Center for Substance Abuse Prevention (CSAP)
Substance Abuse and Mental Health Services Administration (SAMHSA)

Meeting of the

Drug Testing Advisory Board (DTAB)

OPEN SESSION

January 31, 2012

Sugarloaf Conference Room
One Choke Cherry Road
Rockville, Maryland

Table of Contents

Proceedings (9:00 a.m. EST)

Call to Order

Dr. Cook: Good morning. I am Janine Cook, the Designated Federal Official and Acting Chair of the Drug Testing Advisory Board, or DTAB. As the DFO of the meeting, I officially call it to order.

First, I have a few announcements. For those of you here onsite, a copy of the agenda is available at the registration table. For those of you joining us remotely, the link for the agenda was emailed to you yesterday. There are a few changes to the agenda because of conflicts in our presenters' schedules. Dr. Barry Sample will be presenting in place of Barbara Rowland, and he will be speaking after me. Dr. Mike Walsh will then present after Dr. Sample.

The DTAB has its own website, located at the link shown on this slide. The DTAB website is also available through the Division of Workplace Programs' webpage. Included on the DTAB website are the DTAB charter, the roster of Board members, and meeting information, including past, present, and future meetings. Within a few weeks, the minutes, proceedings, and presentations from the open session will be available on the DTAB website.

For those of you that have any questions concerning the material presented during the open sessions, we have two options for you to submit your questions. If you are attending onsite, 3 x 5 cards are located at the registration table in the back of the room for you to record those questions. You may leave your questions with a member of the staff at that table. If you are attending the meeting remotely, there is the option for typing your question into the Q & A pane. All submitted questions are discussed by the Board in the closed session.

The public comment period is scheduled to begin at 3:00 p.m. Eastern Standard Time today, though the exact time is dependent on our progression through the agenda. Currently, there are three attendees who have registered to make public comment. If anyone else wishes to give public comment and has not yet registered, you may register onsite at the registration table, or you may type in that request in the Q & A pane of your web conferencing. The public comment period is restricted to the time allotted, and the time will be equally divided among all of the commenters. All public comments will be included in the meeting minutes, as well as in the transcript. Please provide either a hard copy or an electronic copy of your comments to be shared with the transcriptionist to ensure of the accuracy of your comments. We will not be responding to any public comments at this time, but they will be taken under consideration during the closed session.

Please silence your electronic devices because these will interfere with both the AV, as well as the transcription, equipment.

I have some housekeeping announcements. For onsite guests, restrooms are located just outside the door to the right. The registration table is located in the back of the conference room. If you have not already done so, please sign in when we have our lunch break. The Uncommon Café, which is located just down the hall to the right, is available if you wish to purchase food and beverages. For those who want to eat out for lunch and return for the afternoon session, there are many different dining options available close by. Please wear your SAMHSA badge while you are in the building. If you plan to leave for lunch and return for the afternoon session, please retain your badge to reenter the building. You will return your badge to the security guards at the end of the open session. For our guests who are attending this conference offsite, the Verizon operator now has some instructions for you.

Now I will put on my acting chair hat to welcome the members of the Drug Testing Advisory Board: Bobby Bonds, Jim Bourland, Larry Bowers, Lawrence Brown, Phyllis Chandler, Laurel Farrell, Courtney Lias, Donna Smith, Jim Swart, and Steve Wong.

Barbara Rowland is not able to be with us today. I want to extend our sincerest sympathies to her and her family at this time.

I'd also like to introduce members of the Division of Workplace Programs (DWP), because without their invaluable assistance, this meeting would not have been possible: Carol Rest-Mincberg, Donna Bush, Jennifer Fan, Ron Flegel, Gene Hayes, Giselle Hersh, Charlie LoDico, Hyden Shen, and Elaine White. Our intern, who just joined us a few days ago and jumped right into the fire with this meeting, is Courtney Bannister. I also want to recognize our contractor, Bill Sowers, who mans our Drug-Free Workplace Helpline.

I also want to recognize some other distinguished guests that are here with us today, including Administrator Hyde, CSAP Center Director Fran Harding, Dave Mineta and Jack Stein from the Office of the National Drug Control Policy (ONDCP), Marilyn Huestis and Antonello Bonci from the National Institute on Drug Abuse (NIDA), Dean Raab from the Department of Justice (DOJ), and Paul Harris and Will Smith from the Nuclear Regulatory Commission (NRC). If I have forgotten anyone else, I am sorry.

We have the save the dates for the two next DTAB meetings. They have been tentatively scheduled for August 27th and 28th and September 24th and 25th, 2012.

Welcoming and Opening Remarks

Dr. Cook: I want to introduce Captain Carol Rest-Mincberg, who is the Director of Division Workplace Programs. I sadly report that this will probably be the last DTAB meeting that Carol will officially attend. She is scheduled to retire in May, after 35 years of service to the U.S. Public Health Service Commissioned Corps. All of us at the Division of Workplace Programs want to take this opportunity to publicly thank her for her leadership that she has provided the Division over the last 18 months.

CAPT Rest-Mincberg: Good morning, everybody, and thank you, Janine. You have now pretty much outted me on what my age is. Thanks. Good morning and welcome to everybody who is here and thank you for coming. Last year, after 18 months of a hiatus, the DTAB reconvened. And as luck would have it, a major snowstorm was scheduled for the second day of the DTAB. I think all of you remember that. Eager to proceed with the agenda, the DWP staff, on their own, made arrangements to stay the night in the building. They arrived with backpacks, sleeping bags, and changes of clothes. They called the Office of the General Counsel (OGC) to determine whether it would be okay for the DTAB to convene on the second day if the Federal government was closed. The OGC said yes, they could, and nothing could stop the momentum that started with that first meeting. No snowstorm was going to stop DTAB and its progress, and it set the momentum for the rest of the year. And a productive year it was. The highlights were the two recommendations concerning oral fluids and prescription drugs. We know the impact of these DTAB recommendations will far exceed the programs for which SAMHSA is responsible. They are applied to many programs, other places in the Federal government, in the private sector and, in fact, in other countries.

Based of the commitment to use the best science available for the foundation of the changes that we propose for the Mandatory Guidelines, the standards developed through this process are adopted, published in the Federal Register, and applied to many workplace scenarios. The science that we apply is the foundation that provides credibility for what we do and is evident in the Guidelines. And for that, we have to thank NIDA, especially Drs. Bonci and Marilyn Huestis. The research conducted at NIDA provides the foundation, contributes to the integrity, and allows us to advance this program. And that is why this program is recognized outside of the government and is applied in so many other places. Thank you for all the work that you do and for helping us keep the momentum going.

We are also grateful to our other Federal partners who help us to both develop and confirm the science. They do it in many ways, whether by research or regulation, and share their data across the Federal government. Dr. Courtney Harper Lias oversees the unit at FDA that is responsible for approving the devices that we would be using, whether it is for oral fluids, urine, or other specimens.

From the radio and the TV, you learn that kids are using drugs. Testing devices to check for drug use are available. Unfortunately, many of these have not been approved and are not reliable. But people believe because they have seen them advertised on TV or on the internet that they are acceptable. There are many

programs in this country, even public programs, which are using devices that have not been approved or processes that have not been validated. We rely on FDA and Dr. Lias to approve these devices. It is synergy and partnership that moves us forward. Thank you.

I would also like to thank Jim Swart at the Department of Transportation (DOT) and Paul Harris at the NRC, who between them are responsible for testing most of the regulated industries.

DWP and HHS kept pace with the ambitious agenda set by the DTAB and the expectations from ONDCP. Our General Counsel, Rina Hakimian, regularly guides us through the maze of Federal regulations and laws that we must be cognizant of because this is a regulatory process. Rina often relies on the external counsel from our DOJ Judge Advocate General (JAG) Counsel, Colonel Dean Raab. Dean, thank you for what you do. And Rina, we appreciate what you do too.

I also want to recognize the DWP staff: Janine Cook, Acting DTAB Chair and senior chemist; Charlie LoDico, senior toxicologist; Ron Flegel, senior forensic scientist; Jennifer Fan, senior pharmacist; Hyden Shen, senior policy advisor; Commander Eugene Hayes, policy analyst; Giselle Hersh; and Elaine White, travel preparer.

This ambitious schedule, which requires that we work together with our other Federal partners, with the DTAB, the other agencies, happened under the leadership of SAMHSA Administrator Pam Hyde, CSAP Center Director Fran Harding, and CSAP Deputy Director Mike Etzinger.

The Drug-Free Workplace Programs, particularly the testing standards, contribute to the mission of the National Drug Control Strategy from ONDCP of the Executive Office of the President. We appreciate the continuing support and engagement of our partners at ONDCP, including Dave Mineta and Jack Stein, who are with us in person today, Martha Gainey, Dan Augustine, Terry Zobeck, and Ed Jurith. We are fortunate they take the extra effort to either attend the DTAB meetings in person or to call in. And with that, I would like to introduce Dave Mineta, who will say a few words.

Mr. Mineta: Thank you, Carol. I wanted to start off and welcome everyone and thank the DTAB members for all of your work, both at the meetings and between the meetings.

This is clearly a very important endeavor for the Federal government and for all of us. We are looking forward to this meeting today because this is a very significant meeting and important for our timeline as we move forward. Also, I would like to thank Pam and her staff, and in particular, the DWP staff. As Janine was saying earlier, that this likely will be Carol's last meeting. I want to say how fortunate we all feel that she was actually here for today. She is, and has been, a great leader and a delight to work with on this very, very important work that you all do. I will reserve the rest of my comments for a little bit later in the agenda, after the Administrator makes her remarks.

CAPT Rest-Mincberg: Thank you. As a brief introduction to CSAP Director Fran Harding, in addition to being the Director of the Center for Substance Abuse Prevention, she is also the lead for SAMHSA's Initiative on Prevention. Through this, and the other initiatives that she is involved in, Ms. Harding regularly highlights the work that is done here with the DTAB and in the DWP as a public health prevention program.

Workplace drug testing is the largest universal prevention program within SAMHSA because it protects everybody in the United States from injury and death through testing in the workplace. Every time you board an airplane, ride on an bus, are passed by a truck on the highway, travel by train, know that the people who are driving or are responsible for these modes of transportation have been drug tested. Using the definition from the Institute of Medicine (IOM), the Drug-Free Workplace Testing Programs have both universal prevention, defined as strategies that benefit the entire population, and selective prevention, defined as targeting specific subgroups.

The selective substance abuse prevention program targets 400,000 Federal employees that are drug tested and over 12 million workers in Federally-regulated industries, plus those in non-regulated private sector

industries that have applied the Mandatory Guidelines. Empirical evidence demonstrates selective prevention among tested workers has resulted in a continuing decline in illicit drug use since the creation of this program. Universal prevention effectively decreases injury and death among the general population. This is the work that Fran Harding is doing as the lead on prevention, spreading the word on the impact of this program. So with that, I present Fran Harding.

Ms. Harding: Thank you very much. I did not realize that this was going to become a public goodbye to Carol. I am not prepared for that because I am still in denial, as May quickly approaches. I am honored that I am here at her last official meeting with you. She talks about the work that comes out of the Board all of the time. I vowed to you the first time I stood before you that we continue to support you through your recommendations and the work that you do.

I truly believe that drug testing is a part of the prevention portfolio here at SAMHSA. I was not here when you were placed under CSAP, but I absolutely believe that you are in the right place. I don't have to defend that too often, especially recently, because we are able to show the American public all of the work that you do and put it into perspective by telling the public you are assisting us in keeping Americans safe on the roads, in the air, and in the workplace in general. I personally thank you for your work and your patience. Even though people on the outside feel that the government works a little slow, we are persistent here at SAMHSA. We have a leader that is even more persistent than me, and I did not think that was possible. Pam has been an incredible supporter of the work that you do. Carol has been, what I call in a very fondly, loving way, a gnat that doesn't go away. We have been very, very fortunate that Pam is the co-chair with Dr. Howard Koh of the Behavioral Health Coordinating Committee, the group that reviewed your recommendations. You responded to their questions, allowing us to proceed through the channels of chain and command. I want to thank you for your work and your patience. I look forward to the great work that is continuing, especially around prescription drugs and everything that that has to offer. As you know, prescription drugs are slowly becoming, probably quicker than any of us are comfortable with, an issue in this country for our young people, our middle-aged population, and our older adults. We are monitoring this issue, and any recommendation and guidance from you are taken with us.

I have the pleasure of introducing you to Pam Hyde. All of you know her, so it does not have to be a formal introduction, other than to know that through all of the work that we do, she always finds time to listen to the needs of DTAB. When she first came, we explained to her what DTAB was and why you were in prevention. I'm hoping that we have convinced her, and I think we have, that you are dealing with some very important issues for the country and that you are truly a part of a public health movement in the rubric of behavioral health. Without further ado, I give you, whether you know it or not, one of your biggest supporters here in SAMHSA, who is championing the messages and the recommendations that you give us. Thank you and have a very good meeting.

Update: Proposed Recommendations

Ms. Hyde: Thank you, Fran. It is great to be here with you. I did not have to be convinced about your importance; I just had to be educated about what your role is. SAMHSA has seven advisory committees, addressing issues for tribes, women's services, treatment, prevention, mental health services, and national services. DTAB is one of those seven critical advisors that provides us with information and advice about how we do our responsibilities and our programs as a Federal agency.

I want to offer some thanks and then tell you a story or two to help you understand how your work gets translated in the background, the part you don't often see. But first of all, I want to thank all of you. I often first meet advisors through the nomination paperwork, which describes your background and says why you should be appointed. I review this paperwork and send it forward to either appoint or reappoint council members. I also examine who is currently on the committee and compare that to the other candidates that we need to appoint to ensure balance. So I have met all of you through that process. I remember once, walking by while you were having lunch and sticking my head in to say hello to you. But I have actually had less time to spend with you as an advisory board than some of the other advisory councils, so I am really pleased to have this

opportunity. On the other hand, I have actually touched and been touched by your work, probably more directly and more intensely than the other advisory councils. So in this way, I have dealt with you less personally, but I have dealt with your work more. So I appreciate what you have done, and again, I will say a word about that in a minute.

