: That Website we never would expect kids to go there, that's not what we're -- that's not what

it's there for. We have town hall meetings, we go to community -- we do community outreach. We are working with partners to, in fact, get the message out to people who work with teens. Slide on.

We work with all of the different groups, go ahead. And we have all of these ideas -- we do use twitter. We do use the grassroots campaign. We do work with other organizations. We don't do -- we do community town halls, we sponsor them. And then we get the local people like Becky to come in and talk to the group because they have a better credibility than I do coming from Washington, D.C.

MR. MULLINS: I know, but the problem I have with that is that whenever you have a campaign like that, social media campaign, you have metrics. And you measure the level of engagement. So in other words, impression means nothing. What is their response? Did they register? Are they coming to you? Are they becoming ambassadors? Are they taking actions? Are they becoming involved in a ambassador campaign?

If they don't -- because in other words, to get them to change behavior which is very challenging, you have to show that they are engaged. So you can have a trillion impressions.

DR. SUYDAM: We understand that.

DR. KRAMER: Can I --

MR. MULLINS: The question is what have you done to --

DR. KRAMER: -- interrupt for a second?

MR. MULLINS: Right.

DR. KRAMER: I realize I may have started this down this path of we're having sort of a debate with the sponsor. And yet, I really think that I'm hearing from the committee members opinions about the questions that we were asked to deliberate. I hear you expressing some opinions. Could we limit for the last -- for the remainder of your questions and the next person, only those things you think the sponsor itself needs to clarify before we have our own discussion about adequacy of programs, et cetera, et cetera.

MR. MULLINS: Well, I think the sponsor needs to talk about the campaign because they're the one that would be conducting the campaign.

DR. KRAMER: Right. Is there anything --

MR. MULLINS: And also about Dr. Schuster, he mentioned that this was isolated to a small group without any quantifiable data. And I had that question I wanted to clarify that.

DR. KRAMER: Go ahead.

MR. MULLINS: So these are very much directed toward the sponsor.

MR. PASIERB: The answer to the first part is yes. That is why we're doing all of these new things. We'll do all of the different on-line spaces, the Facebooks, the MTV.coms, the membership sites, the MySpaces, all of those things. And we will put metrics against all of them. You're right. Impressions are ridiculous. I think we've served 2.5 billion media impression in the digital space last year. So we've basically talked to the planet. So impressions are no measure. But really we can get those metrics going forward. What sites were used, what was the traffic, what was the level of engagement of the traffic, what parts did they use, what parts didn't they use?

That will all lay out in this much heavier teen-focused effort. On top of that, you mentioned the counter-message that's out there. That's one of the reasons why viral video and things like that need to be very heavy because we can't get the crap off youtube, we're going to have to go in there an fight fire with fire.

We're going to have to go to MySpace and fight Website with Website. We're going to have to fight the

aerowits. And that is really the program that begins now and goes forward, that opening up of the new front on teen to do exactly the things that you said. So we hear that and that is exactly what we intend to do.

MR. MULLINS: And then my last on messaging because how we will -- how will you combat your own messages which are conflicting to the teens because you have two messages that are diametrically opposed because a young person, they're seeing a image of safety, a photo of -- a image of a child, a baby on the packaging, then you're going to come with a campaign that says, hey, this is un -- you see why that would be conflicting and how will you balance those two messages?

MR. PASIERB: The message that we're going to deliver and I can't really comment on, I mean, the studies of what industry marketing does here because those studies haven't been done, but we're clearly going to go in a teen-to-teen voice. It's one of the reasons why. We're not going to put adults in ads. We're not going to do slick produced ads or any of that. We're going to put real cough medicine abusers, kids with credentials out there in ways to communicate with other kids and let them know how bad this high is, the mistake that was made, how it doesn't fit, all these different ways. So the choice of the

messenger is enormously important in all of this. And that's going to require, frankly, additional research to understanding not only what the message should be, but once the message is derived that it's right and that it works and then it has the intended effects in the marketplace and none of the unintended impacts.

So from that standpoint, my area of working, that's what we have to do.

DR. KRAMER: You had a question for Dr. Schuster too?

MR. MULLINS: Yes, the question for Dr. Schuster was, Dr. Schuster, the majority of his information emphasized adults greater than age 33, over age 25, and the affected profile of the most at-risk profile that we're discussing is from 12 to 25. And you mentioned that this was an isolated group that most of these abusers of dextromethorphan were troubled use, they had other issues.

I don't know if that's supported by the evidence. So I wanted you to explain why you made that statement that this was isolated to teens that had or young people that had other issues or other challenges.

DR. SCHUSTER: Well, first of all, let me point out that the National Survey on Drug Use and Health which is a nationally representative sample, showed that about

two percent of the 12 to 17 year olds were -- had abused dextromethorphan once in the past year.

On the other hand, prescription opioids which are controlled under the Controlled Substances Act are about almost three and a half to four times as prevalent in that same age group. So the issue of controlling this through diversion and abuse with this population in that age group by simply scheduling it, I think is not quite as effective as you might believe.

Number two, what I demonstrated was that children who are using marijuana as opposed to those who are not, are seven times more likely to have used dextromethorphan to get high. Those who are using OxyContin are 15 times more likely. We also have data showing that the abusers of -- more frequent abusers of dextromethorphan are those who are abusing multiple other drugs.

And I simply would submit to you that it is very likely that even if we were to totally abolish the existence of dextromethorphan tomorrow, it would not solve the problem of drug abuse in those kids who are abusing it on multiple occasions. They're using many, many other drugs.

Now, do I know what the co-morbid psychiatric disorders they have? No. But we know on the basis of

adolescents who come in to treatment programs and here Dr. Woody could speak to this better than I since he has run adolescent substance abuse treatment programs, they are oftentimes have many, many other problems, psychiatric problems, emotional problems, educational problems, and social problems.

That's the only data that I have is the existence of -- the high prevalence of co-morbidity in kids who are using multiple drugs on multiple occasions.

DR. KRAMER: Do you have any --

MR. MULLINS: No, that's fine.

DR. KRAMER: Okay. Leslie Walker.

DR. WALKER: Yeah, I had a question, given the number of years that we've had this on the market, I really, I'm a little disturbed that we don't have more research on the abuse and kids that are dependent. I have treated kids I in substance abuse, adolescents who have been dependent and had dextromethorphan as their drug of choice. And I have not seen or heard that there's any research that you're looking into, how does that occur, how do we help these kids get in recovery? Because it does happen and prevention alone is not enough.

And I've had kids from all walks of life, all levels of mental health, all levels of parent involvement

be involved with dextromethorphan. So I'm wondering, is there any amount of funding that you're putting aside to actually look into the abuse and what the mechanics are of dependence.

DR. SCHUSTER: The only thing I would like to say is as the ex-director of the National Institute on Drug Abuse, I think that that is a role for the National Institute on Drug Abuse to be funding that type of research. It's obvious that it is needed. We need to know more about the co-morbid psychiatric disorders to better address this. What I think you're suggesting also is that we need perhaps increased research in terms of appropriate treatment approaches for these kids who may have these multiple problems.

And the other issue is getting them into treatment. We must make treatment more available and make certain that it is truly an effective intervention. And there I see a role for the National Institute on Drug Abuse. I don't think that is a role for industry.

DR. KRAMER: Did you have any other questions. Dr. Walker?

I think we'll close off the questions to the sponsor at this point. And let me check with the

committee. We did have a scheduled break at this time. And the question is, do you wish to have a quick break, biologic break, or just keep moving.

All right. Those in favor of a break? Okay. A 10-minute break. But we're going to have to work fast when we get back. And we're going to turn to the questions as soon as we return, 10 minutes. See if you can get back by 20 to, that's even less than 10 minutes.

(Recess.)

DR. KRAMER: For the committee, we need some -- we need to talk about some instructions about how we'll do this. You have all received the questions in advance and they're in your packets at the present time. The good news is we only have three questions. And the even better news is that only one of those questions is a voting question.

The first two questions are meant for us to discuss the issues to give the information to the FDA in their deliberations because our conclusions are only a recommendation. And I have talked to Dr. Klein and asked specifically if every single -- if we have to go around the table and have every single person comment on each of those first two questions, and the answer is we just need -- we don't need to do that. And I think that would take the pressure off of you if, you know, you're the first one to

speak and you're not moved to speak right then, it doesn't work too well in my experience.

So what we're going to do on these first two questions is have a discussion where people who feel moved to speak or who strongly have opinion or a particular expertise, we hope that on questions of pharmacology that our pharmacologists will speak up. We have a rich array of expertise here, we have abuse experts. We have psychiatrists. We have adolescent experts. And we have patient consumer representatives. We want people to express their point of view on each of these questions.

On the first one, I will read the first question. And it states do the available data, including receptor binding, animal behavioral effects, and human behavioral effects, and the epidemiology data suggest that dextromethorphan has abuse potential? Do the data identify a particular population at risk for abuse of dextromethorphan?

And before we open it up to full questions, let me say that one committee member, Dr. Maxwell came up to me at the break and commented that one of the issues today is that we have a paucity of data and especially frustrating is the difficulty with some of the epidemiologic data. And she has some specific data from Texas that she would like

to share with us. It will be very brief. But I think that might inform the committee.

So, Dr. Maxwell.

DR. MAXWELL: Thank you. I'm citing my June 2010 report to NIDA's Community Epidemiology Workgroup. And the report is online. But let me tell you a couple of things including some brand new data.