It is great to meet all of you in person, and it is great to have you doing this work for us. As Carol said, I have been impressed about learning and being educated about the millions of people whose lives are touched and whose work life is touched by the work that you do. Multiply that out by the millions of people who are touched by the work done drug-free, and you truly are touching America and you truly are, as Carol said, one of the most important and fundamental public health prevention programs in our country. I hope you are awed by your responsibility in doing that every day. I am awed by your work.

I also want to take an opportunity to thank Carol. I am more than in denial because I have helped a couple of times extend her time here. We have to ask permission for her extensions, and so I am pleased that she has been willing to continue to that. From a person who works 24/7, you always get a flavor for somebody when you write him/her at midnight on a Saturday or on a Sunday at 8:00 in the morning and they respond. Carol is one of those.

I have had lots of questions personally and lots of questions I had to answer in order to move your recommendations up the chain for vetting before I could sign off on them. I do want to thank Carol for her responsiveness, her leadership, and getting the process done and completed.

I also want to thank Janine. We have staff that is terrific, especially all of the DWP staff. Here is one of my stories. Months ago I became engaged in your proposed recommendations that we were able to approve. My deputy came to me and said, there is this issue that has a long history that you need to know about. And then, sometime after that, when not too many people were around, I got a call that I needed to hear about the recommendations that you were proposing. I met with Janine and Rina, and I want to thank both of them because they very quickly informed me about what the issues were. These are complex issues, which on their face seem straightforward, but they are very complex scientific, public policy, and legal issues. I want to thank Janine and Rina for taking the time with me, to help me understand what the issues are. Even yet this morning, Carol and I were emailing back and forth about some questions from the powers that be about what we are doing. I am now able to answer them fairly quickly and easily, with just a little help from Carol once in a while. Anyway, I appreciate their work. And obviously, Fran's leadership on our strategic initiative on prevention is another story.

I remember that we have been doing a lot of work on our eight strategic initiatives, which range from prevention, to trauma and justice issues, to military family issues, to health reform, and to health information technology. Our number one strategic initiative here at SAMHSA is prevention. I remember early on when we were discussing these strategic initiatives in one of our managers' meetings that Carol, as is her wont and her strength, raised her hand and asked a question. And she said, I don't see how our regulatory programs fit into these strategic initiatives. And I replied that I think otherwise. Let's think about the role that this regulatory and scientific process actually plays in prevention. It is a huge part of our prevention portfolio. We may not give it as much airtime, and we may not underscore it or put it out there in the public as much as we should, frankly.

As already discussed, the importance of your work and the entire Federal government's strategic initiative around prevention, whether it is in healthcare, in our national drug control strategy that ONDCP leads us on, or in SAMHSA, are incredibly crucial in saving lives and saving people from the scourges of drug abuse. Nevertheless, Carol and her staff under Fran's leadership have been significant in this area.

I also want to say just one more word about the advisory committees that I meet with regularly. The other six advisory committees meet together once or twice a year. They are provided with lots of information about the strategic initiatives and how the work of the different centers fit into that. While you are different enough as an advisory board that we have not typically had you come and meet with us, I do want to invite you, if you are interested, in identifying maybe one representative from your committee to sit in. Those advisory committee

meetings are also available to the public online on the web. So I would encourage you, if you are interested, to either send a representative to one of those meetings or to participate online, so you can get a flavor for what the rest of what SAMHSA is doing and how your work might fit into that. There may be specific times that it makes more sense to have you be aware of that than others. So I will leave that to Fran, Carol, Janine, and others to figure out.

We also have a new person I want to introduce, Geretta Wood. Geretta is our new committee management officer for our National Advisory Committee who coordinates the joint meetings of all of our advisory groups.

I also want to just take a special moment to recognize our colleagues at ONDCP, including David, Jack, and others. Martha, thank you so much for your support, your advocacy on these issues, and your financial support for the experts, and the other things that you have done to help us get through this process for these particular recommendations. They are so critical, so thank you for that partnership.

I also want to thank our other Federal partners. We could not do this without you. Less the public think that Federal partners and agencies never collaborate, we are here to prove differently. We have lots of work going on with NIDA, and we appreciate you all, including the FDA and others. In fact, NIDA and FDA are part of the reason, in a positive sense, why this recommendation approval process took a while, from you providing the recommendations to me, to me giving you back approval to proceed. That was because we have a new Behavioral Health Coordinating Council within HHS, started by the Secretary, which brings all the operating divisions together. It's co-chaired by myself and the Assistant Secretary for Health, Howard Koh. We have a number of subcommittees of that group, representing the operating divisions, which are the agencies across HHS, such as SAMHSA, FDA, NIDA, Centers for Disease Control and prevention (CDC), CMS, HRSA, etc. We work together on a variety of behavioral health issues that impact across everything HHS does. NIDA and FDA co-chair the subcommittee on prescription drug issues, with Fran representing SAMHSA on that subcommittee. When these recommendations came forward, even though we had FDA and NIDA representation on this Board, I wanted to ensure that the structure and that subcommittee could support us in going forward with these recommendations. Fran presented these recommendations to the subcommittee members, including NIDA, FDA, CMS, and others, to engage them. There were many things going on when you provided the recommendations to me, including the Secretary's interest in the prescription drug issues and the Surgeon General's soon-to-be released call to action on prescription drug abuse. At about the same time, CMS was being questioned in Congress and by the public about their work with prescription drugs and how they were managing that in the Medicare program. There were other related issues about scientific boards and how they were used, and what the department does with the information these boards provide. These goings-on, which are part of that black box that people do not always see, occurred when the recommendations come forward. During this process, from Fran to Carol to myself, we were providing the right people with the right information, helping them understand what your recommendations were, and that we supported them. We wanted to ensure, that as we went forward, that people understood what we were trying to accomplish and would be supportive throughout the process. Even though the approval process took a little, frankly, it didn't take as long as many bureaucratic issues do.

I hope that you have now received the letter from me, saying that I have approved the recommendations. Though I had approved them a long time ago, I have now formally approved them, so that you can proceed with making the actual Guidelines changes. While this will take another few months, it is an important part of the process.

I want to thank you for your patience with this process. I want you to know it was not because we were not paying attention to the recommendations. It is because, in fact, we were paying attention to them in the right ways, to ensure that everybody knew what we were trying to accomplish, could really buy into it, and help us get it accomplished as we go down this path.

What I wanted to say to you is just thanks and that there has been a lot of work going on about this. There is much work occurring at SAMHSA concerning the recommendations, including the work that you do here. But I probably know more about your recommendations and their implications, including legally, scientifically,

publicly, politically, etc., than many things that we have to do. Hopefully, you know that means we are paying attention and trying to make the process work in a very positive way because this does affect almost every American out there in a very positive fashion.

Thank you again for your work, thanks again to the staff for their work, and thank you again to our Federal partners. I am going to leave you to it. I look forward to hearing the next steps in this process, and know that I will be informed, educated, and ready to rock and roll. Thank you again.

Dr. Cook: Dave, you had requested to provide more comments at this time.

Mr. Mineta: Thanks, Janine. I wanted to just thank Pam and Fran for their work in getting these recommendations through. One of the things that I want to stress that Pam spoke about was the inner agency clearance. Now, one of the things I learned in coming to D.C. is that the word clearance now has an entirely new meaning, significance, and timeline standard for me that I never would have understood if I had not actually been employed by the Federal government. And that process of looking at the issue on all different many levels takes a while. Because of your recommendations and scientific background and our desire and the Administration's desire to base policy on science, it appears to me right now that, not only does the United States have the best system in the world for drug testing for regulated industries and for all, but as a result, people come to us all the time from the international community, asking for our opinion and guidance. Much of that actually is based around the table right now, is based in this building, and with the collaborations between Federal interagency partners to make sure this happens.

I want to say thank you all again and to stress how important the role you all play in this is. All of your efforts are greatly appreciated, from HHS, as you heard Administrator Hyde say, through Director Kerlikowske, to the Executive Office of the President. It is again a special privilege for our office to be involved. We made sure that we were doing our part to ensure that that clearance process was moving along as quickly as possible.

I want to again say thank you for your expertise. I want to thank the DWP staff for their ever-vigilant efforts to make sure this kept moving and to our Federal interagency partners. I had more than one conversation with Jim Swart about how we really need this and how we are all looking forward to our next DTAB meeting and especially making this deadline. So, I want to thank everybody for that help, especially Pam and Fran. Again, with that, I am very, very proud.

This group reminds me of something that Director Kerlikowske tells us all the time - we punch above our weight class. This is one of the efforts that I enjoy the most in our office on demand reduction for prevention, intervention, treatment, and recovery. I get probably some of the most praise when we meet with international partners for our drug testing program and drug-free workplace programs. So with that, I want to again thank you on behalf of the President, on behalf of the Executive Office of the President, and ONDCP for all of your work. Thank you.

Dr. Cook: I want to personally thank you. ONDCP, if people are not aware, has been a tremendous supporter the Drug Testing Advisory Board, the Division of Workplace Programs, and the initiatives we have been trying to achieve.

Twelve Year Prescribing Trends for Fifteen Different Opioid, Benzodiazepine, Amphetamine, and Barbiturate Prescription Drugs Correlated with Reports of Prescription Medication Abuse and Diversion

Dr. Cook: I am going to give a presentation today. I have been mute the whole time I have been with the Drug Testing Advisory Board. But I wanted to tell you about a study that was done collaboratively between SAMHSA and the FDA. We examined a database, which included 12 years prescribing data on 15 different drugs as well as the demographics of the people to whom the drugs were prescribed. I will compare these study data to the demographics of those who abuse prescription drugs, as well as those who abuse all illicit drugs. Then, I will examine the impact of prescription drug abuse on health care, as well as the judicial systems, in the United

States. To do this, I will provide data from several different databases. What I have listed in these next two slides are all the different databases from which I have extracted the information to provide the comparison data that are used in this talk. In the upper left and right-hand corners of each slide containing data are the sources from where that data were obtained, the year the data were published, as well as the report from which I abstracted the data.

I am preaching to the choir when I say that both medical and non-medical use, where non-medical use is defined as the use without a prescription or solely for the feeling or experience caused by the drug, of prescription drugs are increasing in the United States. And because the number of prescriptions is increasing, you expect to see an increase in prescription drug misuse, abuse, and diversion. Because of this misuse, abuse, and diversion, tremendous adverse impacts are experienced by the individual, the community, and the health care and judicial systems.

I have organized this talk into a series of questions followed by a series of answers. I will use the databases that I have shown you previously to provide the answers to these different questions. And hopefully, what you will see is that regardless of the source of the data, the message is still the same: prescription drug abuse, misuse, and diversion are increasing.

These are data from the Centers from Disease Control in 2010 where they researched legitimate prescription medication use in the United States. For all ages, from 1999 to 2008, 48 percent of people used one or more drugs. Two or more prescription drugs were used by 31 percent of the U.S. population, and 10-11 percent used five or more drugs during this time period.

If we examine the demographics of those who use legitimate prescription medications, the majority is prescribed to those who are 60 and older. As we age, we have more health care issues to address, requiring more medications.

What is the volume off prescription drugs being dispensed in the United States? These data are derived from the study that I described to you before. The researchers in this study were Sean Belouin and Hina Mehta, currently both of the FDA. At the time when Sean designed the study, he was working at the Division of Workplace Programs within SAMHSA. Their database is the Surveillance Data, Incorporated from Vector One National. What this database does is capture information on the dispensing of prescriptions. It captures physician's specialty, patient age and gender, and whether patients are continuing and beginning new therapy. The sources for this data are retail chains, mass merchandisers, mail order pharmacies, pharmacy benefit managers, and provider groups. The number of pharmacies that are currently captured in this database is 59,000, which accounts for nearly all retail pharmacies and represents about half of the retail prescriptions dispensed nationwide. So remember, when I present the statistics, that these data only reflect half of retail pharmacy prescriptions, and it does not include prescriptions that are dispensed, for instance, by hospital pharmacies. This database includes all of the prescriptions from about a third of the stores and a significant number of prescriptions from the remaining stores. The database includes a prescription volume of greater than 2 billion prescription claims a year and represents more than 160 million unique patients that are receiving these prescriptions.

Sean utilized three different criteria when he designed this data-mining study. The drugs that he had selected were within Schedules II through V. They were selected based on their use relative to other prescription drugs, and they had to have potential for misuse, abuse, and diversion. One thing that is unique about Sean is he was actually a practicing pharmacist. Besides working full-time in the Federal government, he also keeps his hand day-to-day in the pharmacy world. So he is personally aware of what is flying off the shelves.

The study examined prescriptions from 1998 to 2009. It combined all drug strengths. It combined both brand and generic drugs and included the total number of prescriptions written for each drug. Also captured was the total volume of drugs dispensed, which is expressed as extended units, whether it is given as a tablet, a capsule, a patch, a mL, etc. The demographics of the prescription recipients included their gender, as well as their age in 10-year intervals.

This is a summary table showing you the actual number of prescriptions written. The table on the left includes the total prescriptions written in the year 2009. The table on the right shows you the percent change in the number of prescriptions written during that 12-year time period. The red line demarcates between those that had positive increases versus those that had negative increases. Notice that our top two medications for the number of prescriptions written in 2009 were hydrocodone and oxycodone. And if you are familiar with the DTAB recommendations, they are two of the drugs that we have recommended for inclusion in the Guidelines.

Looking at the number of extended units actually dispensed, in 2009, there were 8 billion extended units of hydrocodone dispensed. Now, if you compare that to the population of the United States in 2009, this meant that 27 units were dispensed to every man, woman, and child in the United States. Since I did not get mine, someone else did. So fork it over. And remember, these data represent only half of the retail prescription volume. In the table to the right, you will see the percent change in extended units during this 12-year time period. Methadone tops the list at a 1,200 percent increase during those 12 years. And again, hydrocodone and oxycodone top the list for the actual number of units dispensed. This slide graphically depicts the data for the change in extended units dispensed. Notice the dramatic increase in this 12-year period for hydrocodone and oxycodone.