In 2010, the Texas school survey reported that 5.4 percent of Texas secondary students indicated they had ever used DXM. Two years ago it was 3.1 percent. So we've gone from 3.1 to 5.4. Texas school survey is the largest school survey of the nation. It's representative only of Texas. But it gives another set of numbers. Past year use between 2008 and 2010 has gone from two percent to 3.1. Now one of the things that we haven't really talked about that the Texas School Survey gives us is grade year. And the highest prevalences of use for the last six times now is kids in the ninth and tenth grade, that set bunch that are just going to high school. After that the use drops off pretty dramatically, but that's your target group is kids in grades eight and nine.

One thing that wasn't reported, and I'm sorry it wasn't, NIDA -- not NIDA, but SAMSHA did a really nice study looking at the national survey in January 2008. And

what they found was that when looked at the 12-to-17 year olds who had ever used cough syrup, 68 percent had used marijuana, 22 percent had used LSD, PCP, or ecstasy. This is the 12-to-17 year old.

Of the 18-to-25s who had ever used cough syrup the proportion using marijuana is now 82 percent. So you go from 68 to 82 percent as they age. But the proportion who had ever used LSD, PCP, or ecstasy goes from 22 percent to 44 percent, it doubles. And there were some other indications in the literature about that relationship if you like cough syrup you like PCP, you like dissociative drugs later. So that's good solid data.

Also, Poison Control Centers, the Texas data, this is looking at cases that meet the PCC criteria of abuse and misuse, not just calling in because the dog ate it. The misuse cases involving dextromethorphan rose from 99 in 1998 to 505 in 2009, so from '98 to 2009, 99 cases to 505, average age of dextromethorphan was 21 years. Cases of abuse and misuse of Coricidin HBP, which is the little red Coricidin, the triple Cs, the Skittles that the kids like, we went from seven cases in 1998 to 126 in 2009. So those have also gone up. And the average age for those was 17. And if you look at them, they look just like red M&Ms. So that's easy to put in your pocket.

Deaths, there were 12 deaths in 2007 in Texas in which dextromethorphan was one of the drugs mentioned on the death certificates. Now the death data that's been presented is pretty sparse for two reasons. One, the event reporting system is not a uniform system, you report in if there's been an adverse event. So that was under-reported. Poison control centers also, to my knowledge, do not report all cases to the American Association of Poison Centers. I think it's a sample.

So again, we really don't know because the ICD code doesn't specifically break out dextromethorphan, so that the data on deaths is shaky. But at least I found seven when I just looked at the death certificates in Texas for 2007. So basically that's it. But let me bring it back once more. Eighth and ninth graders down at the shopping center this past weekend were across the street from the middle school, two kids come flying out of the drug store, hop on their bikes, and you can see they've got the packets in their hands. And as they go off, you can hear the comment, "See I told you it was really easy to steal it."

And I challenge each of you to go back to your drug stores and look at where the dextromethorphan is in the drug store now. And I've been on my pharmacist's case,

it's always on an aisle that is not under observation. It's down low, each of you could pinch five or six boxes and do it easily.

So, I mean, that kind of brings it back into perspective of what we're really talking about, how easy it is to get it. But it's young kids. But once they start, then the can progress, they're going to progress in the use of dissociative drugs.

DR. KRAMER: Thank you very much.

So other panel members?

Yes, Dr. Krenzelok.

DR. KRENZELOK: Thank you. I'd like to clarify a comment that Dr. Maxwell made too about AAPCC data. Poison Centers report all cases. They're auto uploaded every six to 10 minutes into an active, real-time database. So all cases are reported.

Now, understand that we only hear about the living. Somebody doesn't call us up and say, "You know, we had three kids that died from dextromethorphan poisoning last week," we hear about the case where we have three children in the emergency department who are suffering from dextromethorphan overdosage; can you help us. So we don't know what the total denominator is, we just know about the cases that are reported to us.

DR. KRAMER: Thank you.

DR. KRENZELOK: Can I make a couple other comments as long as I have the floor?

DR. KRAMER: Sure.

DR. KRENZELOK: So I have a simple, you know, I call it kind of Ed's checklist about determining whether a drug has abuse potential. And I always think if it's cheap, available, and it's mood altering, that sort of fits, you know, that's my template. And so we've been talking all day about dextromethorphan. And everybody on both sides of the aisle has agreed that there is abuse potential, that it's cheap, it's available, it's everywhere. We're talking about restricting use and so on. So this first question to me, and especially with the data now talking about who's at risk, I think it's been answered. And I think it's just sort of academic.

And I personally think that, you know, question number is where we have to go at this point in time.

DR. KRAMER: Could you specify what you see as the answer there? Will you answer that question?

DR. KRENZELOK: For number one?

DR. KRAMER: Yeah, since you think it's been answered, answer it.

DR. KRENZELOK: Sure, I would say yes to the

first part of the question that I think there's been enough data that we've had that we've read independently that we've had submitted to us that certainly confirms that it has abuse potential. And I don't think anybody so far, I don't think I've heard disagreement anywhere today. And then I think we've seen, to a large extent with the data, I know I've looked at AAPCC data. We've heard the data from Texas. We've heard other data from the sponsor and so on that the population at risk seems to be the kids that maybe don't have access to wheels, you know, they can't get out and buy other drugs. It's easy access. They have it at home, they can go to a pharmacy, they can go to a 7-11 store, they can go to a convenience store. So they have easy access to it. And so I think they are a very vulnerable group.

As somebody gets outside of that age spectrum, then maybe they tend to go for things with a bit more impact and a bit more zing than say dextromethorphan has. Thank you.

DR. KRAMER: Thank you.

The next person on the list is Leslie Walker.

Did you -- no? Okay.

Lawrence Carter.

DR. CARTER: Yes. To just follow up on that, I

would agree that I think that there's general agreement, or at least I'm in agreement that dextromethorphan does have potential for abuse. But if we think about the first factor in the eight-factor analysis that's generally used for scheduling decisions it speaks to actual and relative potential for abuse. And I think in this case if we thoughtfully consider the relative potential for abuse, the relative potential for abuse is pretty low.

And that's been evidenced by the data that was presented by Dr. Schuster in procedures that we use in the laboratory such as drug self-administration and drug discrimination showing that this drug is a relatively weak reinforcer. And it's also consistent with, essentially, all of the epidemiological surveys and data that we have that show that the relative abuse of this drug is relatively low.

Now each of those things are not without their own flaw. But the relative abuse potential of this drug, I think across all of the sources of data that we have is relatively low.

DR. KRAMER: I'm confused. Could you tell me what you're quoting as it's a requirement for us to comment on relative potential for abuse, relative to other agents.

DR. CARTER: That is to say relative to other

drugs.

DR. KRAMER: Yes.

DR. CARTER: Yes, so, for example, the rates that were shown relative --

DR. KRAMER: No, I don't mean what the data are for relative, but in what --

DR. CARTER: in the eight-factor analysis.

DR. KRAMER: It says actual, actual or relative potential for abuse.

DR. CARTER: Correct.

DR. KRAMER: It doesn't say both actual potential for abuse and a high incidence relative to other agents.

DR. CARTER: My understanding of that is considering actual or relative potential for abuse relative to other drugs.

DR. KRAMER: Could we get some -- I think that's an important -- I haven't been thinking of it that way. I've been thinking of a small number of deaths having significance that, you know, if we could prevent them without any negative consequences, that would be good. And now you're saying that it has to be a large number in order to --

DR. CARTER: No, don't -- no. That's not what I'm saying.

DR. KRAMER: Okay.

DR. CARTER: Certainly any death is substantial and significant and a problem. What I'm saying is when -- all drugs have risks. And no drugs are without really the potential to cause death. But when we think about this relative to other drugs that are available and even what younger folks are using, if you look at other scheduled drugs like benzodiazepines for example, the rates of abuse for this drug compared to other scheduled drugs is lower.

DR. KRAMER: Okay. We definitely need some guidance from FDA. We need to know whether we're being asked, scientifically, whether this drug itself has the potential for abuse and has some data to suggest it's really abused, or are we being asked to describe its relative abuse relative to other agents?

MS. MEHLER: Hi, Lynn Mehler. If you go back, way back to the beginning of the day when I put my slides up, I don't know if anybody can call them up. You'll see in there that I outlined eight factors that the Controlled Substances Act says to consider and then the findings that go with each schedule. And that's what was being quoted, the actual relative potential, that's one factor, the first factor.

FDA in making, doing its scientific analysis and

recommendation works through each one of those factors and analyzes it. And then we make our findings by comparing, if you look over at the findings for the schedules which should be slides seven and eight, you'll see it's all about comparing the drug you're considering or the substance you're considering scheduling to drugs that are already scheduled because it's about potential for abuse -- Schedule III is potential for abuse less than substances in Schedule I or II.

Schedule IV is potential for abuse less than substances in Schedule III. So it's all about comparing what does this compare to, where does it fit in to already controlled drugs? We take our eight factors, we make our three findings. And that's what work from because that's what -- that's the framework the statute requires.

DR. KRAMER: But what I'm concerned about is going down the path I interpreted Dr. Carter going down which was comparing the frequency of abuse of DXM with opioids, for instance, obviously much less frequent. But on the other hand, PCP is a Schedule II. And they have similar effects and you're talking about potential for abuse. So someone seeking hallucinogenic effects could get that from PCP or from DXM.

So what's the -- I think we're distorting a

regulation that, actually when you think about it, a regulation that's based on well, if it's worse than this class, then it's in this class is kind of shaky when you try to extend it over a number of years.

MS. MEHLER: That's the statutory scheme congress set out for --

DR. KRAMER: I understand, congress wrote it, not scientists. But I think for our deliberations, if the FDA is okay with this, it seems to me that we should address specifically the question we were asked here, which is what are the data receptor-binding, animal behavioral effects, human behavioral effects, and epidemiology suggesting that dextromethorphan has abuse potential. And we can commented on has documented abuse, no?

Warren Bickel.

DR. BICKEL: So you know, one thing I like about science is it's built on understanding of details an nuance. It's not a black or white thing. And I'm afraid what I hear this committee wanting to do is say yes or no. And that would be the equivalent, I think, taking Dr. Carter's tack, that saying that yeah, it's like cocaine. No. It's not like cocaine. Now it may be much worse than some other things, but there is a gradation. And there is a continuity. And you have to understand where it fits in

that continuity or I don't think we're doing justice to the science. I think we are, you know, lumping together apples and oranges.

DR. KRAMER: So specifically you recommend in terms of dealing with this question --

DR. BICKEL: I think we have to think about where it fits in the full arena of drugs of dependence that we're concerned about.

DR. KRAMER: Okay.

DR. CARTER: One way to think about this is that, you know, another sort of class of drugs, if you will that shows a similar pattern of abuse are the inhalants. Right? Typically used, predominantly by younger folks, perhaps because they're pretty widely available. So you might also think about this in the same way as the potential scheduling of inhalants, would that be a good thing? Well, there might be other things you could do to make them less available to young kids or to discourage young kids from using them. I think that might be an apt analogy to think about.

DR. KRAMER: Any other comments? Let's see, we have a list, I think. Did you put Elaine on the list?

Janet Engle.

DR. ENGLE: You know, I'm going to -- I actually

wasn't on the list, but since you called on me, I just want to make some practical comments here about this whole scheduling issue, if you'll allow me because it sort of goes with this whole abuse potential.

Everybody's assuming, and in a perfect world it's true, if something's scheduled and it's Schedule V and it's in a state that doesn't require prescription it should be accessible. But reality tells us that most pharmacies do not carry Schedule V drugs. So I just want to make sure this group understands that if you schedule it, doesn't mean it's going to be available and in fact, especially in poorer neighborhoods where there's issues of theft and that sort of thing, these folks who need cough medicine for legitimate uses will not have access.

So I just want to make sure that point's clear because I'm sure most people in this room don't go buy Schedule V things very often. And I, at my institution, I run seven out-patient pharmacies and I can you tell you the physicians who want their patients to use Schedule V drugs and patients who come into the pharmacy that can't get them.

And that's very common, at least in Chicago. So just a practical thing to think about.

DR. KRAMER: Right. Okay.

DR. WOODY: I just had a question for Dr. Maxwell about the deaths. From what I've heard today, we heard five deaths that were clearly attributable only to dextromethorphan and those were from that Indianapolis group that's out of business now. It sounded like the deaths that you picked up were -- dextromethorphan was there but there were other drugs involved in all of them; is that correct?

DR. MAXWELL: Yeah. I get the deaths certificates on all the deaths in Texas it mentioned drugs and there were seven where dextromethorphan in 2007 was on a death certificate.

DR. WOODY: Was that the only thing or it sounds to me like it was marijuana and --

DR. MAXWELL: Well, I can go back and check. I've got it here on the computer.

DR. KRAMER: Okay. While you're looking that up we had a question from Richard Honsinger.

DR. HONSINGER: Basically my answer to both questions is yes. There's abuse potential. We know the population risk. And I would say if say if anybody doesn't object to that yes, let's move on to number two.

DR. KRAMER: Okay. Is there anyone that objects to the yes?

Dr. Hendeles.

DR. HENDELES: First of all, I want to say that we're talking about a drug where there is absolutely no evidence that it's effective in children as a cough suppressant. Secondly, there is -- what evidence is available in adults, it's meager. So we're not talking about a drug that has an important therapeutic role, although it is used in high frequency because it's sold and advertised for cough but so is guaifenesin has the same kind of indications. Lay people don't differentiate between a productive and non-productive cough.

So there are other medications available. Now having said that I think that the data indicates that it has just a slight or mild -- a limited potential for abuse and yes there is an identifiable population this adolescent age group where it really is important. But if you look at all of what was presented today, there is very -- no evidence of steep increase in sales, there's no increase in emergency room visits. If you take the whole thing as a whole, it seems to be a very small problem in a limited age group. And it is also clear that scheduling a drug would not solve any more problems than scheduling OxyContin.

It obviously hasn't kept that -- that scheduling hasn't kept OxyContin out of the hands of abusers.

DR. KRAMER: Actually, I've been bothered throughout the discussion with the comparison of risk of abuse with opioids because certainly the people that have described the classic person that might want to abuse hallucinogens, a 12-to-17-year-old person just looking for a thrill or experimenting is really in quite a different class than opioid physical dependence, drug seeking behavior. And I'm just not sure why we -- how we make that transition and say that scheduling something that everyone admits is abuse -- is most often abused because it is relatively accessible, wouldn't have a different effect than the effect of scheduling OxyContin.

So, I mean, there was a different -- I'm not an expert and we have experts here. Maybe you could speak to the abuse experts, if people are these adolescents, as somebody said, get in the mindset of someone in high school who's just looking for an experience or a high, gets something because they can get it easily and stick it in their pocket and try it and drink -- everyone knows, I've talked to some young people in preparation of this committee, they say oh yeah, you drink the four ounce bottle and everyone knows it's good.

So is that different than what you expect for people that are abusing opioids?

DR. HENDELES: Why don't we schedule food? There's a lot of food abusers in this country.

DR. KRAMER: We haven't gotten to complete saturation so we have some differing opinions. So I'm going to leave it open to people who want to speak to their opinions.

Let me make sure I haven' left people off.

Dr. Honsinger. Okay.

Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: I had a comment from before lunch actually, you owe me.

So I believe that the answer to this question has to be yes because we have been discussing how to solve the problem so I think we all agree that there is a potential for abuse. So that's an easy question. But I believe now we are pushing ourselves to a harder question relative to what. And for that we have been changing our reference that in epidemiology is not a good thing to, as you were pointing out, so we were comparing for efficacy, we were comparing dextromethorphan with other things like guaifenesin now.

But for drug abuse potential, we were comparing it with opioids. Regarding the comparisons from this morning when we were trying to compare the abuse potential,

well, I think the data is very compelling it stands that it doesn't have an abuse potential at the level of opioids, that I think it was clear.

But in the data presented both from deaths and for emergency visits, it was also compared with diphenhydramine. And the abuse potential presented from emergency visits was lower for dextromethorphan both in relative terms and in absolute terms given the use of the medications. But I think that we have to differentiate two steps from going to abuse to end up in the emergency room visit in the sense that one is the number of persons abusing and other is the number of persons having adverse effects from the abuse and ended up in the emergency room visit.

And since there was data suggesting that there are more emergency room visits from diphenhydramine and it seems that at least the public knowledge is that dextromethorphan is abused more frequently, that to me, as an epidemiologist, means that there are more severe adverse effects from abusing other medications than from abusing dextromethorphan, not saying that this is a safe drug, but perhaps we should be worrying about the effects of abusing other things like diphenhydramine and perhaps other things.

In summary, I think we have to differentiate the

abuse from the deaths and emergency room visits. And if we want to focus on the severity of the adverse effects of abusing or the numbers of teenagers abusing dextromethorphan or other drugs.

DR. KRAMER: Thank you.

Dr. Bickel, did you express your -- did you have another comment or question?

DR. BICKEL: Once again, I want us to think about the continuum of abuse liability, right? So and we can do it on all the different dimensions that we would like to characterize it. We could look at prevalence of use, you know, in the target populations. We would clearly indicate that the abuse liability of dextromethorphan is perhaps equivalent to inhalants, perhaps less than tobacco because I think the prevalence rates of eighth or ninth graders are substantially higher. We could look at, you know, emergency room. And that's the kind of subtle discussion I think we need to have.

We need to go through each of these dimensions and understand where we're putting this thing and not just putting it into one global category, it's abuse potential because that's, to me, that's tantamount to saying it is like opioids. And I'm agreeing with you, it's not like opioids. It's very different. So we have to have just a

nuance view of it and not just a zero-one category. We need to have an understanding of the continuity of different levels of dependence across all the different dimensions if we really want to understand where this thing sits.

Now if we don't want to do that and if our -- and if we think that anything that could potentially be abused should be scheduled then that's a different discussion. Right, that's a different discussion then, you know, we should get tobacco scheduled quick. We should be getting other things scheduled. But I don't think that's discussion we want to have because that sounds much too unlike science as I understand it.

DR. KRAMER: Dr. Bickel, could you start off by stating those nuances as you see the data?

DR. BICKEL: Sure.

DR. KRAMER: I think the FDA is looking for our interpretation and if you want to break it down that way, that would be fine. Just start --

DR. BICKEL: You know, I don't have all the data in front of me. And I don't want to just make guesses, right, but, you know, some sense of prevalence, right? Well, it seems like the prevalence of the problem based on the presentations here would put it somewhere close to

inhalants, you know, solvents that are sometimes abused by kids of this age, substantially less than tobacco.