The Drug Enforcement Administration (DEA) has a reporting system for monitoring substances from the point of manufacture to distribution. Notice during this time period that there is a ramping up of the supply to meet the demand, especially, for instance, for oxycodone, hydrocodone, and morphine.

Here are data also from Verispan that rank the prescription volumes for the year 2009. Hydrocodone with acetaminophen, excluding all its other formulations, is ranked number one with 120 million dispensed. Lisinopril is number two with 75 million dispensed in that time period.

Sean conducted a survey in 2008 of three different pharmacies in our region to determine what they were charging for these prescription medications. Many of these prescription drugs that are being abused are generic, meaning that they are very, very cheap. For instance, Lipitor, which is a cholesterol-lowering drug, is very, very expensive because it is a brand name medication.

What are the demographics of those that are using legitimate prescription drugs? The Verispan data captured age and gender. And, by and large, the people that are actually receiving valid prescriptions are over the age of 41, with more females than males receiving them. The exceptions are highlighted in blue, and these are amphetamines being predominantly prescribed for attention deficit hyperactivity disorder (ADHD) and phenobarbital being predominantly prescribed for seizures in children.

From the CDC data, we see that prescriptions are increasing with increasing age. Notice what are the top drugs that are being prescribed to these groups. Only in one age group, for the adults age 20 to 59, do analgesics appear. Antidepressants are also found within this age group. We also know from the CDC that, just like our Verispan data, medications are predominantly prescribed to those that are older and are prescribed to women more than men. What is not captured in the Verispan data, but it is in the CDC data, is the race/ethnicity. Most valid prescriptions are prescribed to those that are white.

Conversely, what is the prevalence of prescription drug abuse in the United States, and how does that compare overall with the illicit drug abuse? We know from the National Survey on Drug Use and Health (NSDUH) data that 7 million individuals, 12 years of age or older, are current, defined as past month use, non-medical users of prescription psychotherapeutic drugs. For the purpose of this survey, psychotherapeutic drugs were defined as opioid pain relievers, tranquilizers, sedatives, and stimulants. There has been a slight increase from 2003 to 2010 in the nonmedical use of prescription psychotherpeutics.

For all illicit drugs, 22.6 million Americans are currently abusing illicit drugs, which represent about 8.9 percent of the population. The number one abused illicit drug is marijuana, representing 6.9 percent of the population. Number two is the psychotherapeutics group, with 2.7 percent of the population currently abusing them.

Looking at the trends specifically for the abuse of psychotherapeutics, pain relievers are number one for that group.

Let's examine the demographics of those who are abusing prescription drugs and compare and contrast it with those that are using illicit drugs. 18 to 25 year olds are primarily the non-medical users of psychotherapeutic drugs. From both CDC and Verispan data, it is predominately the older populations that are actually being prescribed these drugs. So somehow, these younger groups are obtaining these prescription medications. On the far right are the data from 2010, which shows that psychotherapeutic abuse in the 12 to 17 year olds had decreased somewhat in the last year.

Comparing this to illicit drug abuse, lo and behold, it is the same age group, the 18 to 25 year olds, who are predominant abusers of all illicit drugs. If we look at gender, again, males abuse illicit drugs more than females, regardless of the drug type, whether marijuana or psychotherapeutic drugs. This is related to the risk-seeking behavior of males when compared to females. If we look at the ethnicity and race of those that are abusing non-prescription drugs, we learn that they are predominantly those of two or more races, American Indian/Alaska Native, and Native Hawaiian and other Pacific Islander. I put a star by the White race, even though it is number four in the list. As I will show you later on, the reason it is starred is, if we examine who is actually seeking and receiving treatment for prescription drug abuse, it is Whites, by and far. But that is not who actually are the predominant abusers.

The race/ethnicity data for all illicit drugs is shown here. Again, you see that it is your American Indians/Alaska Native and those of two or more races that are predominantly abusers of all illicit drugs, which is very similar to what we saw with prescription drugs. Also shown are the data for 2010, which is highlighted in red. Notice, thank goodness, that abuse among those of two or more races and American Indian/Alaska Native categories have decreased in the most recent years.

Though not included in the Verispan data, I do show how illicit drug use varies by employment status. The percentage of illicit drug use is higher among those that are unemployed. Unfortunately, these individuals have the least resources to seek help. Looking at the actual number of users, illicit drug use is much higher among those that work full-time, and hence, why we have a work-free drug place program.

One of the things we always consider when we discuss illicit drug use is at what age did they begin to abuse drugs. How does initiation into the nonmedical use of prescription drugs compare to other illicit drugs? We know from the NSDUH data that currently there are 3 million initiates every year into illicit drugs in the United States. The gateway drug is marijuana at 59 percent. Surprisingly, number two belongs to pain relievers. 26 percent of the new initiates' surveyed said their first gateway drug was a psychotherapeutic. Examining how the number of new non-medical users of prescription drugs increased with time, the trend is very dramatic for the pain relievers. The data for 2012 is shown on the far right, with just the numbers listed. If we look at the mean age when drug abuse started, the majority initiate with illicit drugs. The mean initiate age for pain relievers is age 21. Also shown is the mean initiate age was for OxyContin, which appears to be the prescription drug of choice, which is 22.8 years. But also notice that pain relievers are ahead of some of the other illicit street drugs.

What is the geographical distribution of drug abuse in the United States for prescription drugs and how does that compare with illicit drugs in general? Those states that are shaded in red and orange have a higher abuse rate for pain relievers. The highest abuse rate belongs to Arkansas at 7.3 percent. The lowest rate is found in South Dakota at 3.4 percent. If we examine all illicit drugs, the geographical distribution by state is slightly different. Rhode Island is highest with 11 percent, and North Dakota is lowest at 5.7.

I like this slide because it breaks the data down by urban and rural areas. The majority of prescription drug abuse is occurring in small metropolitan or rural areas. These are the areas that have the least resources to handle treatment. Conversely, it is the large metropolitan areas where the most abuse of illicit street drugs occurs.

From where are these prescription drugs being obtained? We know from the NSDUH data that the majority of these prescription drugs are obtained through what I call the friends and family plan. Fifty-five percent are obtained for free from a family or friend. Another 16 percent are bought from a family or friend. Of those that are obtained from a family and friend, the prescription recipient primarily (79 percent) obtained the medication from one doctor. The common perceptions for the source of diverted prescription drugs are the Internet, drug dealers, and doctor shopping. The data show that those are not the primary routes for diversion. Diversion is primarily happening through the medicine cabinets of friends and family.

What I found was interesting were these data from DEA, who has been monitoring Internet websites. From 2007-2008, they found a 37 percent decrease in the number of Internet sites that were offering to sell prescription drugs, indicating that DEA is doing its job. Interestingly, 85 percent of the sites did not require a physician's prescription in order to order from that site.

I like this comic. Basically, it is take two and do not call me in the morning.

We have talked about abuse; there is a lot of material out there and diversion is occurring. DEA has a database known as National Forensic Laboratory Information System (NFLIS) where they monitor drugs. Also, the System to Retrieve Information from Drug Evidence (STRIDE) records data from drug seizures. Included in the top 10 drugs identified in STRIDE are oxycodone and hydrocodone.

NFLIS publishes their 25 most frequently identified drugs. Seventeen out of the top 25 are prescription medicines, with 7 being narcotics and 4 being benzodiazepines. In the narcotic categories, number one and two are oxycodone and hydrocodone, which matches the increases that we see in what is actually being prescribed. The top tranquilizers/depressants are alprazolam and clonazepam. The top stimulant by far is methamphetamine.

This slide shows the NFLIS trending data from 2001 to 2010. On the top graph are illicit drugs. Based on the search and seizure drug analyses, illicit drugs have either maintained relatively constant or they have decreased during this timeframe. Compare this to prescription medications, which, except for diazepam, have shown somewhat dramatic increases, indicating drug diversion during this same time period.

Now, there are different methods in place to control this drug threat. DEA has instituted several Take-Back Days. During the first two events, they collected 310 tons of unwanted or expired prescriptions. Forty-eight states now either have authorizing legislation or operational controlled substance monitoring programs. The two remaining states have legislation that is pending. There are two states, Florida and Texas, which now require registration of pain management clinics. In 2010, Google, Bing, and Yahoo adopted policies prohibiting Internet pharmacies from side bar advertising, unless officially certified. And finally, DEA sets, monitors, and reports the production quotas for various drugs. There are some increases in the production quotas of what are allowed to be made in the U.S.; sometimes these are matching demand. It is interesting to see that some quotas have actually leveled off or decreased during the time period shown.

What are the health-related issues associated with prescription drug abuse? Each year, millions of Americans are treated for a variety of serious medical issues related to prescription medication use, whether medical or non-medical. These are the latest data on the top 25 substances involved in human exposures from the Poison Control Centers in the United States. Analgesics are, by far, number one. By comparison, street drugs are way down there.

If you are poisoned with prescription medications, there is a chance of death. This slide depicts the rates of unintentional drug overdose deaths in the United States. Overdose deaths are dramatically increasing during this time period. One of the primary reasons for this dramatic increase is opioid analgesics. This graph shows opioid analgesic-related deaths increasing while heroin deaths are remaining relatively stable. Notice too the decrease in cocaine overdose deaths. By 2008, 40 percent of the unintentional drug deaths were due to opioid analgesics.

If you didn't die from the poison and you made it to the emergency department (ED), there are data examining ED visits. These data are reported through the Drug Abuse Warning Network (DAWN), which includes the type of drug that was involved in the exposure. Illicit drugs account for about 47 percent, whether alone or in combination, and pharmaceuticals represent 52 percent of the drugs encountered in ED visits. More people are visiting the emergency room because of pharmaceutical-related health issues than they are for illicit drugs.

Examining the trends in emergency department visits involving non-medical use of narcotic pain relievers from 2004 to 2008, this dramatic increase is again seen. The narcotic analgesic increase in ED-related visits was 111 percent in that four-year time period. Considering age and gender, males and females are both similarly seeking medical treatment for narcotic pain reliever overdose issues. And again, the predominant age group is age 21 years and older. This is consistent with the data shown previously.

Looking at specific different pain relievers, oxycodone and hydrocodone again top the list as the top two for which people had medical issues. This is interesting data from the CDC, showing how motor vehicle traffic deaths, poisoning, and drug poisoning death rates in the United States are related to each other. Reported about a month or two ago, drug-poisoning deaths outnumbered traffic fatalities in 2009 for the first time ever.

Examining dependence issues, both for specific drugs and pain relievers, marijuana is the number one drug reported for dependence, with the number two being pain relievers.

The Treatment Episode Data Set (TEDS) data, which are the statistics of those who are seeking treatment for substance abuse, incorporate about 80 percent of the treatment facilities or about 1.8 million admissions. Five different classes of drugs represent about 95 percent of the total admissions. Alcohol, by far, is number one at 39 percent. But opioids come in second at 18 percent.

The ranking of substances for which people are seeking treatments is pain relievers third behind alcohol and marijuana. Notice the dramatic increase in those that are seeking treatment for pain relievers.

Interesting, looking at the percent increase in admissions from 2000 to 2006, the percent increase for oxycodone was 1500 percent while the percent increased for all opioid analgesics was 168 percent. Some people have argued that these increases are related to the overall increase in treatment admissions. Correcting for the total number of admissions, there is only a 12 percent increase in total admissions during this same time period, indicating that the dramatic increase in the number of admissions related to opioids is real. Some people wonder the cause of this increase in opioid treatment admissions. I love this slide because it shows treatment admission rates with time for opioid analgesics, as related to when oxycodone was introduced into the U.S. market. There appears to be some correlation between the two.

The demographics of those who are admitted for abuse of opioid analgesics are predominantly male and predominately White. Previously shown data indicated that Whites are actually ranked fourth by race/ethnicity among those abusing prescription medications. But Whites are the ones seeking treatment. The biggest change in that 10-year period, from 1997 to 2006, was the majority age of those receiving treatment. More and more younger individuals are seeking treatment for opioid analgesic dependence. Remember, these are the ones that are predominantly abusing them.

This slide shows overall treatment rates by age and gender, with males are seeking treatment a little more often than females; but again, males are the ones who are abusing more. There is really no second place to Whites when it comes to other race/ethnicities. Treatment is again primarily sought by the 20-somethings.

I love the next two slides, which show admission rates for primary non-heroin opioid synthetics from 1996 to 2006. As I flip through these slides, focus on those states that are in shades of red. Notice how the admission rates are increasing dramatically during this short time period.

Most of the people seeking treatment for synthetic opioid abuse are located in the rural areas. These facilities have the least resources to handle these increases in admission rates. Historically, people received treatment

primarily for alcohol and street drug abuse. Treatment staff at these facilities was historically trained to treat alcohol and street drug dependence. Now, patients are entering treatment because of prescription drugs, and the staff has to learn completely different skill sets to treat them appropriately.

What are the crime-related issues associated with prescription drug abuse? From the National Prescription Drug Assessment from 2004 to 2009, pharmaceuticals was the only category that showed a dramatic increase in their high availability, as reported by law enforcement during this time period, meaning the drug was available for diversion on the streets.

In 2010, state and local agencies were interviewed as to what they perceived were their greatest drug threats. Notice where prescription drugs fall in relationship to cocaine, methamphetamine, heroin, and marijuana as the greatest drug threat by drug nationwide. Methamphetamine is number one, followed by crack cocaine. Pharmaceuticals show the most dramatic increase. In the insert, the increase is more easily seen.

Law enforcement agencies were also queried about whether they saw a correlation between drug type and violent crime in the United States. Pharmaceuticals show a dramatic increase in the percentage of law enforcement agencies reporting a correlation to violent crime from 2.2 percent to 4.8 percent in 2009. In the insert, the property crime increase related specifically to pharmaceuticals is shown in blue and the violent crime increase in red.