So that's one way of categorizing, right? It's a way of placing it in the array of potential problems. I think we could look at the self-administration literature and we, once again there, would put it that it's self-administered under several conditions but not all conditions which makes it somewhat less than the prototypic opioids and cocaine and all that jazz, right, but maybe more a kin to some other elements -- substances that we're concerned about.

So I think, you know, other people can jump in who have the relative expertise, but I think, I'd like to know where it sits in the array of things that we're concerned about because I think that guides us in understanding what the nature of the problem is and how we should more specifically have a detailed approach to it.

DR. KRAMER: The next person was Dr. -- oh, you already spoke, never mind, so Dr. Woods.

DR. WOODS: I'd just like to follow with Dr. Bickel's discussion with -- a short discussion on acute toxicity and talk about the five cases that have been brought to our attention and they've been -- I believe the have been over-emphasized. And I was struck by our first

open commentator this afternoon who said that those people have been put away at IPA in Indianapolis and there hasn't been any acute toxicity that can be totally attributed to dextromethorphan by itself since then.

Did I hear wrong? Or is that the case as far as we know it?

DR. MAXWELL: I don't think we know (off mic)

DR. KRAMER: Could the FDA comment on whether there are any remaining manufacturers of bulk DXM? That's one of the questions buried in your question, I think, because they've been put away. Are there other sources of concentrated bulk dextromethorphan on the Internet?

DR. THROCKMORTON: I can't give you numbers. There are still bulk manufacturers, many of them are overseas I understand. We don't have our compliance people here. So we wouldn't be able to give you exact numbers.

DR. KRAMER: But it is not been removed from accessibility? You're saying that --

DR. THROCKMORTON: Well, it's not removed from manufacturing. Accessibility would be a separate issue. You asked about Internet and things like that. That'd be a different kind of thing. But as far as bulk still being made, my compliance people tell me yes, that's still occurring. Now what you don't know is whether that's

being, you know, sent into proper channels and made into appropriately manufactured drug product or whether it's being diverted to illegal sales. That's the piece that I don't have, unfortunately.

DR. KRAMER: We don't know if there's non-pharmaceutical -- this product was described earlier as non-pharmaceutical grade powder --

DR. THROCKMORTON: I don't know that answer. I think Dr. Suydam said earlier that in fact there are unapproved products available, unapproved dextromethorphan-containing products on the market. So those, in some senses are being manufactured. And we don't know anything about where they're getting their bulk product if you will.

DR. KRAMER: Dr. Kukoski -- oh, yes.

DR. WOODS: I'd just like to continue with the acute toxicity. So if you grant the possibility, and it's only a possibility, that we don't a lot of acute toxicity to dextromethorphan that is clearly demonstrated in the open public literature, okay, at present, then what we have, I would contend, and this is a discussion point, my opinion, is that we have a contributor usually a contentious contributor to toxicity associated with other drugs of abuse in which it is a -- it could be a major participant to an immaterial portion of a mixed set of

toxicants. That being the case, what we're talking about is something that may have an acute toxicity that would put it something like a weak benzodiazepine, just as a comparator.

So I offer that discussion point to you to fill out part of Dr. Bickel's panorama of interesting scientific facts.

DR. KRAMER: I just need to tell the committee we're quickly running out of time. So I think Dr. Kukoski seemed to indicate by your facial language you had an answer for one of the questions Dr. Woods posed.

DR. MORRIS-KUKOSKI: I did. You talked about whether you can purchase bulk dextromethorphan. And absolutely, you can always buy -- there is chemical grade dextromethorphan that's available for laboratory use that does not require a controlled substance form to be filled out to purchase. You can also buy pharmaceutical research grade in bulk for pharmaceutical preparation as well.

DR. KRAMER: Thank you.

DR. MORRIS-KUKOSKI: And on that actually, if I can interject, my question goes back to with the bulk drug back to the FDA where they talked about on the legal slide on page -- on slide 14 for potentially controlling dextromethorphan, but the DEA can grant an exception or an

exemption to the OTC drug products that wouldn't be scheduled. Can someone clarify that please?

MS. MEHLER: The way the statute works, the Controlled Substances Act, because dextromethorphan is not a narcotic and it is available in lawfully marketed OTC products, there is an exception in the Controlled Substances Act for those lawfully marketed OTC products where they can apply to DEA for an exemption from scheduling and those particular products, my understanding of how the exemption will work, could be granted an exception from scheduling.

So they would not be scheduled. But anything doesn't meet that definition. So bulk prescription, illegal products would not get the exemption. So they would be -- assuming we scheduled it, they would be controlled.

DR. KRAMER: So that suggests that that would be a roundabout way of getting congress to make the bulk drug illegal?

MS. MEHLER: Well --

DR. THROCKMORTON: Scheduled you mean? Not illegal but controlled.

DR. KRAMER: Controlled.

MS. MEHLER: We would be --

DR. KRAMER: Still allowing the manufacturers of the OTC product to ask for an exemption be granted and be able to sell it not scheduled?

MS. MEHLER: That's how the statute's set up, so yes.

DR. KRAMER: And no one can comment on the likelihood of that exemption being granted?

MS. MEHLER: That is DEA's to grant, and they have not received an application. There's a process in the regs under which you ask for and you give the right information and you can look at your regs, but we can't -- obviously, nobody could say how that's going to come out.

DR. KRAMER: And no one would have done that since it's not schedule, okay.

MS. MEHLER: Well, there's -- not for dextromethorphan, other drugs that meet the definition there is lists in the reg of some other OTC drugs that have gone through that process and granted the exception.

DR. KRAMER: Okay. Tom Kosten.

DR. KOSTEN: Just, I agree we're kind of running out of time and it seems to me that we should move on to the second question. The first question is just it's abusable, if you just don't think that there's enough data, by God, I don't know what people are looking at.

As to whether it's a particular population, it's fairly, it's early adolescence, they start with dextromethorphan, they then go on to PCP and ecstasy and those type of drugs, I mean that's what it is clinically. I quite frankly can't understand what we're arguing about right now or what we're spending time discussing. And I really think we need to get on to the second question fairly quickly and voted on this.

DR. KRAMER: If we hear no -- let's see, we had Sharon Stancliff and Bill Cooper, do you -- you waive it?

Sharon?

DR. STANCLIFF: I just have a bit of a process question. It appears to me from the three questions that we have that we have either the choice of having the CHPA continue with their efforts or scheduling the drug, are we allowed any other sorts of recommendations?

DR. THROCKMORTON: Yeah, thank you for asking that question. We're looking -- so there are sort of two questions, two steps if you will, the first step you're being asked is the scientific question about the abuse potential. Having, let's just say you've past that or with that first question. The second question is asking how you might mitigate the risk as you understand it and scheduling might one aspect of that risk mitigation. The things that

CHPA has suggested might be another aspect, they could be done together, whatever. There might be other thing all together that you would see as useful for mitigating the risks that you would perceive, again. And so then we would ultimately make a recommendation both as to regards the science to the DEA and then depending on what that recommendation was, we'd have to decide how to mitigate that risk.

And so, no, any conversation you had about that kind of risk-mitigation strategy you think would be effective would be very helpful to us.

DR. KRAMER: Is it fair to represent the conversation we've had today on question one to be that I think there's general agreement that receptor binding, behavioral effects, and human behavioral effects, and epidemiology suggest that it has abuse potential, but the question has been raised about the relative potential relative to other compounds.

So I think we've said everything we can about that at this point. And if people are okay, I think we'll move on to the second question which has to do with methods of mitigation, one of which is the program that CHPA has put forward, but I see that Dr. Honsinger feels the need to ask a question.

DR. HONSINGER: I'd like to ask a question of the FDA. We realize that the FDA cannot tell the DEA what to do, can the advisory committee advise the DEA that this drug be scheduled, but not require prescriptions?

DR. THROCKMORTON: I think in some senses we're very fortunate because we have -- the DEA and the FDA are sitting here and listening very carefully and there are a number of people from the DEA as well as the FDA. You are advisory in the sense that we're listening very carefully to the ideas that you have. And again, how to manage that risk if you perceive that there is an abuse liability is something that both agencies are going to have a part in having to, you know, come up with the right answers. So, yes, I'm sure the DEA is listening in the same senses as the FDA is listening.

DR. KRAMER: Thank you for asking that and clarifying that. So the second question says as written, please discuss the Consumer Healthcare Products Association, CHPA, educational program on DXM abuse and prevention and its goal of preventing or reducing abuse of DXM. Do you believe such programs can help prevent or reduce the abuse of DXM? Please recommend any modifications or other measures to enhance the success of such a program. What effect do you believe that any of

these efforts would have on drug availability and patient care?

And I interpret Dr. Throckmorton's comments to be that in this discussion you could also, if you have other suggestions of mitigation approaches then you can bring that up.

Does anyone want to kick it off?

Dr. Kosten.

DR. KOSTEN: I think that the program that was presented is a very good effort to be done. I would hope that this effort would in fact continue through at least 2013 and further. That I think is an opportunity to do something that's great. Do I believe that -- will they prevent the reduced abuse? I think the data that we were shown were relatively weak and very limited and so somehow I leave -- whoever's doing this is going to have to come up with much better metrics of does this have any effect, and if it does have an effect, that it's actually due to this intervention not trends over time, cohort effects and various other things. I think the data that was shown with Dr. Schuster for marijuana is very interesting kind of data if some similar data could be demonstrated for dextromethorphan that is attitudes changed toward it that use actually is modified, that would be quite interesting.

But there's no data whatsoever to suggest that for dextromethorphan, PCP, or any of these other types of drugs.

So modifications, as I said, is really -- I don't pretend to know what measures would be best for such a program. But I think other programs like the D.A.R.E. program, in fact, did not show any efficacy in any of the studies that I've seen. And so the suggestion that that was a model for outcome measures and successful programs, I just find not credible.

And so what do I -- on drug availability and patient care, well, what was proposed was just an educational program that I don't think targeted necessarily the people may not in fact use the Internet and who are the abusers of these drugs. That just doesn't fit the clinical profile of the patients I see. So I hope that answers the question.

DR. KRAMER: Leslie Walker.

DR. WALKER: With the question do you believe such programs can help prevent or reduce the abuse of DXM, I think we've gotten in a lot of trouble in the past believing our conventional wisdom is actually accurate. I think we have to really look at evidence with that. So whether I believe or not that would be helpful I think is

not very valuable in the face of no evidence that it is valuable. So I would -- my feeling on that is that we actually have to set up, like you said, great metrics to actually see if any of this is useful.

Education, of course, is important, without it you don't have anywhere to start. But it is absolutely not a solution by itself. What effect to I believe any of these efforts would have on drug availability, my feeling without any data would be that there's no effect on drug availability with education, you know, especially if it's targeted education because who do you target?

All adolescents could be at risk. The availability is in every -- on every corner. So I'm not sure that education would change that unless it was developed in a way that showed evidence it would work. And patient care, again, looking at adolescents and children, there was no evidence that it actually -- dextromethorphan is useful for cough so I'm not sure how it would affect patient care. I think it would affect people's perception of patient care. But whether or not it really affected patient care, I would like to see the evidence of that.

DR. KRAMER: The next person on the list is Dr. Nelson, Lewis Nelson.

DR. LEWIS NELSON: Thank you. I too believe that

they've done a very nice job. They've got the right people at the table and they've put a lot of thought into developing this program. It is a little bit limited to, you know, Web-based, you know, projects right now and perhaps this could expand out.

I do think it's a little bit naïve to think that the users don't know the risks that they potentially face or that they're willing to hear the risks and listen to them because, you know, adolescents are typically not really, you know, very insightful as to the fact that they're not going to live forever and that there is risk involved with doing stupid things. And I just don't think that if they hear the risks they're going to take it to heart and they're going to do anything differently.

Now the parents maybe, if you could find the right balance of educating the parents, perhaps, but, you know, again relationships between parents and adolescents, it's often very adversarial and it may not necessarily help to get this in. So I think there's some, you know, it's good intentions. I'm wondering if it's a little bit naïve to think that just plain-old education is going to make a difference because I always sit here at this table and say education is almost, it's always helpful, but it's never the answer. And I don't see why it would hurt here,

notwithstanding the comments about educating people too widely about some of these things and actually inciting drug use, that's a very fine balance. I'm not sure how to approach.

But I do think if you were able to find the right target population and actually give them the right education and they listened to you, it would probably be beneficial. But that's a very tall order. So I don't really think that's going to probably happen.

In terms of affecting availability, I don't think it will. And patient care, you know, I sometimes wonder whether, you know, using less of this drug in the big picture might actually be a good thing. So maybe it will have positive impact on patient care.

DR. KRAMER: Okay. We have seven more comments on question two. And we really need to leave at least 25 minutes for the key question FDA needs to vote on.

Elaine Morrato, very succinctly, hopefully, everyone.

DR. MORRATO: Very succinct. I'm a big advocate that when you actually use state-of-the-art consumer marketing strategies, not just lip service to education that you can and should apply that to public health in these safety issues. And I'd like to get on the record

that I actually -- having had to sit through prescription drug-side of the world and listen to their REMS, arguments, et cetera, that it was actually refreshing to have presenting specific mitigation goals, strategies, and success metrics and that it could be a model in terms of at least having greater clarity with what's presented on the prescription side.

With regard to can this work or not and whether or not to believe, I mentioned a bit earlier that there is a national program called the Meth Project. And their core message is a tag line that I think it's relevant to teens, "Not even once." And it's trying to speak to the highly addictive nature of meth which I recognize is of a different order of magnitude than what we're talking here. But it has many of the same goals. That is, everyday people are faced with a decision to try the drug, many perceive benefits in using the drug, but little-to-no risk.

And their whole goal of the project is to arm teens and young adults with facts about the drug so that they can make informed decisions. And they do have data that shows it's effectiveness. They report that there's been a 63 percent decrease in meth use in their state, a 72 percent decrease in adult meth use reductions, 62 percent in crime, and so forth. And so it's expanded beyond just

Montana and a few other states. And I've seen the ads myself. I've seen them with my teens. And my teens can report back the tag line not even once.

So I think when you have teens that are picking up that message, that it is getting out there and is effective. Now, what is the level of investment that has been made on it? The project also claims to be research-based as we heard from CHPA. They have a highly impactful graphic advertising that portrays visually a teen-to-teen view of what does it look like to be a meth abuser.

But I think it's important to know that the campaign, they sustain a 70 to 90 saturation rate. So it's hard for me to interpret the mentions or what they're talking about in terms of marketing hits if you will with whether or not what's the percent of teens. That would be important to know. They talk about in this program that they're hitting a prevention messaging on TV, radio, billboards, newspapers, and the Internet three to five times a week and that their ads are very graphic such that they're on youtube and you have over, you know, I think over two million hits on some of the ads.

So it's obviously being viewed and being spread beyond just the immediate audience. And they're won awards for it. So I would like to suggest that at least it be

benchmarked. And I know meth is not the same thing as what the abuse we're seeing here, but I think it can be used as a model.

And I'll just add two more points for the sake of time and that is as we -- I thought it was very good that they have impression, but I would like to see actual research that evaluates the value of those impressions or what did they actually do in terms of changing attitudes, et cetera, not just the impression. And that there also should be goals or metrics for frequency of the message. So all we talked about is how many people are going to be exposed to the message, we're not talking about how frequent and what's needed to reinforce and sustain the message over time which some have mentioned.

And I think companies can do this. *Ad Age* came out last week I believe with the top 10 viral marketing ads. They include soap, chips, deodorant, soda with over 30 million online video views. So the companies here have the expertise to apply the same know-how to public health issues. And I'd like to lay out the challenge that we think is creatively about public health as we do about advertising.

DR. KRAMER: Dr. Hendeles.

DR. HENDELES: I think once you remove the threat

of decreasing the profit for these companies through this organization, you'll have no way of holding their feet to the fire. So I'm not really optimistic about that. It's much like letting the fox guard the chicken coop to me.

I think the only thing that mentioned that has any chance of helping is having an age requirement on the purchase of it. And I don't think any of the other things will really -- I mean, maybe they'll have some benefit. But I think the greatest potential benefit, knowing that there's limitations, would be an age limit.

DR. KRAMER: Sharon Stancliff.

DR. STANCLIFF: I'd like to suggest something a little bit different perhaps, whatever we do, I think it needs to be measured and I think it would be interesting to try either a time limited or a geographically limited trial of behind the counter as opposed to scheduling and of course to continue educational efforts. I think that Dr. Walker described that very well though that there are some limitations there.

DR. KRAMER: Allen Vaida.

DR. VAIDA: Just real quick, I agree with Dr. Nelson on education alone is a low-level strategy. And I know the FDA wants -- likes to listen to comments and I think they did hear a lot of comments on this question

being asked, but I think one of the things, you do need the education, it's just you need some more. And I think the age restriction and like Dr. Hendeles said, but also the bulk. I mean, the bulk product is, from what I heard with the fatalities, and the combination drug, may not be the best thing to take and to keep taking like that.

So I think those two restrictions, whatever could be done along those lines is going to be very important.

DR. KRAMER: Could FDA clarify whether there's any mechanism other than scheduling to control the bulk?

DR. VAIDA: Well, it sounds like regulation. I mean, aren't you trying to put in regulation alone?

DR. KRAMER: A congressional act would be obviously the other, but is there anything short of that?

DR. THROCKMORTON: To the extent that it's, legally it's used in a legal way to make a legally manufactured product, at present I would think we probably have limited other mechanisms to the extent that it's being diverted or to the extent it's being used to make an illegal, unapproved product, obviously we'd have our compliance standards and we'd be able to invoke.

DR. KRAMER: Next person is George Woody.

DR. WOODY: A lot of my questions were answered, but one that came up was the issue of making it behind-the-

counter versus over-the-counter, is there an intermediate step to address what Jane Maxwell said about making it less than behind the counter, but, you know, visible or at some place where somebody's sure to watch it to reduce the chances for shoplifting? I'm concerned about shoplifting with the way it's displayed.

I'm just curious what another option would be.

DR. KRAMER: Who are we -- at this point we're supposed to be -- I'm sorry, but I think we've cut off the questions to the sponsor and we're trying to get your opinion about the quality of what they've recommended as opposed -- is that correct Dr. --

DR. THROCKMORTON: How about if we just say we hear your interest in other ways of limiting ready access to the drug and over-the-counter setting, something like that?

DR. WOODY: Yes.

DR. KRAMER: So on the discussion questions from Dr. Throckmorton's comments, what you're realizing is that they're listening to our conversation. And it's informative to them even if, you know, you just express, they're taking that all in. They have a transcript and that will be considered.

We have Almut Winterstein.