Finally, law enforcement agencies are reporting greater gang involvement with pharmaceuticals. If there is money to be made, the gangs will be involved, which will further contribute to diversion.

Hopefully, I placed the prescription drug issue into perspective with the health care and the judicial systems issues. Because we are running behind, I will defer all questions until later.

At this time, I want to introduce our next speaker, Dr. Barry Sample. As I had mentioned previously, one of our DTAB board members, Barbara Rowland, was scheduled to give this presentation. But because of a family issue, she was unable to do it. Barry kindly stepped in at the last minute and agreed to do this. Barry is with Employer's Solutions at Quest Diagnostics. Barry, are you on the line?

Trends in Urine and Oral Fluid Positive Rates for Opiates

Dr. Sample: Yes, I am here. Can you hear me all right?

Dr. Cook: Yes, we can. Barry is the Director of Science and Technology, Employers' Solutions at Quest Diagnostics, Incorporated. Go ahead, Barry.

Dr. Sample: Thanks, Janine, and thank you for asking me to join you today. It's my pleasure to provide an update and some follow-up information on positivity rates for prescription opioids, both in oral fluid as well as in urine drug tests. I, too, was there in January last year during the great snowstorm and gave an earlier snapshot of our positivity rates for oral fluid testing. Also, I presented at the August 2008 DTAB meeting that focused on prescription drugs in general.

This data set is derived from our routine testing of urine and oral fluid specimens and includes specimens tested between January 2005 and June 2011. There were approximately 5 and a half million oral fluid tests and 37 million non-regulated urine specimens that were analyzed, and the data that I will be presenting came from this data set. This is just workplace data; we have eliminated any test results that might be rehabilitation-related, those from criminal justice, and confirmations from employers that are utilizing point of collection testing. These data represent the true prevalence rate of positivity. These are laboratory-positive data, prior to MRO review.

From the demographics by testing reason for both the urine and the oral fluid tests, the two data sets are relatively comparable.

In the testing of oral fluid for opioids, the immunoassay screening test is designed to detect primarily morphine, with morphine chosen as the target compound. Although depending upon the specific assay, cross-reactivity varies. The one that we are using has significant cross reactivity with the heroin-specific metabolite, morphine, as well as the semi-synthetic opioid, hydrocodone. When we test for opioids in oral fluid, approximately 50 percent of the specimens that we test include confirmatory testing for the semi-synthetic opioids at our customers' request.

Our data clearly demonstrate that hydrocodone is the most commonly detected opioid in our oral fluid testing, as shown in the data from 2005 and to the first half of 2011. We are seeing increasing overall positivity for the opioids, which increased from 0.71 percent in 2005 to 0.9 percent in the first half of 2011. This increase is not driven by codeine and morphine.

In the codeine and morphine data, there was not much change over the course of that period of time, indicating that the overall positivity rates for the opioids was driven primarily by the much higher positivity for hydrocodone. Also of note is the fact that we see such higher positivity for morphine in this data set. Clearly, hydrocodone is the most commonly detected opioid in our opioid testing.

Our urine expanded opioid panel includes codeine, morphine, and such semi-synthetic opioids as hydrocodone and hydromorphone. I will discuss oxycodone and oxymorphone a little bit later. During this time period, our customers asked us to test for expanded opioids for not quite 10 percent of all of our non-regulated specimens. Between January 2005 and the first half of 2011, we tested approximately 3.2 million urine specimens for the expanded opioids. Although we see similar data to what I have just reported in oral fluid, one of the most significant areas of concerns in these urine testing results is the difference in positivity rates or positive prevalence rates by testing reason, specifically post-accident testing as compared to pre-employment testing. Post-accident has up to fourfold higher incidence of positive tests for certain semi-synthetic opioids.

This slide shows the data during this time period for overall positivity, not by testing reason, for codeine, morphine, hydrocodone, and hydromorphone. While codeine is clearly the lowest and morphine has about twice the positivity rate of codeine, the codeine positivity rate, while there have been some ups and downs over this six and a half year time period, has really remained relatively flat.

In contrast, and I think not dissimilar to the data that Dr. Cook presented in the earlier presentation, we have seen significant increases in hydrocodone, as well as hydromorphone, positivity. And in fact, both of those are approximately 47-48 percent between 2005 and the first half of 2011. Today, hydrocodone is the most commonly detected prescription opioid when we are asked to test for this wider range of prescription opioids. Within this data set, hydromorphone is also higher than morphine.

Of interest, as I alluded to a little bit earlier, is the difference in positivity rates between pre-employment and post-accident test results. There are much higher positivity rates in our post-accident tests as compared with pre-employment. I will look just at the first half of last year. In the case of morphine, positivity is 0.27 percent on pre-employment tests, as compared with 1.1 percent on post-accident tests. For hydrocodone, it would be 0.85 versus 3.7, and for hydromorphone, 0.47 versus 2.2, respectively, for pre-employment versus post-accident. Essentially, there are four-fold higher incidences of positives in post-accident tests than pre-employment tests for these drugs.

Looking at these data graphically over the course of the last four and a half years with random positivity rates included, for codeine, there is not much difference between the pre-employment and random positivity rates in our general workforce non-regulated testing, but clearly, there are higher positives on post-accident tests. For morphine, random positives are slightly higher, more than one and a half times higher, as compared to pre-employment. Again, much, much higher positives are seen on the post-accident tests. In the case of hydrocodone, which I think one of the items of note here, while similar to what we saw in morphine, we are seeing one and a half to two times more positives on random tests, as compared with pre-employment, and up to four times more positives on post-accidents as compared with pre-employment, for hydrocodone.

If you look at these data, it would appear that a large part of the increase in positivity rates for hydrocodone is related to post-accident tests, because the pre-employment positivity rate is relatively constant. In contrast, the random positivity rate is increasing a little bit, and the post-accident positives have increased from about 2.7-2.8 percent in 2007 to 3.5-3.6 percent in the first half of 2011. Thus, a large part of the increase in the overall positivity that we are seeing for hydrocodone appears to be driven by increasing positives, especially on post-accident tests, and to a certain extent, by increases on random tests. In the case of hydromorphone, similar patterns are seen to what I just described for hydrocodone.

Due to the lower cross reactivity of oxycodone with the opioid immunoassay screening test, to more sensitively and accurately test for oxycodone, it is necessary to use an immunoassay screening test that specifically tests for oxycodone, as opposed to just relying on cross-reactivity. We saw large increases in oxycodone positives between 2005 and the first half of 2011; positivity has about doubled in that period of time. Looking at the positivity rates by testing reason, while we have seen a slight increase in pre-employment positives for oxycodone in this time frame, we are seeing much larger increases in random positivity rates for oxycodone. And while it is down a little bit in the first half of 2011, as compared to its peak in 2009, for the post-accident positives, it has still increased since 2007. Again, we are seeing much higher positive rates on post-accident tests as compared with the pre-employment and the random tests.

These data, in terms of post-accident positives as compared with pre-employment positives, do not prove that the drug that was measured in the post-accident test was the approximate cause of the incident in the workplace that caused a drug test to be performed. It certainly does raise the level of suspicion that they used drugs that may have played a role.

In summary, opioid drug positivity for some of the semi-synthetic opioids has increased. While morphine positives are essentially unchanged in this time period, hydrocodone and hydromorphone positives increased 48 percent. Today, in terms of rank order, hydrocodone, oxycodone, and hydromorphone are the most prevalent drugs that we find in opioid positives. Our data show that up to two times more positives are found for these prescription opioids in random testing as compared with pre-employment testing. In the case of post-accident, as opposed to pre-employment testing, we are seeing approximately four times as many positives for certain of these drugs on post-accident tests as compared with pre-employment. That concludes my presentation, unless there are any questions from the Board before I sign off.

Dr. Cook: Does any member of the Board have questions for Barry? Larry?

Dr. Bowers: I was just wondering if you had any data on presence of multiple drugs, especially in that post-accident data that you talked about.

Dr. Sample: We have not looked at that. If that is something of interest to the Board, we may be able to go back and mine the data a little bit further to see if there might be other drugs involved, as well.

Dr. Cook: Would you like to see that, Larry? He smiled and said yes, Barry.

Dr. Sample: I would be happy to do that.

Dr. Smith: On the data that you presented for oxycodone, does that subset of specimens represent the same number as were tested for the other quote “expanded opioids” or is it a smaller subset?

Dr. Sample: It is essentially the same data set. Almost all of our testing for the so-called expanded opioids would include expanding the opioid panel to include hydrocodone and hydromorphone and also testing for the oxycodone and oxymorphone, which represents about 500,000 tests a year.

Dr. Cook: Any more questions for Barry? Barry, I want to thank you for giving a wonderful presentation and for agreeing to do it at the last minute.

Dr. Sample: My pleasure, thank you.

Dr. Cook: Thank you. Our next speaker is Dr. Mike Walsh, who is president of The Walsh Group, and he will speak about MRO-verified data for synthetic opioids.

Testing for Synthetic Opiates: MRO Review vs. Illegal Use

Dr. Walsh: I want to say good morning and greetings to the Board, the SAMHSA officials, and my colleagues from ONDCP. My job this morning is to talk about the medical review officer (MRO) review process in testing for synthetic opioids and the data that are we seeing in terms of prescription versus illegal drug use.

I will focus on a seven-year project that was a collaborative effort between SAMHSA, RTI, and The Walsh Group. The principle objective was to evaluate the relationship between laboratory-reported drug test results and MRO-verified results reported to employers in Federally-regulated and non-regulated workplaces. Annually, we purchased data from a very large MRO firm over the seven-year period from 2003 to 2009. Each data year represents a calendar, January through December, year. After receipt of each year's data set, it typically took a couple of months to resolve all of the issues. We usually received the year's data sometime in April. Over these seven years, we examined very detailed results from more than 7 million urine specimens, approximately three quarters of a million oral fluid specimens, and roughly 100,000 hair tests.

SAMHSA tasked us to breakdown the data on synthetic opioids, beginning with year 2006, in the non-regulated workplace. Obviously, in Federally-regulated testing, synthetic opioids were not authorized. Today I will share the analysis of the urine tests done on unregulated specimens for the synthetic opioids from 2006 through 2009. During this four-year period, roughly 1.3 million specimens were tested for the hydrocodones and about 0.8 million were tested for the oxycodones. Virtually all of the specimens were analyzed in SAMHSA-certified labs. In fact, about half of them were analyzed in various Quest laboratories. All blind QC samples were excluded from the analysis. Each specimen had a data record that contained 254 elements, including donor demographics, employer information, collection site information, laboratory results, and the MRO determination. Throughout the project, HHS human subject protection criteria were followed. The specimens came from roughly 5000 different private sector companies located across the United States.
As an overall summary, during this time period, the non-regulated records that we had for 2006 represented over a million specimens with roughly a 4.19 percent lab positive rate. The MROs verified 79.95 percent of the lab positives as illegal drug use. Over the four-year period, there was a fairly significant decline in the volume of specimens, which parallels the economic downturn of the United States at the time. We wondered, in looking at these data, if this volume decline was unique to the MRO firm from which we were purchasing these data. But checking with several of the large laboratory chains, most everybody experienced a decline in volume, primarily because most of the workplace urine testing is pre-employment testing; virtually nobody was hiring during this time period.

It is interesting to note that the lab positive rate remained substantially equivalent across the four-year period. But also, it is interesting that during this same period, the MRO-verified positive rate declined significantly. You will see, as we go through the breakdown of the analyses, why this decline happened.

MRO-verified positives are those for which there is no legitimate medical reason for having these drugs in the donor's system. A frequency distribution of the total number of MRO-verified positive tests by drug shows that marijuana makes up about 70 percent of the verified positive test results. In 2006, cocaine represented nearly 20 percent but declined over the four-year period as the opioid positives began to increase. The other drugs represent a very, very small portion, less than three percent of the total number of MRO-verified positive tests in this program.

In the upper left-hand corner of this complicated slide, the first column lists the drugs - oxycodone, oxymorphone, hydrocodone, and hydromorphone. In 2006, though over a million specimens came through the system, only 18 percent were analyzed for oxycodone and about 28 percent were analyzed for hydrocodone. In the second column are listed the actual absolute number of specimens tested each year. In the third column

are the percentages of specimens testing positive. Although these numbers are relatively small in terms of the percentage of specimens testing positive, they are increasing every year. Though these numbers are a little lower than what Barry showed in the last presentation, our data are relatively consistent overall, even though we did not separate out these data by reason for test. In the fourth column are the absolute numbers of lab positives. In the fifth column are the MRO-confirmed positive results, including all those where the MRO actually discussed the result with the donor and those whom they were unable to contact. It is often very difficult to contact the donor who knows he/she is a drug user. In the next column are the absolute numbers of specimens that were reversed by the MRO. In the final column are the percentages of lab positives that were reversed by the MRO. For the oxycodones, the important thing to notice is that each year there is an increasing percentage of specimens testing positive overall, with a decreasing number of MRO-confirmed positive results given in terms of percentage, but an increasing number of absolute number of confirmed positive specimens. The last column is one that I am a little concerned about. This column shows that each year the MRO reversals increase consistently for oxycodone, oxymorphone, hydrocodone, and hydromorphone. Similar to what Barry said, we saw that the hydrocodones are a much higher percentage of the lab positive specimens. But the data in the last column indicate that the MROs are reversing these lab positive results. 80-90 percent of the lab positives are due to legal drug use, whereby the individual has a valid prescription as the basis for the use of that drug.

Overall, the absolute numbers are not huge, but they are, relative to the other drugs that are included in the Federal panel, significantly greater than PCP and other drugs. One concern is the increasing trend in the number of MRO reversals, which has increased every year for these four target analytes. Another concern is that the percentage of illegal use of the oxycodones is significantly higher than the hydrocodones. Whereas, while hydrocodone is only about 12 percent of the lab positives that are confirmed as legal use, about 25 to 35 percent of the oxycodones were positive.