DR. WINTERSTEIN: I wanted to get back to the discussion of the putting the drug behind the counter or scheduling it in terms of risk and benefit because I don't think that we can thoroughly and scientifically comment on the effects of any kind of mitigation strategy that has been presented by the sponsors just because we just don't know even though the word evidence-based has been very often used, I don't think the evaluation has been done or either by the sponsor or by anyone else to really assess right now whether any of this would be effective or not and I must admit that some of the parts of the presentations were a little bit confusing to me. And I still am worried a little bit about the infrastructure that is in place to put all of this or to roll all of this out.

So going back to if we schedule this, what happens then and what are the risks and benefits of this. I think that's the final decision or the final question we need to have to ask ourself in order to vote. And so looking at that, there's risk and benefit. The benefit is that I disagree with Dr. Hendeles that this wouldn't have an affect on access for teenagers because it seems that teenagers use this medication because it is so readily available. And I think that's a little bit different from a narcotic and the issues there with scheduling a narcotic.

So in that perspective, I think that would be a benefit of scheduling it. And it would hopefully, or I think it would mitigate some of the risks for that particular risk group you're talking about.

Now in terms of risk of scheduling, that goes back to availability. The availability issue means that if we schedule the drug we essentially move it away, we move it into pharmacies and off the shelves, that's the only thing we are doing because we are not talking about prescription issues and everything related like this. So if we move this drug into a pharmacy and off the shelf, it's still available to those who need it, obviously it is not available potentially in rural areas 24 hours a day. But I don't buy that picture of a mother who is trying to get this drug for her kid to have some acute respiratory tract infection and needs it because we just realized, I think throughout this day, that this drug has low efficacy anyways in this population. We have ACCP as well as APA both stating that it doesn't make any sense to use it in this population.

So this whole issue of access doesn't really seem to be a big issue. So from that perspective weighing risk and benefit, I really don't see the risk for scheduling it and I see some benefit, just to summarize that portion, for

whatever it's worth.

DR. KRAMER: Thank you.

Janet Engle.

DR. ENGLE: I wanted to address the specific question do the programs help or prevent or reduce the abuse of dextromethorphan. In my view as a pharmacist, we've seen parents much more informed on this whole issue since these programs have come out. I think that over they've matured. In the beginning I'm not so sure that just a hit on the Website was going to do much good. But now that there's all these print materials in the schools, parents are coming into the pharmacy educated, they're asking questions about this, things that I haven't heard in the past.

And I have to believe that they're getting this information from some of these educational efforts. Can I prove that it's, you know, solely from there? No. But I think the more we talk about it, the more important it is. Beyond that, I think in general, it just makes people understand that whether it's prescription or OTC, just because it's a legal drug doesn't mean you can abuse it. And that message has not ever been put out there. That's a new message that we're trying to get out to consumers is that just because it's a legal drug doesn't mean you can

take it any way you want. And I think that these educational programs have been very helpful in this regard.

DR. KRAMER: Edward Nelson.

DR. EDWARD NELSON: Thank you. I'd like to make a few comments also. First of all I'd like to comment to my esteemed colleague on the left here, but I counter his point, CHPA has been reliable I think in their endorsement -- when they-- when they commit to a program, I believe the history at least, my experience with that, like, 16 years, they've been true to their word. You know, take that for what it's worth.

But one of the things I think that's really important is that the law of unintended consequences of moving this product away from availability and shifting people to essentially prescription codeine has not been emphasized enough and is something to really think about. In fact, I noted one of the public speakers used the term unintended consequences. I thought as I read all this material, the law of unintended consequences could really have a significant role here.

If we move this product Class V it really will not be available most of the time. Very few pharmacies, as we've talked about, 24 hours, there's not going to be there. The CHPA is in fact proposed, besides the

educational program, besides Web-based is also educational-based is an extensive program, essentially trying to restrict the bulk sales which I think everybody here agrees to and making it over 18. I think that is a very reasonable way of making it available to people 18 and over, a very reasonable way to approach this and allowing the public to have available a product that does deliver cough reduction, maybe it's not as potent as some of the other high potency opiates. But it clearly, at least in a number of studies, has at least in adults.

DR. KRAMER: We are going on to the last question which is the voting question. And I would suggest, the question just says in consideration of the issues that we've discussed, do you recommend that DXM be scheduled under the Controlled Substances Act which is what the DEA asked FDA to comment on in terms of the scientific basis which is -- the way the questions are structured reflects to me the FDA's explanation that they're trying to go from a scientific basis of what the potential is, what existing programs or recommended additional programs you could come up with and then to the final question of should it be scheduled.

Before we actually take the vote, I would like to allow, I think some people have already started this, I

think Dr. Winterstein's comments kind of get to this issue of risk-benefit. If people have some general comments that directly reflect on this that they want to share with each other on the panel, then I'll open it up to a few, but we don't have long.

Am I correct that when we vote we're going to have to all simultaneously vote and then we'll go around and ask for an explanation. So we need to go around the whole table. So we may be a little late if you talk too long.

DR. COOPER: I think in order to vote on this issue I need to -- I still don't understand what the implications of it being scheduled are even despite our conversation this morning. So if that could be clarified that would be helpful.

DR. KRAMER: Can I take a stab at summarizing what I think I heard? And I've been asking this question since before the meeting. I think I heard that if the drug were to be scheduled that the federal law would mean that it would likely be put in Schedule V, that would not require that a prescription be written, but that it be controlled with registration by a pharmacist as I understand it.

However, there are, at least from what I'm told,

18 states that have more restrictive laws and in at least three of those 18, those laws require that anything in Schedule V would require a prescription. So at least in California, Colorado, and what was the other one, Hawaii, three of those 15 would definitely require a prescription. And what is unclear to me is whether if this committee would actually recommend, if it were scheduled that it not be required, a prescription not be required if it would have any effect on anything. That's what I know. And if I'm wrong, correct. I thought I'd put a straw man out there for the FDA to respond to.

DR. CARTER: May I add that I think another potentially, not inconsequential result of scheduling is that it may result in a number of children who make a youthful mistake to bear some sort of criminal result or consequence as a result of abusing this drug as opposed to what it stands right now. So that's another potential consequence of scheduling.

DR. KRAMER: Could you explain that, what you mean by that?

DR. CARTER: If now by abusing a scheduled drug they are now breaking the law, there may be criminal consequences that they would bear if this drug were scheduled as if it were not.

DR. KRAMER: A Schedule V drug? Could someone educate us about the legal consequences of use of a Schedule V drug?

MS. MEHLER: I'm going to try to quickly knock some of these off. If HHS recommended scheduling and DEA scheduled it, whether or not -- whatever schedule it's in, it is still an OTC product. So from the federal perspective, you would not need a prescription. Because of the exemption of the CSA, over-the-counter drugs could be exempted from scheduling. And they would not be scheduled. State law may require that in that particular state it be dispensed by a pharmacist or require a prescription. We know that there's about 18 of those. We know, I think four of them now we know would require a prescription.

But from the federal perspective, the drugs that would stay on the market OTC, whatever schedule we would recommend would still be OTC. Now as far as the criminal penalties associated with possession or sale of a scheduled drug, it depends on the schedule --

DR. KRAMER: Schedule V, specifically.

MS. MEHLER: I am not a DEA criminal attorney. But I will tell you that it is illegal to possess a scheduled substance for a non-medical reason or, you know, obviously if you had prescription or whatever, but whether

that would apply to an OTC drug that were used, I can't tell you. But I think that's an interesting -- I mean, there's clearly -- that's why things are scheduled, they come with penalties.

DR. KRAMER: Thank you. I've been -- excuse me.

DR. CARTER: My point's not so much about the consequences, but it just moves from doing something stupid to breaking the law.

DR. KRAMER: Whether that would become a reality, we can't tell from the answer we heard in terms of how realistic that is. That something that's OTC somebody would be prosecuted for that. But could I just say that someone pointed out to me that one of the most obvious things I didn't say about what would happen if it were scheduled, and it is true, and that is that this drug could not be sold in grocery stores and outlets that don't have a pharmacy. So I didn't say the most obvious.

That's not true? No, if an exemption were not granted --

MS. MEHLER: Yes, you are correct. If no exemption were granted and were not applied for.

DR. KRAMER: I hear you that they can go around this, but if an exemption were not granted it could not be sold in a grocery store; is that correct?

MS. MEHLER: According to DEA regulations, if you are scheduled drug, but you're OTC, you have to be only sold through a pharmacy and you have to be, I think over 18 and there has to be a log kept if you don't get the exemption.

DR. KRAMER: Question answered? Okay.

Any other comments that people need to -- oh, we have people who want to speak.

William Cooper. That was you, you asked your question.

Richard Honsigner. No, Edward Nelson.

DR. EDWARD NELSON: Just a brief comment on that question of the exemption or the issue with the exemption. If the product is taken to classification V or it could be -- I mean nobody here today is saying it's going to be V, we're assuming it's V, but it could be -- obviously it won't be I, I think we could all agree there.

But the question is -- or the point I would like to make is, once that happens without exemption, this drug product becomes very restricted. And these exemptions could, you know, they would be petitions, they'd be under review, my experience with the petitions and review is that could be one week and it could be five years.

DR. KRAMER: And we don't know if it's individual

-- the question was asked early in the meeting whether each individual company would have to apply or whether the whole class --

DR. EDWARD NELSON: That's a very good question --

DR. KRAMER: -- and we don't know the answer.

DR. EDWARD NELSON: -- of a mixed products versus, you know, combinations with decongestants as well as an antihistamine. So if you vote to regulate this as a Class V, you could be in fact voting to remove this from the market for several years or making its availability extremely limited.

DR. KRAMER: You would move it to the pharmacy where you'd have to sign a log.

DR. EDWARD NELSON: That's right. And in some states --

DR. KRAMER: Let's be clear, you're not removing it from the market. You would restrict it to sales in pharmacy and you'd have to sign for it so a teenager who's 12 or 14 and wants to get a high would unlikely go to the pharmacist and ask to receive it. All right.

Janet Engle.

DR. ENGLE: Just some practical issues that I see as a pharmacist with this. I'm predicating my comments on

that I believe it's efficacious in adults, not in kids, all right. If you believe that there's enough evidence --

DR. KRAMER: Could you specify for what indication?

DR. ENGLE: Dextromethorphan is efficacious for a hacking cough, the ACCP guidelines say not necessarily for URI, but what they did say is that there was not enough evidence one way or the other. They didn't say that there was data that showed it was not efficacious. So in the community pharmacy setting when you have a patient coming in, an adult patient, it's at night, or it's some time where they have no access to healthcare professionals and they need cough medicine to help a dry hacking cough and it's a reasonable indication for self-care, if this becomes scheduled there's a couple things that happen. One is if my pharmacy doesn't carry it, the only thing I'm left with is either camphor menthol which I don't think anybody believes is efficacious, or diphenhydramine.

Diphenhydramine is completely inappropriate in most patients during the day. You get presentees and you get issues. So right there you've restricted what a patient can have in that out-patient setting. The other thing that we're not considering is that there's over 100 dextromethorphan products. And as a practitioner, there

are times when one product's better than another. Some patients can't swallow pills so the gel caps are no good and you want to use the liquid. Certain patients don't like the taste of one versus another.

So to have choice in the OTC setting is really important. And that would be taken away because if it goes behind the counter, there was no way those products are going to fit back there and most pharmacies will end up carrying maybe one, if you're lucky. So I think there's a consumer choice issue there in terms of what they can use for the products if you end up scheduling it. So it's not just a matter of scheduling it, there's all kinds of practical issues that go with it. And I hope that people will consider that when they vote on this.

DR. KRAMER: Dr. Woody.

DR. WOODY: Just a historical comment. I was at the Drug Abuse Advisory Committee meeting in 19 -- 1992, '82, 1992, when this was discussed. So we're sort of working with a historical process here. To me what the CHPA has suggested sounds very reasonable. But their two hookers, two of the components of it require congressional action which is a little bit uncertain. So I just sort of wonder if, in my mind, if there's a possibility of the trade organization has been pushing with congress that

could be successful the next couple of months, see what happens and make a meeting in a year with additional -- certainly the educational program would go forward. And if congress puts an age restriction on it and made the law so that the bulk wasn't there that would -- that could really have an effect.

DR. KRAMER: I think the FDA wants to hear what the committee members would recommend in terms of unlimited access and recognizing we can't control whether congress acts or whatever.

Just one comment I would like to just -- Dr. Engle, you made the comment that if this were scheduled it would not be stocked. You predicted the pharmacists wouldn't stock it because it's their choice whether they sell it. But having lived through this whole thing from the '60s on and worked in drug stores myself, I think that -- I know why people stopped stocking products containing codeine and it was because opioid abusers were trying to abuse them. And it was very obvious. And there was a threat of that kind of use.

I think, again, the profile of this type of abuse is different. And I think -- I don't think there's much risk to a pharmacist stocking dextromethorphan-containing cough syrups other than the space limitation. There's no

reason they should not choose to sell it because somebody has to sign a log. They're not going to be -- people aren't going to break into their drug store to get that drug.

And so I think the assumption that it wouldn't be stocked is purely an assumption. I don't think we have any data to suggest it suddenly would be unavailable.

DR. ENGLE: I would agree that it's an assumption. But I also know, again, I have seven pharmacies that I'm responsible for, the paperwork and the recordkeeping, it's just not worth it. And so --

DR. KRAMER: It's just a piece of paper with a line on everybody that bought it.

Lawrence Cooper. Lawrence Cooper? There's not a Lawrence Cooper.

Richard Denisco.

DR. DENISCO: Real quick, I agree that we absolutely have to get the bulk sales off the Internet and that's just got to stop no matter how it gets done. And I hope the DEA can use all their creative ways to do that. The second thing is just buying this or having it very easily stolen by adolescents is not a good thing.

However, there's another thing, I mean, I have a hard enough time in this area getting a prescription filled

to go through the pharmacy, get the pharmacist, oh, we've got a lot ahead of you, come back next week. Okay. So that's a problem. The second problem is we're going to have to consider putting masks in the front of the drug store because of hacking coughs. In Canada now if you go into a doctor's office there's a cubicle before you enter the waiting room that if you have a cough you put on a mask or you don't get in.

You know, it creates other problems. And I do know that we're asking people to self-diagnose and self-treat for self-limiting conditions. And we do have to be careful when we ask people to do that to not take away their tools because they get very upset when you do that.

DR. KRAMER: We have one more comment.

Mr. Mullins.

MR. MULLINS: I wanted to speak to the issue of accessibility because I do believe scheduling is a necessary component of this whole strategy. But I want to address the way -- the acquisition issue because young people or the person that's trying to abuse this drug, age alone is not a deterrent. If you have someone say you have to be 18 to purchase this medication, what happens, if you don't define bulk in the retail setting, what the dealers do is they come in and they purchase two or $300 worth of

Robitussin. So I think age is okay. But I think we have to have a issue that addresses the dealers of the dextromethorphan.

So I think you have to address the whole issue as far as retail bulk purchases. Also in online purchases, we have to address the whole issue of how you authenticate the age because right now someone could go online and purchase a product. How do you authenticate age in online purchases for the finished product. I think that's a issue. So I think there has to be some controls there.

And I think I heard several people mention that there will be a void in the market. But I think based on the market, based on historical sales, I think marketers would move very quickly to fill this void of available medications for a market that's already proven demand. So I don't worry, I mean, with billions of dollars of sales, they'll figure it out. And they'll get in. And we will push innovation because I don't think there will be a void in medications in this area. So I think -- I don't believe that's an issue.

Thank you.

DR. KRAMER: We need to move on to the vote. Here are the instructions. Listen carefully. I have a long pink sheet here. Voting procedures, we will be using

the electronic voting system. Each of you have three voting buttons on your microphone, yes, no, and abstain. Once we begin the vote please press the button that corresponds to your vote. After everyone has completed their vote the vote will be locked in. It will then be displayed on the screen. I'll read the vote from the screen into the record. Next, we'll go around the room and each individual who voted will state their name and vote into the record as well as the reason why they voted as they did.

The question in consideration of issues discussed above, do you recommend that DXM be scheduled in the Controlled Substance Act?

Ready? Are we ready for everyone to vote? Okay, you can vote. Do we just press once? I've been told before to press it more than once to make sure. You have it by name. They have it by name so if you press twice they'll know it's you pressing twice.

Pardon?

(Comments off the mic.)

DR. KRAMER: With the same button, right. You can cancel your vote if you'd like.

UNIDENTIFIED: Why does the button keep flashing?

(Pause for voting)

DR. KRAMER: One person hasn't voted. It should be yes, no, or abstain.

All right. Everyone push your button one more time.

(Pause for voting)

DR. KRAMER: How many took, people?

Have you counted? How many people are voting?

MS. FERGUSON: Yeah, they've got a list. They just have to figure out who --

DR. KRAMER: What's the verdict? Still missing one vote. Okay. Whoever's not voting or not pressing it firmly enough is keeping us here. Let's do it one more time. Vote one more time. Press the button again.

(Pause for voting)

DR. KRAMER: So all people voting, "Yes, it should be scheduled," need to raise their hand now and hold their hand up until I read your name into the record, okay? Ready, set, go.

All right. Dr. Honsinger, Dr. Walker, Dr. Nelson, Dr. Winterstein -- is that Marilyn Eichner -- Dr. Kramer, Mr. Mullins, Dr. Maxwell, Dr. Kosten. How many is that? All right. Got it all?

Next we have no's. Hold your hand up.

Dr. Hendeles, Dr. Woody, Dr. Engle, Dr.

Krenzelok, Cynthia Morris-Kukoski, Dr. Hernandez-Diaz, Sharon Stancliff, Dr. Woods, Allen Vaida, Bill Cooper, Elaine Morrato, Richard Denisco, Lawrence Carter, Mary Ellen Olbrisch, and Warren Bickel.

MS. FERGUSON: And abstains.

DR. KRAMER: And abstains, anyone abstain?

No, what have we got? Nine yeses and 15 no's. Now we have to go around the room and have you say why you voted the way you did.

Dr. Hendeles.

DR. HENDELES: Because I think the -- I don't think that the putting it on the --

DR. KRAMER: You have to say how you voted first and then say --

DR. HENDELES: Sorry. I voted because I don't think that scheduling it will solve the problem.

DR. KRAMER: Dr. Honsinger.

DR. HONSINGER: I voted yes. I voted yes because I think this is the only means of restricting access to this drug. This has been in congress three years, four bills, most bills don't make it to become law, and as I read the description of Schedule V, this drug fits the description of Schedule V.

DR. KRAMER: Dr. Walker.

DR. WALKER: Leslie Walker, and I voted yes for the reason that I think it's one of the only ways to decrease easy access to the target population that tends to abuse it.

DR. WOODY: I voted no because I don't think that it's going to solve the problem. There seems to be a relatively small proportion of people who abuse it and I think that putting it on Schedule V isn't going to impact on that very much. I think you have a much better -- at least other things should be tried first.