The next slide provides a more detailed breakdown. Some of these numbers are exactly the same, but what I wanted to do here is point out that if you look at the oxycodones and the hydrocodones, the lab positives for oxycodone and the lab positive for oxymorphone, there is a significant percentage, roughly 60 percent, are positive for both target analytes. Among the hydrocodones, it is slightly less, but it is in the neighborhood of 45 to 50 percent of the tests are positive for both hydrocodone and hydromorphone.

In the first summary slide, only about 55-56 percent of the lab positives were verified as positive by the MRO. Most of the reversals are with amphetamines and the opioids. For both regulated and non-regulated amphetamine-positive laboratory data in 2003, the MROs were reversing only about 25 percent on the Federally-regulated side of the program and about 50 percent of the non-regulated. But every year since, the reversal rates have increased to where they come together in the neighborhood of 81-82 percent of all of the amphetamine positives being overturned by the MRO and called negative.

We have tried to undercover the reasons for this. We wondered whether people were using the ADHD excuse as a way to get the drug. In looking at the pharmaceutical industry over this same time period, there has been a very significant marketing of a new clinical symptom called adult ADHD. Many people entering into their 30s, 40s, and even 50s are continuing to take these kinds of medications. It is an interesting trend to note, especially with regard to the overall MRO review program.

In Summary, we have seen from 2006 to 2009 a significant decline in the overall volume of workplace tests coming through the system, while the lab positive rates remain relatively consistent at approximately four percent. The MRO reversal rates increased significantly in both Federal and non-regulated testing. In Federally-regulated tests, the majority of MRO reversals appear to be due to prescription use of opioids and amphetamines. For non-regulated tests, there are not only the expanded opioids, but amphetamines, barbiturates, and benzodiazepines with very, very high reversal rates of close to 90 percent.

And I showed you in the last slide, the MRO reversal rates for amphetamines have increased since 2003, from about 25 to 82 percent for Federally-regulated and from 50 to 82 percent for non-regulated.

With regard to the expanded opioid panels seen in non-regulated testing, synthetic opioids account for roughly half of all of the non-regulated opioid laboratory positive test results. MRO reviews identify higher illegal rates for oxycodone and oxymorphone, at roughly 25-35 percent of all lab positives, in comparison with the hydrocodone and hydromorphone, with only are about 12 percent verified positive as illegal opioid use. The MRO reversal rates for synthetic opioids have risen over this same period with reversals for oxycodone increasing from 65 to 74 percent and hydrocodone from 88 percent. Are there any questions?

Mr. Bonds: Were you able to determine if there were any other reasons, other than prescription drugs, for the reversal rates from the MROs?

Dr. Walsh: No, we don't. We only have the timeframe that it takes to resolve positives. We know if additional specimens or analyses were requested.

Dr. Cook: Do any other Board members have any questions for Mike? Thank you, Mike.

I know it's not on the schedule, and if it is okay with Jim, I would suggest we take just a quick 10-minute break, and we will reconvene at 10 after.

(Brief Recess)

Opiates: Drug Metabolism and Disposition

Dr. Cook: Our last speaker for the morning is Dr. Jim Bourland, who is the Scientific Director at Alere Toxicology.

Dr. Bourland: Thank you, Janine. It is a privilege to be up here speaking, and it is a little bit intimidating, too, because of some of the audience members. Just a word of advice to current and future DTAB members. If you make a comment, you may be asked to present. That is how this happened. But I do thank you for allowing me to do this.

I will review the drug metabolism of opioids since we are adding four new compounds to the regulated list. I will then look at some potential interpretation issues that you might encounter in urine and oral fluid.

This is a terminology issue and a little pet peeve of mine. Opioid and opiate are sometimes used interchangeably. I use the term opiate to refer to a compound that is either a naturally-occurring alkaloid of the opium plant or a semi-synthetically derived compound from the opium plant. Opioids are compounds that simply act on the opioid receptor and can include compounds that are structurally dissimilar to opiates, like fentanyl and methadone, for example, which are opioids. All opiates are opioids, but not all opioids are opiates.

I may use the term, free, for example, free hydrocodone, as opposed to unconjugated. I am using those interchangeably, although free really refers to non-protein bound. If I use that term wrong, I apologize for that.

Morphine is the model opiate and the model opioid, and its structure is a phenanthrene derivative. Basically, it contains a benzene ring with a phenolic hydroxyl group at position three, an alcohol hydroxyl group position six and also nitrogen and methyl groups. Primarily, opiates undergo phase one oxidation reactions where either a functional group is exposed or added, and then they can undergo phase two conjugation, along with the parent drug itself, either through glucuronidation or sulfation. That is what is happens metabolically with biotransformation with these compounds. Morphine is a schedule II drug named after the god of dreams, Morpheus, in 1804. This was popular drug during the Civil War. It was associated with the introduction of the hypodermic needle and used in the treatment of war injuries. Morphine became perhaps an issue or an epidemic with Civil War soldiers. It has a half-life is about two hours, and it has several metabolites.

As far as its metabolism goes, morphine is extensively conjugated and forms both glucuronide and sulfate conjugates. Through another pathway, it is demethylated to normorphine through perhaps cytochrome P450

CYP 3A4. About 75 percent of the dose of morphine is present as morphine-3-glucuronide, and about 10 percent is unconjugated or free and found in the urine. Probably about five percent of a morphine dose may be detected as its normorphine metabolite. There are some minor metabolites, such as morphine-6-glucuronide, morphine-3, 6-diglucuronide, and morphine ethyl sulfate. Cone et al. reported this biotransformation.

What we have discovered recently, and which was reported by Cone in 2006 or 2008, was that hydromorphone can be produced from morphine through a minor metabolic pathway. With high concentrations of morphine, morphine can be metabolized to hydromorphone, through the postulated intermediate morphinone, which is formed from the metabolism of morphine. If one sees hydromorphone in a specimen when someone is prescribed morphine, it does not necessarily mean that they have been taking hydromorphone; it could just be there as a minor metabolite. This is very important when we try to interpret what the results actually mean.

Codeine is either a schedule II or III drug and also a schedule IV drug when formulated in cough syrup. Unlike morphine, it is a weak opioid analgesic, having about 50 percent of the potency of morphine. It acts like a pro-drug, being metabolized to morphine to deliver more of the analgesic effect. It is the cytochrome P450 2D6 enzyme that metabolizes codeine. About 7 to10 percent of the Caucasian population and about 50 percent of the Chinese population are poor metabolizers because of a CYP2D6 deficiency. For those poor metabolizers, the therapeutic or analgesic effects may not be very prevalent, useful, or efficacious for those patients. The FDA has warned nursing mothers about codeine. Apparently, ultra rapid metabolizers can produce significant amounts of morphine in breast milk.

Here is a diagram of codeine metabolism. Codeine undergoes OD methylation through cytochrome P450 2D6 to form morphine. It also undergoes N-methylation through the cytochrome P450 3A4 to produce norcodeine. All three of these compounds can be conjugated with glucuronide. Free codeine or unconjugated codeine can be detected in urine, but the conjugated form is present at about double of what you would see for the unconjugated codeine. Trace amounts of norcodeine and morphine can be detected, and they are probably more prevalent in the conjugated form in urine. Typically, in the laboratory, we utilize a hydrolysis procedure for both morphine and codeine detection because they are heavily conjugated. Like morphine, codeine has another minor metabolite reported first by Oyler et al. Codeine can metabolize to hydrocodone, the minor metabolite associated with codeine. The detection of hydrocodone, in the presence of high levels of codeine, does not necessarily mean separate hydrocodone use. You can see how interpretation can be a little confounding when both codeine and hydrocodone are detected. The ratios of the two drugs, although not unequivocal, give us some idea of what may be going on or what the patient may have taken.

Let’s move on to some of the new drugs that we are adding to this regulated list. Hydrocodone, as we learned in Janine’s talk, is the most prescribed and popular opioid or opiate. Brand names include Lortab and Vicodin. It is a schedule II or schedule III drug, depending on the preparation. Typically, in pure form, it is schedule II. If it is with acetaphetamine or ibuprofen, it is a schedule III drug. It is a weak mu agonist, similar to codeine, so therefore, it acts as like a prodrug. The hydromorphone metabolite is an active metabolite, and is a strong mu agonist. This is a cartoon of the hydrocodone biotransformation. There is demethylation to hydromorphone by cytochrome P450 2D6 and also demethylation to norhydrocodone. When hydromorphone is prescribed, norhydrocodone is probably the more significant biomarker for determining whether someone has taken hydrocodone rather than hydromorphone because hydromorphone can be present due to Dilaudid ingestion as well as a metabolite of hydrocodone. Hydrocodone then undergoes a keto reduction to form hydrocodol, which is also known as dihydrocodone. That can, in turn, o-demethylate to hydromorphol; hydromorphol can also be produced by keto reduction of hydromorphone. These compounds also are conjugated with glucuronic acid to form glucuronides. Beselt found about 12 percent unconjugated hydrocodone, 5 percent norhydrocodone, 4 percent conjugated hydromorphone, and about 3 percent hydrocodol and about 3 percent of unconjugated and conjugated together in a 72-hour urine.

Hydromorphone, also known as Dilaudid, is a schedule II drug. It is a very potent analgesic, with about 7-11 times the potency of morphine. It is highly water-soluble and has high oral bioavailability. Onset of action is about 30 minutes and duration of effect is about 4 hours. Since it is such a potent opiate, it is formulated as a 1

milligram per one mL injection or 1, 2, 4, or 8-milligram tablets. The biotransformation of hydromorphone proceeds through a keto reduction to hydromorphol. It is also extensively conjugated with glucuronic acid. About 30 percent of the dose is found as conjugated hydromorphone in the urine. You can find some of this hydromorphol present, as well.

Oxycodone, the second most prescribed opiate according to Janine's data, is a schedule II drug. It is not a prodrug like codeine or hydrocodone. The parent drug does have efficacy as an analgesic. It is fairly potent as a mu agonist as well. It is typically prescribed in 20, 40, and 80-milligram tablets. These tablets are crushed for smoking or snorting by drug abusers. There is a new formulation, which makes it more difficult to crush the tablets. Cytochrome P450 2D6 plays an important role in the metabolism of oxycodone. Oxycodone is OD methylated by P450 2D6 to oxymorphone, and then undergoes ND methylation by cytochrome 450, primarily 3A4, to noroxycodone. Both the oxymorphone and oxycodone are conjugated with glucuronic acid.

Oxymorphone, also known as Opana, has a high infinity for the mu receptor, thus acting as a very potent analgesic. The interesting thing about this compound is that there is no involvement of cytochrome P450 2D6 or 3A4. If someone is a poor metabolizer, for example, because of 2D6 deficiency, oxycodone can be prescribed for pain relief. For metabolism, there is keto reduction to oxymorphol. Primarily, unconjugated and conjugated oxymorphone are found in the urine.

What about interpreting these drugs in biological specimens, whether it is in urine or oral fluid? We are not in Kansas anymore. Dorothy, and then the lion, succumbed to poppy exposure.

I want to talk a little bit about minor metabolites. We brushed on that with hydromorphone and hydrocodone. While I was moderating a session at a Society of Forensic Toxicologists (SOFT) meeting, I listened to Ted Shults give a talk on some process impurities. But first, let's review some of the minor metabolites. With high levels of morphine and codeine, hydromorphone and hydrocodone can be found above your limit of quantitation (LOQ). Just know that that doesn't necessarily mean that the person is actually taking hydromorphone or hydrocodone. It could just be from their morphine or codeine prescription, if they have one.

What about process impurities? What I mean by a process impurity is an impurity derived from the manufacturing process of the pharmaceutical grade compound. There are some postulated and some reported in the literature. Some of the process impurities are also metabolites themselves; for example, morphine is a metabolite of codeine and is also potentially a process impurity. With codeine and hydrocodone, you may find trace amounts of these compounds. The U.S. Pharmacopeia has guidelines for the limits on how pure the compound has to be to be labeled as that. For example, in oxycodone, up to 0.15 percent hydrocodone is an acceptable impurity. That does not mean that every oxycodone tablet has 0.15 percent, but it potentially could contain trace amounts of hydrocodone. If you are analyzing specimens in a population with high concentrations of oxycodone, it may not be unusual to find hydrocodone as a process impurity. Thus, to make the conclusion that that person is using hydrocodone may not be accurate. We need to be careful about what conclusion we draw from what we see in these specimens.

We have minor metabolites and process impurities that you need to be aware of. I have noticed a slight difference in the abundance of metabolites in urine versus oral fluid. I want to quickly review three studies and discuss some findings. The first study was presented as a poster at the SOFT meeting in 2009. 12 subjects were dosed with OxyContin, 160 milligram every 12 hours and then Naltrexone every 24 hours. Oral fluid specimens were frozen and analyzed later by a liquid chromatography- mass spectrometry (LC-MS/MS) method to detect oxycodone, oxymorphone, and noroxycodone. In the 12 subjects, the mean concentrations were 388 ng/mL for oxycodone; 2.5 mg/mL for oxymorphone, which is the 2D6 O-demethylated metabolite detected in only two subjects above the LOQ of the method; and 113 ng/mL for noroxycodone. It was interesting that we could easily detect noroxycodone, but oxymorphone was more of a challenge. These subjects were naïve prior to being dosed OxyContin, so these results do not represent a chronic pain population. Even though there was some steady state involved because of the three to four day dosing regimen, it is a fairly acute scenario of oxycodone dosing. This may represent what you may encounter in the workplace.