DR. KRAMER: Dr. Engle.

DR. ENGLE: Jan Engle, I voted no because I don't think there's any data to show that scheduling this drug necessarily decreases abuse.

DR. KRAMER: Dr. Krenzelok.

DR. KRENZELOK: Ed Krenzelok, I voted no. I think the risk in minimal compared to the benefits of using it. And then when you compare it to other substances of abuse, solvents, ethanols, cigarettes, prescription drugs, tobacco, natural substances, I think it's minimal.

DR. KRAMER: Dr. Nelson, Lewis Nelson.

DR. LEWIS NELSON: Lewis Nelson, I voted yes. But I will tell you that there's so many unknown's here that it was a very qualified yes. I mean, I kind of feel

like if we knew some of the data that would subsequently happen, it would make it a lot more comfortable of a vote. So it was a very qualified yes.

DR. KRAMER: Dr. Kukoski.

DR. MORRIS-KUKOSKI: I voted no. A couple reasons. I thought that scheduling wouldn't solve all the problems. I do agree we do need to restrict the bulk and restrict the product to more than 18 years of age. I was concerned however on how much -- what the availability would be in the 18 states that would -- if we control it to Schedule V, what their access would be.

DR. KRAMER: Dr. Winterstein.

DR. WINTERSTEIN: I voted yes for the reasons stated earlier and my most recent comment. I also simply went by the eight criteria for scheduling and it seemed to fit those criteria quite well. So at the end the absence of a lot of evidence and I agree that I wish there more, I simply went with those criteria.

DR. KRAMER: Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: I voted no because the way they present it to support the effective scheduling was not strong enough. But I would like to also recommend evaluation and follow-up of our decision so that 20 years from now we don't come back saying that we wanted more data

and we still don't have it.

DR. KRAMER: Marilyn Eichner.

MS. EICHNER: I voted yes because basically I believe that we have a drug on the market targeted mainly toward pediatrics and we have -- we lack efficacy showing that this drug even works. I'd more interested in people putting their time and energy into doing clinical trials that would show -- give us some more data and it's not even clear that it does that well in adults either. So limiting the drug, to me, wasn't a problem if it's not working, it's just out there for the teenagers to get their hands on.

DR. STANCLIFF: I voted no. While I agree that it is perhaps not a very efficacious drug, I felt that that puts a lot of burden on people that have grown to count on it over the years. And I'd like to see it moved away from the market in other ways. I do think we need to continue to work on restricting access to it for that particular population. But there are other means to do so.

DR. KRAMER: That was Sharon Stancliff, sorry for not introducing you.

Dr. Woods, James Woods.

DR. WOODS: I voted no. I feel like we're in a bit of a time warp with the Controlled Substances Act trying to apply it to things that need a totally different

kind of approach with the Internet and the way young people are being influenced to take drugs. And I think that the Controlled Substances Act is almost inappropriate for the present day.

DR. KRAMER: I voted yes, this is Judith Kramer. I voted yes. I think that the information that was available at the time the final monograph was determined did not have the awareness that we now have about the NMDA receptor effects. And I think our young population has discovered that before we may have discovered that in terms of the hallucinogenic effects. It seems like a very clear-cut example of a target population that has this potential for abuse and has this ready available access.

It seems to me that this scheduling is the only way to reliably control the bulk, access to the bulk drugs since I am not confident that congress is going to act in a timely manner or at all. And I think it is completely unrealistic that an age restriction could ever be enforced for a cough syrup and the number of outlets and the number of employees and the level of education and reliability of those employees.

Oh, and one more thing, I think that if we did schedule it, I think we should -- I would, as recommendation, make very clear that those 18 states

reconsider their requirement for a prescription for all Schedule V drugs and have this in a category by itself as a scheduled drug but specifically not requiring a prescription in any state.

DR. VAIDA: Allen Vaida. I voted no and part of that was I was afraid of the limited access and not enough information on the exemption. And finally, also have to totally agree with Dr. Woods. I mean, I think with all the discussion we've come to learn that this scheduling may have outlived its purpose for everything that we want to work around it.

DR. COOPER: This is Bill Cooper. I voted no because I think that the drug does have risk for abuse and it's important but limited in scope and in weighing the risks and benefits as scheduled. And I don't feel that there was any evidence presented that suggested that scheduling will reduce access to the target populations.

DR. MORRATO: Elaine Morrato, and I voted no. I also was interested in ensuring that OT access to the drugs was protected. I was particularly persuaded by Dr. Engle's comments on the practical considerations of how this would play out in pharmacies and for patients used to taking the drug.

I do agree though with the risk mitigation goals,

CHPA outline, and specifically limiting access to teens via legislation. It was my preferred route. However, if legislation passage is uncertain as we know and it doesn't pass within a time frame, let's say two years as CHPA says, then I would have changed my vote to yes and we should proceed with scheduling.

MR. MULLINS: I'm Rodney Mullins. And I voted yes for controlling this medication through scheduling for a couple of reasons. One, I believe that scheduling sends a message to the American public because right now they're very calm and cool about -- and relaxed about the efficacy and the safety and the dangers related to this medication. I think they look to us to send a signal. And I think by not making a move today we send a signal to them.

I think, secondly, in talking to all the young people I've talked to in hundreds, accessibility is a key thing. I think we've not done anything about accessibility. So today, tomorrow, and next month there will still be people stealing and making bulk purchases of dextromethorphan. So that's why I voted yes.

Thank you.

DR. MAXWELL:: I voted yes because the questions, as written, actually gave us no other choice in terms of doing something about it. I agree with putting it behind

the counter, age limits need to be addressed. I also think although the yes votes did not win, it's sending a message to the producers that you, the producers and the pharma need to start working with your local stores to get that product moved where it could be supervised.

I don't want to go in the drug store a month from now and see that it hadn't been moved. And that's something the industry needs to address and can address now because if it doesn't happen, next time it comes around, it will be scheduled.

DR. KOSTEN: I voted yes. It's abused by young people. It's a gateway drug into PCP and a variety of other hallucinogens. There is no data that the current strategies are working. The medication itself has got very poor efficacy. Congress hasn't done anything to in fact move ahead with legislation that would do some of the things we're describing here. We had no data from the 18 states that do in fact have restrictions on this cough syrup use and what happens there. We have a natural experiment. I didn't see any data presented from everyone. And I think that was -- I'm sorry, I just think that's criminal that we don't have that kind of information when it's been done.

I think restricting the bulk sales is extremely

important. And I think this is the way to do it. And I view an otherwise paralyzed system for doing this. And I think as Dr. Maxwell has said, I'll be very distressed to see that the access is going to look exactly the same with it hidden on a lower shelf in a very easy place. Kids don't buy this, they steal it. I just -- sorry.

DR. DENISCO: Richard Denisco. I voted no, but it was close. I viewed this as two public health concerns. One is a low level, relatively, I'm sorry, but it's still relatively low level addictive substance that is abused by specific target age group compared to a huge public health problem of upper respiratory infections. These medications are dependent on, we do not have the pharmacy or physician staff to handle this in ways that were suggested. And I think it would ultimately result in a tremendous lack of access whether people do not view things with double-blind studies. They view it with their own practical experience. And again, we are asking people to self-treat on certain diseases.

However, I must agree that if bulk sales don't change, if access to all age groups, and all unlimited amounts doesn't change, I would have viewed this vote as a mistake, if in two years things don't change.

DR. CARTER: Lawrence Carter. I voted no.

Primarily because I believe that we should try and find the appropriate sized patch to fix this hole that we're trying to fix. I think that scheduling is a relatively drastic move to fix a problem that's far from epidemic. I do support the age restrictions and the attempts to control the sale of bulk dextromethorphan.

DR. OLBRISCH: Mary Ellen Olbrisch. I voted no because I feel that there other approaches to addressing the problem. And I feel that scheduling is probably not going to be very effective in addressing this problem. And while I feel that probably there would be no great loss if this drug disappeared from the market at all. And it might be nice if other drugs were developed that were actually more effective. In the meantime, I did think that in terms of proportionality, there would be difficulty in terms of lack of access for people who had legitimate uses for it or legitimate uses for whatever they thought it was good for.

DR. BICKEL: Warren Bickel. I voted no. I think there's a low level of abuse. And I think we need to have a scalpel to address the problem, not a big hammer. And I think I'd like to encourage whoever is appropriate to encourage to think about what other scalpels can be used instead of the big hammer for these subtle cases.

I agree with Dr. Woods, perhaps the Act covering

this is no longer doing the job that it needs to. I would like to encourage the FDA in future meetings of this type to provide more information about the impact on availability than we are able to have at this meeting. I would also like to see the FDA incorporate other sources of data such as Monitoring the Future data when asking questions about abuse so that we can have a fuller plate of information by which to make these decisions.

DR. KLEIN: You know, I would like to thank the committee for your thoughtfulness, for your advice. We will pour over the transcripts in the days ahead and learn things that we probably missed in your recommendations. And your advice is certainly helpful.

I would like to thank you, particularly, Dr. Kramer for the interactions we've had on this issue and for leading this very difficult topic today.

DR. KRAMER: I've been asked by Elaine, if everyone could leave their name tag, maybe attach it to your tent cards because the FDA invested a fair amount of money in getting us nice name tags. We'd like to save them pennies.

DR. KLEIN: Thank you.

(Whereupon, at 5:21 p.m., the meeting was adjourned.)