Another study that I retrieved from the literature evaluated whether oral fluid was a good candidate to replace plasma to regulate oxycodone levels in cancer patients. Their conclusion was that oral fluid was not a really good substitute because there was not a correlation, but that is not the point that I wish to draw from this study. In this study, there were 43 participants producing 139-paired plasma and saliva specimens. The OxyContin doses ranged from 5-300 mg. The collection device used was a Salivette device, producing, what I believe, a neat oral fluid specimen. The collection occurred three to four hours post-dose, but it ranged anywhere from 15 minutes to 20 hours. This study also tested for oxycodone, oxymorphone, and noroxycodone. Their results are similar to the results from the 2009 SOFT poster presentation. The mean concentrations were 336 ng/mL for oxycodone and 91.4 ng/mL for noroxycodone. They did not report any oxymorphone in the oral fluid, and I found that to be an interesting finding.

This is a study performed at Aegis Laboratories by Heltsley et al., including Drs. Cone and Caplan who are in the audience. This retrospective study of 6,441 pain patients involved screening by enzyme-linked immunosorbent assay (ELISA) and confirmation by LC-MS/MS. They recorded drug and metabolite concentrations and the number of specimens that were positive. They also compared the prevalence of opiate metabolites in oral fluid, relative to parent drug. But they also compared the prevalence of the median concentrations of opiate metabolite in oral fluid versus urine.

The green represents the number of positives in this population for each particular analyte while the red represents the actual ng/mL concentration. In oral fluid, the more prevalent metabolite by far was noroxycodone versus oxymorphone. Unlike the previous two studies, this is not a controlled dosing study where they are only dosed with OxyContin or oxycodone; this population could have been dosed with oxymorphone. I still find it interesting that the prevalence of the nor metabolite is more abundant in oral fluid. Looking at the concentrations, there is a similar pattern to what the other two studies found. For hydrocodone, the nor metabolite is more prevalent versus the hydromorphone. The laboratory may have to incorporate this nor metabolite in their analysis scheme to bolster their detection of true hydrocodone and oxycodone use. Here are the prevalence of codeine, morphine, and norcodeine in that same population. Comparing the three studies, for oxycodone, oxymorphone, and noroxycodone, they have very similar patterns to what we saw in oral fluid. Again, the most prevalent compound is the parent drug. When you think about the mechanism of how drugs incorporate from the bloodstream into the oral fluid, this may not be a surprise since the more non-polar compound is more prevalent; thus, we see that pattern in oral fluid. In the Heltsley study, overall, compared to urine, the parent compound is more pronounced in oral fluid. You will find at least relative abundance of parent versus the metabolites. This will be true in oral fluid versus urine. The laboratory will be looking at a little different pattern of relative abundance of metabolites in oral fluid compared to urine, requiring an adjustment. Perhaps the detection levels or cutoff levels either need to be sensitive enough to detect this metabolite. Or the lab may decide to really target the nor metabolite.

This, in a nutshell, is urine versus oral fluid metabolism. I bracketed the P450 2D6 metabolites to show how oxymorphone, hydromorphone, and morphine produce oxycodone, hydrocodone, and codeine, respectively. They may not be as abundant or as prevalent in oral fluid as in urine. That should not be a surprise, but certainly the nor metabolites are readily detected. It is not that these are not detected in oral fluid because the Heltsley study showed that they are. It may be that those first two studies examined acute dosing or that detection levels may not be sensitive enough.

That is the end, so thank you. I will field any questions you might have.

Mr. Bonds: Thanks, Jim. Based on your impurities findings, would it be possible that someone could have a prescription for Vicodin, and yet the test comes up positive for a hydrocodone?

Dr. Bourland: Yes. You mean oxycodone? An oxycodone prescription and positive for hydrocodone?

Mr. Bonds: Because of the impurities, could have a prescription for one thing, and the MRO see a different positive for a different drug? Is that possible?

Dr. Bourland: I would think you would see oxycodone, but if it is a high enough level, you might see hydrocodone. That has been reported in the literature in a recent article whereby hydrocodone was characterized as an impurity and not a metabolite. For example, even though hydromorphone is a metabolite of morphine, oxymorphone is not a minor metabolite of morphine. If that were found, that would be either from oxymorphone itself or potentially could be from some sort of process impurity. There is more work that needs to be done as far as characterizing what these impurities are and if they are significant. You have to examine the relative abundance of what you find in the specimen to characterize whether it is coming from a process impurity or from the actual drug itself. Does that answer your question?

Mr. Bonds: I guess you are suggesting that there has to be more work done in order to be able to verify that the prescription is what the positive is showing.

Dr. Bourland: Yes. There can be more work done, but I think there are enough data that show these potential process impurities are only typically there when there is relatively high concentrations of the other drug present.

Mr. Bonds: So you would see the other drug, as well?

Dr. Bourland: Yes, in most cases, yes.

Mr. Bonds: If an impurity produces a positive result, could the MRO decipher that there was a higher quantity of the actual prescription versus the impurity?

Dr. Bourland: The MRO would have to call the toxicologist and the lab. Yes, Dr. Cone?

Dr. Cone: We see this often in pain management, where there is one million ng/mL morphine with 100 ng/mL codeine, which is a process impurity and not a metabolite. If you analyze the morphine prescription medication, you will find 0.1 or 0.15 percent of codeine in the morphine. This is true for many of the prescribed opioids, including oxycodone, which contains 0.1 percent of hydrocodone. With these very extreme levels associated with very high parent drug concentrations, it could be confusing if the laboratory does not understand that a million ng/mL oxycodone and 100 ng/mL hydrocodone are actually being measuring accurately. They really shouldn't be reporting out the hydrocodone because it is a process impurity. But because some labs do, it causes some confusion.

Mr. LoDico: I would question one thing about laboratory procedures. If, in fact, there was a specimen containing one million ng/mL morphine, the laboratory performs a dilution of that sample. As a consequence, that impurity, which would be also present in the sample diluted, would almost be eliminated or at least be so diminished that it would not appear in the analysis.

Dr. Bourland: But it could be reported from your first analysis. In laboratories that I have worked in and currently work in, if there are two compounds, compound A and compound B, and compound A is within your linear range and below your upper limit of linearity (ULOL) but above your LOQ, you will use that data. But if compound B is above your ULOL, then it will be diluted. Though compound A may not be detected upon dilution, the second extraction with dilution result for compound B is reported.

Dr. Cone brings up a good point about how significant is the hydrocodone when there is one million ng/mL oxycodone and 100 ng/mL hydrocodone? Should the lab really report it? That is a very good question, and I could see arguments on both sides. But unless you have an experienced certifying scientist that recognizes that, you can understand how labs could report out these compounds as process impurities. There are some interpretation issues with these synthetic opiates.

Mr. Bonds: Did we recognize this in urine specimens? Did the same thing occur in urine specimens?

Dr. Bourland: The process impurities are urine primarily. Dr. Cone may have experience in seeing them in oral fluid, but I have not. I have just seen them in urine specimens.

Mr. Bonds: Does it detect it more in oral fluids, Ed?

Dr. Cone: We have somewhat limited experience in oral fluid with the process impurities. When we did a pilot study where we collected urine and oral fluid specimens from the same subject, we saw the process impurity in urine and oral fluid. Oral fluid is not immune to this issue. Concentrations were lower, of course. This finding, to some extent, validated our interpretation that it was a real finding, and not an artifact, but a process impurity.

Ms. Chandler: Jim, I would like to make two comments on behalf of the laboratory. One thing we will not know in the laboratory is what prescriptions the donor has, so we are not going to have any knowledge about what we should and shouldn't ignore. In addition, we might not know that there are one million ng/mL of drug there. We are only required to ascertain that there is drug present. The concentration may be above our upper limit of linearity, so we are not necessarily going to take it to completion on that dilution. We could do that on request, and certainly offer the MRO all of this information if they needed it to make that determination.

Mr. Bonds: Then it is possible that an MRO could receive information about one specific drug, yet the donor has a prescription for another?

Ms. Chandler: Yes.

Dr. Huestis: I think that comes to the education of the MRO. This issue has been around for a very long period of time, and they ought to know this information.

Dr. Smith: Jim, I have a question in terms of moving to further opiate or opioid testing. Is some knowledge or some understanding of additional medications that may affect the metabolic process for a given donor going to be important?

Dr. Bourland: I think it might. I don't know if that would be important. It is obviously interesting information, but I do not know how much you would gain that. I am not advocating doing pharmacogenomic testing on a patient to determine if he is 2D6 deficient or something. Is that what you are alluding to?

Dr. Smith: I know in pain management there has been some attention paid to that. I was just wondering if you think in workplace testing that there would be any need to even address those issues.

Dr. Bourland: I certainly see it as an application in the pain management field. But I am not the authority to answer that question in workplace, either. I do not see it as needed in workplace as it is in the pain management arena.

Dr. Huestis: I think from a pain management point of view, it is really important to make sure that there is an efficacious use of the medications. But you are still going to see the analytes. They may be in a different ratio to each other, but I don't think it would be necessary for workplace to do that at all.

Dr. Smith: The only reason I even brought it up, Marilyn, is because I know eventually we will reach the point of discussing it even if an individual is in the workplace, in a safety-sensitive position, and has a script. If a fitness for duty issue, the quantitative level may indicate a misuse or abuse of something that is legitimately prescribed. That is part of the reason that I was asking that question. I do not think we are going to avoid that discussion, quite frankly, although we might want to.

Dr. Cook: Thank you, Jim.

We will break for lunch at this point. Because I had to change the agenda around this morning, instead of two shorter presentations in the afternoon, there is now one longer and one shorter presentation. I suggest that we reconvene at 1:15, so that these two presentations will fit in the afternoon session.

(Whereupon, a luncheon recess was taken.)

AFTERNOON SESSION

Dr. Cook: Our first speaker for this afternoon is Dr. Ed Cone, Adjunct Professor of the Johns Hopkins University. Ed?

Pain Management Data – Synthetic Opioids

Dr. Cone: Thank you, Janine. This is a continuation of Jim's talk, which provided a very nice overview of the synthetic opioids. But before I start, I promised my wife I would not mention that I am from Alabama and that we won the National Championship in football.

I will talk about opioids in the context of pain management, and there is a reason for that. Through the pain management data, we are just trying to justify what analytes to test for in the synthetic opioid category and also what the appropriate cut-offs should be. Although we do not have the perfect answers to these, we do have a lot of information available to us. This is an attempt to examine some of the available information about synthetic opioids, which encompasses a fairly large data set. Information is available on both urine and, to a lesser extent, on oral fluid. I will provide a few recommendations to accompany the data.

The basic questions are what analytes should we include and what cutoff concentrations seem appropriate? Though these questions have been preliminarily decided, let's examine them and continue the discussion. I have color-coded the slides because I will be discussing both urine and oral fluid. I have included captions or cartoons to remind me what I am talking about. So if you see a urine cup on the slide, guess what I am talking about?

There are four recommended synthetic opioids. They are structurally similar, but they are different chemically. Oxycodone and hydrocodone are codeine analogs because of their structural similarity to codeine. Hydromorphone and oxymorphone are structurally similar to morphine. They are the more potent compounds of the series, with some being 10 times more potent than their parent compound. Hydromorphone, or Dilaudid, is probably about 10 times more potent than hydrocodone. Additionally, there is some crossover, such as hydromorphone being a metabolite of hydrocodone. There are some other metabolites that may be of interest.

We have seen statistics about the availability of prescription medications that have impressed me. Over the last decade, the number of prescription opioids has increased from 30 to 180 million, a six-fold increase. The number of stimulants, even though the actual numbers are smaller, increased nine-fold. There is a considerable amount of opioids out there, and guess where most of them are? Sitting in our medicine cabinet. It has been recognized that there is a really big problem in this country with prescription opioid abuse and prescription drug abuse in general. A few months ago, the White House Drug Policy website listed prescription drug abuse as the nation's fastest growing drug problem. The bottom bullet, which I thought was interesting and really caught my attention, states that in our military illicit drug use has increased from 5 to 12 percent among active duty members over a three-year period and that this increase is primarily attributed to prescription drug abuse, primarily to opioid drug abuse.

The pain management area, the aspect that has grown over the last decade into a very large business endeavor in the United States is pain compliance monitoring, which serves a number of very useful purposes. Pain management physicians are prescribing scheduled drugs, primarily opioids. Physicians want to know if their patients are compliant with the drugs as prescribed. For safety reasons, they want to know if the patient is taking only authorized medications and not going to another physician or not going somewhere else for

additional medications. Any time a physician prescribes an opioid, there is the risk of the patient developing the disease known as addiction. Addiction is distinct from physical dependence and tolerance that is expected to occur with chronic administration of opioids. Addiction is where it gets out of control because the person is using the drug for non-medical purposes.

There is also a significant component to the illicit drug market called diversion, which is the movement of drugs from legitimate sources into the illicit market. Even though the numbers from NSDUH indicate that the sources of illicit prescriptions are small, it is not really that small. There is a rapidly developing illicit drug market that involves prescription drugs. Diversion from a legitimate source is a major concern of these physicians because they have significant liability; the Drug Enforcement Agency (DEA) will go after physicians who are not prescribing appropriately. There are many reasons why this has actually turned into a very large market and a very large industry.

When Yale Caplan got me involved with Aegis a number of years ago, we realized very quickly that many laboratories, including Aegis, had large amounts of scientific information that rarely ever saw the light of day. He and I both urged and received t cooperation from Dave Black to delve into these data, to analyze and try to make sense of it. Other companies have done the same thing along the way. As a result of our efforts, we have published a number of articles now, through the courtesy of Aegis and the support of Dave Black, on pain management testing, both involving urine specimens, and lately, oral fluid specimens. I will present some of this information and will try to summarize it quickly for you.

What can we learn? We can learn some things, and we are limited in learning about other areas. We can learn about prevalence because this is the population that is tested in the workplace. We may have a very concentrated slice of this population in these data sets, but this is the exact population that you will be encountering at lower frequency in the workplace. These people, many of them are functional and many of them employed, are seeing their physicians for treatment.

Since these are not controlled dosing studies where the drug and its dosage are known with certainty, we have some limitations as well. We can obtain prevalence, concentration distributions, and patterns of metabolite distribution. These are some of things that we think might be useful to review.

This is just a sampling from Aegis, but remember other companies are doing the same thing. We have begun to get the information out. Most of what I am describing to you is from published literature. However, we had to reanalyze the data to pull out certain types of information for this presentation.

What testing does the pain management laboratory do? It tests for panels of drugs, just like in workplace testing, except the panel is larger. Shown here is a typical panel and it is, in fact, abbreviated. Listed are the common drugs that are tested for in almost every pain management specimen that is submitted to the laboratory. The urine specimen is tested for all of these drugs at the various cutoffs, and the results reported back to the ordering physician.

What does the laboratory do? It develops multiple screens, which include multiple drug categories. The lab is continually expanding the panel. For example, the list I showed earlier should now have four or five more drugs added to that list. Labs are continually updating their drug panel. Interpretation of this very complex array of analyses is sometimes simple, but frequently very complex.

One of our studies involved almost 11,000 patients and represents positive results confirmed primarily by LC-MS. This slide depicts the general distribution of the types of drugs encountered in the pain management arena. Opioids, as stated here, usually represent those drugs that are structurally related to morphine. This opiate category accounts for almost 60 percent of the drug positives. Methadone, propoxyphene, meperidine, fentanyl, carisoprodal, amphetamines, barbiturates, and benzodiazepines represent a large segment in this population. And yes, this population does abuse some illicit drugs. Usually around 10 percent of the patient specimens are positive for one of the two key illicit drugs that we can readily identify: cannabis, or carboxy acid THC, and cocaine.

These data provide a distribution of the drugs taken by pain management patients; these drugs are primarily opioids, as you would expect, but a lot of other drugs are taken as well. We see anywhere from one to as many as six different distinguishable opioids onboard at one time in one patient. It is pretty incredible what you can run into out there. I have seen as many eight distinguishable drugs in one patient specimen, indicating that poly-pharmacy is occurring.

Our focus today is the opioid category. Shown here is a simplified version of opioid metabolism, with codeine, hydrocodone, and dihydrocodeine being located in the center. They are metabolized in various ways, including codeine to morphine, hydrocodone to hydrocodone and hydromorphone, codeine to norcodeine, hydrocodone to norhydrocodone, and oxycodone to noroxycodone and oxymorphone. Now, why go back over this? Remember that each one of the boxes in gray is a primary drug that can be administered by a physician. If a patient specimen contains both morphine and codeine in their urine, they may be taking codeine or they may be taking codeine and morphine. We usually cannot tell exactly what the patient is taking, but the different ratios can be of help. If a patient is positive for both oxycodone and oxymorphone, we cannot be assured that he/she is not taking both drugs. We know they are taking oxycodone, but the oxymorphone may be there because they are taking oxymorphone as well or because, most likely, it is a metabolite. We cannot really tell a difference, which is one of the shortcomings of these data. On the other hand, there are three unique metabolites. For instance, the presence of norhydrocodone assures that the patient took hydrocodone. Listed here are the abbreviations that you will be seeing.

The first data set includes information from 20,000 pain patient specimens. We looked at these specifically because, though they were tested for everything, we just analyzed for the 10 opioids and the data were published in the Journal of Analytical Toxicology (JAT). The results were confirmed by LC-MS/MS with a LOQ of 50 ng/mL. Out of the 20,000 specimens, 13,000 plus were positive for at least one opioid. The prevalence is shown in this slide. I don't think it is a stretch to say that this is similar to what you might find in the workplace, but just at much lower prevalence. Hydrocodone is the most prescribed opioid, followed by oxycodone, the second most prescribed opioid. Oxymorphone was probably detected because it is a metabolite. But remember, we cannot distinguish if this patient was on oxycodone and its metabolite was found or if the patient was taking both oxycodone and oxymorphone. Morphine was found; though it used to be the standard treatment for chronic pain, it has fallen by the wayside to some extent, but it is still out there, of course. Though morphine has poor bioavailability, it is still administered as the primary opioid throughout Europe and the Third World. In the United States, the synthetics are primarily prescribed for pain management.

By breaking these data down, we can assess what the appropriate cutoffs might be. I worked with John Mitchell at RTI to develop what we thought was a reasonable scheme to parse the data. How many specimens from this data set would test positive for oxycodone in the 50-100 ng/mL range? In the 101-150 ng/mL range? Using this approach, we can get a feel for the best cutoff to use. There is no perfect answer to that, but at least we can examine the distribution.

To read the data, a number of 100 refers to the limit for the 50-100 ng/mL bin. A number of 150, similarly, refers to the 100-150 ng/mL bin. Another approach, very similar to this one, is the frequency method. How many specimens were positive greater than 50 ng/mL cutoff? Since the LOQ was 50 ng/mL, this number would automatically be 100 percent of all specimens would be greater than 50. The frequency decreases with each increasing cutoff concentration.

Looking at the codeine histogram, the bins are given on the x-axis. The data distribution resembles a reasonable Gaussian curve, with the most frequently found specimen concentrations in the 5000-10,000 ng/mL range, indicating where the bulk of the codeine positives are found.

Using the cumulative frequency number, we can ask questions about codeine. For example, using the 300 ng/mL cutoff with the codeine data, about 25 percent of the positive results would be missed and called negative. It is a really different situation with morphine because we saw mostly very high concentrations and a skewed distribution. Applying the 300 ng/mL cutoff to morphine, very few positive results would be missed.

Norcodeine concentrations are dispersed across the range; there appears no perfect cutoff concentration. Using the 300 ng/mL cutoff, almost 50 percent of the positive results are lost, indicating that this cutoff concentration cannot be applied to norcodeine.

For hydromorphone, remember we cannot distinguish if this is a metabolite or an independently taken drug. Since dihydrocodeine is also a legitimate prescription product, we do not know if this is a metabolite or a prescription product. Since it is rarely prescribed, most of these are metabolites.

The hydrocodone frequency distribution also resembles somewhat a Gaussian curve. Applying the 300 ng/mL cutoff, about 20-23 percent of the positive results may be lost. At the 100 ng/mL cutoff, almost no positives are lost. The situation is a little different for hydromorphone, though.

Dr. Huestis: These are pain management patients who are under the care of pain management doctors who are ordering the whole panel, correct? So these people are taking pain medication every day, versus people who are abusing the drug and not under the care of a pain management physician. The drug concentrations are much higher than you might find in the person who is abusing these opioids.

Dr. Cone: The drug concentrations are across the range and are much higher than you might find. People in chronic pain take medications everyday do go to work. Many of these people are employed full-time. Some of these people are taking the medications PRN, so in these patients low concentrations are seen, as well. I would agree with you that in this database, the bias is toward chronic administration of opioids.

The hydrocodone and hydromorphone frequency distributions are more spread out. Since more hydromorphones are at the lower concentrations, applying the 300 ng/mL cutoff would result in almost a 50 percent loss of positives.

The oxycodone frequency distribution also resembles a Gaussian curve. At the 300 ng/mL cutoff, about 15 percent of the positive results are lost. The oxymorphone distribution is not quite as spread out as hydromorphone was. At the 300 ng/mL cutoff, about 15-20 percent of the positive results are captured.

Examining the data another way, what percentages would be reported as negative at selected concentrations? At the 300 ng/mL cutoff, 22 percent of codeine positives would be missed. For hydrocodone, the most widely prescribed opioid, about 20 percent would be missed at the 300 ng/mL cutoff. Using the 100 ng/mL cutoff, very few would not be captured.

So the cutoff decision, for which I do not have a strong recommendation, should be one of these two or a concentration that is close by. For oxycodone, at 300 ng/mL, about 13 percent of the positives would be lost, and for hydrooxymorphone, about 15 percent is lost.

Looking at the other way to predict the cutoff, all results greater than 50 ng/mL would be called positive for hydrocodone. So, 100 percent of the specimens are positive at 50 ng/mL, the LOQ, or higher. For results greater than 100 ng/mL, 95 percent of hydrocodone results would be positive. At the 300 ng/mL cutoff, the percentage would drop to 78 percent.

For hydromorphone, at the 100 ng/mL cutoff, there is a big drop to 88 percent because hydromorphone concentrations are very low primarily. At the 300 ng/mL cutoff, about half of the hydromorphone positives are lost. At the 100 and 300 ng/mL cutoffs, the percent positives are 97 and 87 percent, respectively for oxycodone, and 97 and 84 percent, respectively, for oxymorphone.

I have shown the data several different ways to give you a feel for either the 100 or 300 ng/mL cutoff. This slide reiterates the same data.

I wanted to mention that some of these metabolites that we monitor are unique metabolites. Norhydrocodone and noroxycodone may be worthwhile as special tests or even for consideration as targeted analytes. Here is

its uniqueness. Of all of the positives for hydrocodone (6,538), 943 of those patients were positive for only norhydrocodone. Norhydrocodone was frequently seen in combination with hydrocodone. A similar metabolite uniqueness was observed for noroxycodone. Conversely, norcodeine was not that great a marker for codeine.

Dr. Huestis: What cutoff did you use to obtain those data?

Dr. Cone: These were all at the 50 or greater ng/mL level.

Per the DTAB recommendations, the four synthetic opioids should be monitored. More discussion is needed to determine the screening cutoff concentrations. I am on the fence about whether the screening cutoff should be at 100 or 300 ng/mL. The more conservative 300 ng/mL cutoff would probably give the MROs a lot fewer headaches. At the same time, many of the hydromorphone positives would be missed. If that is important, then either a lower cutoff for hydromorphone or different cutoffs for the more potent opioids should be considered. Remember, since hydromorphone is 10 times more potent, it is taken in lower concentrations; thus, it is always present in general in lower concentrations. To detect hydromorphone when it is taken independently, the 100 ng/mL cutoff should be discussed.

Let's shift quickly to oral fluid. We, as well as others, have produced some publications in this arena. How do you test for drugs in oral fluid? Well, almost the same drug panel could be utilized. By comparison, shown here are the oral fluid urine drug panels. Of course, the oral fluid cutoffs must be a lot lower in concentration. These are the working thresholds that Aegis uses for oral fluid. You will notice a few small differences, but beyond these, they are very similar. They analyze for the parent alprazolam in oral fluid, whereas they generally test for the alpha-hydroxyl metabolite in urine. They screen with 14 different assays and confirm with LC-MS. The overview is shown here. Notice the similar prevalence distribution, with 50 percent or greater of the positives being opiates, including oxycodone. The benzodiaepines are the next largest class of compounds. Also detected are the illicit drugs, such as the cannabinoids, cocaine, and the others that we saw in urine.

In this slide, the blue represents our limit of quantitation, which was one ng/mL. The data bins are 1-10, 10-20, 20-30, and greater than 30 ng/mL. For oxycodone, the majority were in the greater than 30 ng/mL range for oral fluid. There are some differences with the oxycodone and oxymorphone series. The oral fluid oxymorphone series shows a bias towards lower concentrations; this may be primarily the result of a metabolite, rather than independent use. The majority of oxymorphone results are in the 1-10 ng/mL range. But again, this is probably because this is there primarily as a metabolite.

The majority of hydrocodone positives were in the greater than 30 ng/mL range, with about 15 percent in the lowest range. This bias towards lower concentrations was evident with the more potent compound, hydromorphone, with the majority of positive results in the 1-10 ng/mL range, probably because most of it is present as a metabolite.

Morphine is split into different concentration ranges. About 36 percent is in the greater than 30 ng/mL range, and almost in equal amounts are in the lower range. Sine we did not see many codeine positives, this may not be good representative data. We found only 136 positive results, with most of them were in the low ng/mL range.

Recommendations for the oral fluid analytes would be the four synthetic opioids. We have pretty much agreed from the start that screening at 30 ng/mL and confirming at 15 ng/mL would be the best compromise.

I want to mention a few items that I meant to say at the last DTAB meeting that I never had the chance to. Also, in these large studies, we had the opportunity to make some comparisons between urine and oral fluid. These are not head-on comparisons; these are two separate populations of pain patients. The data included the prevalence of positivity rates for the different drug categories in almost 11,000 urine and 9300 oral fluid specimens. For opioids, the prevalence was 56 percent in urine and 51 in oral fluid. The prevalence rates for amphetamines were one and two percent; for cannabis, six and four percent; and cocaine, two and four percent, respectively, for urine and oral fluid. Since it is more difficult to detect benzodiazepines in oral fluid

than urine, the prevalence is somewhat lower. The remainder of the prevalences was similar between the two matrices, with the exception of carisoprodal, which, for some reason, was almost twice as abundant in oral fluid as in urine and fentanyl, which was about twice as abundant in oral fluid as in urine. Overall, the comparison data appear encouraging, based on the two large independent populations.

In a smaller study with pain patients, we collected paired urine and oral fluid specimens. The urine specimen was collected initially from the patient, who then immediately provided an oral fluid specimen. This is the overall comparison of urine and oral fluid positivity rates for the 40 analytes. Overall, 329 were positive in urine and/or oral fluid while 984 were negative. For the discrepant results, 148 were urine negative and 83 were oral fluid positive. The result from the kappa analysis was 0.64, which indicates substantial agreement. The overall agreement was 85 percent and the agreement expected by chance alone was 58 percent, so it looks pretty good.

Since this is a large number of drugs and analytes, we decided to focus on only the ones that are of interest to the DTAB and to examine just those positives. There were still a fair number of paired results to compare, including 35 positives, 208 negatives, and some discrepancies: 11 and 9. The kappa value actually improved to 0.73, and the agreement was pretty high, as well. And this only involves the codeine, morphine, cannabis, amphetamines, cocaine, so forth.

In summary, for this last part and from the various ways of looking at comparisons, the positivity rates are similar for urine and oral fluid. There are some individual class differences in detection rates that should be expected. And with that, the end.

Dr. Huestis: For that last comparison, was that at the LOQ? What cutoffs were you using and did you use the nor-metabolites in the urine?

Dr. Cone: We used the LOQs. There were two populations. All of this data was based on the LOQs, which actually turns out to be their reporting level.

Dr. Huestis: Did you use the nor metabolite because the nor was so important for the urine?

Dr. Cone: We used it. These are only morphine, codeine, cannabis, amphetamine, methamphetamine, and cocaine, so no other. We did not involve the nors in this case.

Ms. Chandler: Could we go back to the slide on the urine data where you were talking about the large number of hydromorphones that you would miss if you used the 300 cutoff? Do you know what percentage of those was also positive for hydrocodone? Would you truly miss hydromorphone-only users or just miss hydrocodone metabolites?

Dr. Cone: Very good question. I do not know off the top of my head, but I can assure you with great confidence that most of them would have been positive for the parent drug.

Dr. Smith: In any of the data for urine in the pain management populations was any normalization done with creatinine or for the concentration of the urine specimens themselves in relationship to either the LOQ or cutoff?

Dr. Cone: Not in relationship to these data. Aegis does some normalization; they do it routinely. These are raw, analytical data.

Dr. Bourland: On slide 29 or 30 where you showed the pie charts with the cutoffs, you had the high incidence of positives for the low oxymorphone and then the high positive rate and the high cutoff for oxycodone. Did you look at noroxycodone that way? Or what would you predict? Would that be similar to the oxycodone profile or somewhere in between?

Dr. Cone: I didn't break it down that way, but we could certainly do it. It would be worthwhile to examine how important the noroxycodone is in interpreting what is going on. That is a good question.

Ms. Farrell: First of all, the pain management data are very interesting. Do you have the ability to analyze the data to identify whether the pain management patients were using opioids that were not prescribed and to determine what the cutoffs needs to be to identify that usage? I think it will be the most interesting to the workplace and to the MROs when pain management patients are taking additional opioids through diversion, and not just the opioids that they have been prescribed.

Dr. Cone: Yes, it is an excellent thing to do. We have some information on patient prescriptions, and I have done some of that analyses. But I have some reservations about the information that is supplied to us because it is coming from different sources and different clinics. In some clinics, it comes from the patient; it some clinics, it comes from the patient record.

Dr. Huestis: What if we were able to get data from workplace drug testing labs, so we could compare the pain management data to the workplace data? That would be really interesting to compare.

Dr. Cone: We should talk to Barry and see if he could analyze his data, similar to the way we have, for a really good comparison. Thank you.

Dr. Cook: I was remiss earlier when I recognized our special guests. I forgot to welcome Mr. William Smith from the NRC.

Our final speaker for the open session today is Dr. Nick Lomangino, who is the medical review officer for the Federal Aviation Administration (FAA), part of the U.S. Department of Transportation. Nick?

Prescription Drugs and the MRO

Dr. Lomangino: Thanks for the opportunity to speak to you today. I have attended about three or four DTAB sessions, and I am always in awe of the degree of scientific detail and rigor. It would be a shame, from an MRO perspective, to not take advantage of that and to make decisions that dismiss all of that input. This is an important topic and should be understood from an MRO's perspective.

First, a little bit about me. I started out as a clinician, and later came to work for the government, becoming a clinicrat. And then, as I progressed in my career, I became a burician. Now, I aspire to become a clinician again, with a social conscience and an ability to exercise regulatory constraint.

The disclaimer is that these are my own comments and not those of the FAA or DOT. Since I do not differentiate between opiate and opioid, please forgive me. Again, I am a clinician, so a soft science is applied science. My presentation will focus primarily on Federal employment, regulatory requirements, and issues of medical certification, and not so much about employer-based programs. I will talk a little bit about extended panels. I will not discuss issues regarding state regulations or state testing or testing under military rule. My comments represent a summary of my own personal experiences and discussions with other MROs, primarily from the Federal sector. In any recommendations that I have, I strive to incorporate some strategic concepts, near-term practical considerations, with a guiding principle of balancing the rights of the individual and responsibility of system caretaker. At the end of the day, this is about system safety and employee protections, and how we balance those. One of my strengths is that I can maintain in my brain the two opposing concepts at the same time. Now, some say that means I am well balanced. Others say that I have worked with attorneys too much or that I could be suffering from schizophrenia. I will let you decide which one is applicable.

First of all, I support the concept of expanded opiate testing. I don't want anybody to think that I am trying to throw a brick into the gears and slow things down. I really think this is an important initiative. I think we need to proceed, but there are some real world issues that I have some concerns about, and I would like to give you

the clinicians' and MRO's perspective. My goal here is really to raise questions and thoughts. I don't have any answers, but I have a lot of questions. Perhaps we can tease out some clarity of the objectives.

This morning you saw the 2010 data, but I am showing you the 2008 data. There is a shift between 2008 and 2010, with the 2008 data being a bit larger than the 17 and a half percent seen in 2010.

In the first Executive Order, sensitive duties in the Federal workplace program include security as well as safety. The Omnibus Transportation Employee Testing Act focuses on safety. In the MRO's perspective, there is both safety and security, at least in my world. In the MRO certification course, employer-based testing programs and school testing programs are the primary focus. I thought it was interesting that I need to be certified under a Federal regulation to learn about school testing programs. And yet, privacy protections are completely different.

Concerning the migration of societal expectations, first, we began with the concept of illicit drug, which is a legal concept, not a medical one. For workplace and system safety, I must consider not only the individual but also the system. In my MRO world, National Air Space is the big dog on the block. Now, we are considering prescription medications and their illicit use, although these medications are not themselves illicit, their use is. When we talk about illicit use, this is an illicit drug that is used in illicit ways. When we discuss system safety, it is difficult to ignore that as we move into the future. Now, we also examine substance abuse disorders and the concept of addiction, which falls into my clinical arena. Identifying somebody suffering from a particular disorder is where the rubber hits the road to me. It is identifying those people, and not disenfranchising them, but treating, rehabilitating, and getting them back to be productive people and members of society is my goal. If we do not lose sight of that goal and understand that is where we really want to go, then all of this is terrific work. We need to think about rehabilitation, as well, in any type of testing program. I liken it to a major league baseball game. When the pitcher walks to the mound, he is thinking about which pitch he will throw and how he will throw that pitch. The catcher gives him a signal that he will either agree or disagree with. He winds up, steps back, and his arm moves forward. If a testing program does not address rehabilitation and rehabilitation standards, it would be as if the pitcher never released the ball. That is the big issue, from my perspective, in the concept of fitness for duty and returning to work. We have identified this individual and have gotten him into a treatment program. But what did that treatment program really do? I see how many people fail, at the initial time through and also after they have been returned to work. I cannot help but think that maybe we should have been a little bit more rigorous up front with specific standards. I will give you an example. I had one individual who tested positive for marijuana and denied use. The substance abuse professional recommended eight hours of treatment, which comprised four sessions of sitting in front of a video tape machine for two hours at a time. At the end of the eight hours, the individual said, I still did not use marijuana. The treatment provider concluded that he had met all of his treatment objectives. This happens too frequently. I strongly advocate for us to think about that as we move forward.

What is the role of the MRO? A forensic examiner, a safety advocate, an employer advocate, an employer advocate, or all of the above? I find myself playing every one of those roles through the process. MROs try to protect employees' medical information to avoid any discriminatory practice that may result from the disclosure of information. But again, we do not want to interfere with the treatment. If somebody is suffering from a disease, and it is a painful disease, we do not want to interfere with that, either. We are talking about balances. Are we responsible for thwarting criminal activity? Many times, during an MRO interview, a donor does not want to disclose anything because he/she does not want to provide any information that suggests that he/she has been engaged in any criminal activities whatsoever. Is the donor invoking his/her 5th amendment against self-incrimination to protect himself against charges of criminal activity or is it denial of the disease? It could be any number of these things.

What are the actual protections surrounding this information? Is it reasonable to use these data to interfere with somebody else's rights in another arena? Sometimes it is fair, sometimes it is not. What procedures are in place to protect this information from being used by others? My medical license is issued by the Department of Health, not by the Department of Justice, so I do not really know my role is in this particular arena.

Do we determine illicit use, legal use, or reasonable medical explanation? In my practice, I look to see if there is a medical use. If they have a medical use, I have my answer. If they do not, I don't describe whether the activity that they engaged in is illicit or not. I just say that they failed to have adequate medical explanation.

Is safety the MRO's responsibility or the employer's responsibility? Again, I do not have the answer to this. I tend to think it is more of the employer's responsibility than the MRO's. We have certainly a duty to the worker. If they are taking drugs that can cause harm themselves or their co-workers, that is something we are interested in. System safety, especially in transportation, including pilots, air traffic controllers, bus drivers, train operators, has a duty to the public, as well.

What does the MRO do during the assessment? When a positive test is downgraded by the MRO, use of reasonable medical judgment is required. I will give you an example of reasonable medical judgment. I performed an interview the other day on a donor who was positive for morphine. The donor said he has a prescription for MS-Contin at 30 mg twice a day. He is a forklift operator. I asked if he is able to do his job okay on that type of medication. He replied, "Yes. Though the pain is bad, the medication helps me so that I can do my job just fine." He reports he has had no accidents or injuries on the job. I asked if he can really operate a forklift taking that much morphine. He admitted that he doesn't take it while on the job. He takes one pill at night and the second pill when he finishes his duty. I replied that it is still a big dose. He countered by saying that he doesn't take it every day. Notice how this story is morphing. From a medical perspective, is it my duty to warn? Does the company have any medical standards for a forklift operator? No. If the company does not feel that it is necessary to develop medical standards for a person to perform that job, what constitutes reasonable medical judgment on the part of the MRO? I am taking this person's word. I have not spoken to the manager yet. I did not want to release information until I made an assessment. What information do I have to make that assessment? Do I really understand the job requirements? Does this person do something else other than operate a forklift?

For the identification of addiction, the Diagnostic and Statistical Manual of Mental Disorders (DSM) has specific diagnostic criteria. The Substance Abuse Professionals (SAP) do a wonderful job applying whatever data they obtained during their assessment of that individual. If the donor does not meet those strict diagnostic criteria, they do not have a disorder. If they do not have a disorder, education would be appropriate but not treatment.

Looking at the medical standards, for example, DSM dictates two or more events within a 12-month period of time. Our medical standard would say, for a pilot for example, use in the physically hazardous situation, if at any other time. If you had a driving under the influence (DUI) citation five years ago and you got another DUI now, which is at any other time, you lack medical qualification to be a pilot, according to our standards. That would be enough to send somebody to treatment. If you did not have a medical standard in place, what happens to that individual?

In workplace testing, we need to redefine what constitutes the clinical definition for a particular disorder. DSM was created for the clinical model where the patient is having medical problems and difficulties that are related to his/her substance use disorder. He/she goes to the physician for evaluation; he/she seeking help and treatment for the problem. In the occupational setting, it is adversarial. Though I don't want to call people liars, I think they are more in denial than lying. When your job and career are on the line, you become protective. Is it really reasonable to use DSM for standards to determine the diagnosis? Or should we promote the concept of an occupational standard? Considering all your work in deciding what drugs and cutoffs, when it gets to the end of the line, what do we do with this individual? Have we really mitigated the hazard that is out there? It is not as clear.

My personal bias in the concept of fitness to resume covered duties is that the MRO process should be separate from the fitness to duty determination. Does that mean that an MRO should not do fitness for duty evaluations? No, if the MRO feels comfortable and if he obtained the information from the company about that job, I think he can do that. But I think it needs to be separated. All too often, I see MROs blend the information together. Because they do not think it is a safety issue, they will downgrade the test and verify it as negative. Even though there is no basis under the drug testing regulations to downgrade it, they do it anyway.

What category does the donor fall into it? Federal employment, government-regulated employment, non-government employment, employer-based programs, or school athletic programs? The privacy laws are different in each one of those settings and the regulatory applicability changes. When a drug test is performed for Federal employment, the attorneys and the judges almost universally point to CFR 49 Part 40. I must tell them that those are industry-regulated requirements. But yet, they apply those laws to Federal workplace testing. And they come to some bad, unsupported decisions.

MROs should be informed as well as administrative law judges. I cannot tell you how many times somebody will refer to Health Insurance Portability and Accountability Act (HIPAA). HIPAA does not apply to Federal workplace testing or the Federal government. But yet, they feel that they are bound by that.

Let's take a look at the original Executive Order and opiate testing. Was it meant to find heroin, illegal substances, and schedule I drugs? Yes, absolutely; I don't think anybody will question that. For opiates like hydrocodone or oxycodone, is it illegal acquisition, illegal use, or valid medical use? How about opiates prescribed for another person? Not uncommonly, during an interview the donor will say that his wife was sick last week with a real bad upper respiratory infection. Her doctor gave her medicine. She was doing okay now but, lo and behold, three days later, I started came down with it. Since these are tough times, if someone can avoid the doctor's visit and that expense, he makes a choice. Was that choice intended to break the law? No. Is it technically breaking the law? Yes. Technically, does he have a valid reason for having the substance detected in his body? No. Technically, should I make that an MRO-verified positive? Absolutely. The MRO Manual states that using somebody else's medication is an admission and thus a positive result. Is that the cohort that we are looking to go after? Will we have justice in the end, by calling that person a drug user and placing him in a rehabilitation program? What did we gain?

As an example of unused medication, we have the case where somebody was prescribed OxyContin for a kidney stone and placed his unused medication in the medicine cabinet. Later, that person is in excruciating pain from a twisted back while playing golf. It is Sunday afternoon at five o'clock, and the doctor is nowhere to be found. He has OxyContin pills in the medicine cabinet. Since it worked for the kidney pain, it should work for back pain, too. He is drug tested on Monday. Then what happens? Is this valid excuse? Is that result downgraded? This is a legally acquired drug for that individual but for a different condition. What should the MRO determination be? But then again, drug users use drugs without indication. How do you separate those two? This was an example of a medication prescribed to the individual but used for a different condition at a different time.

For a chronic recurring condition, such as chronic low back pain, the donor has a prescribed medication that he uses intermittently because their pain waxes and wanes. Could that be iatrogenic addiction? Possibly. When was that drug prescribed? This prescription is from nine months ago and prescribed for lower back pain. The prescription directions are to take two tablets every four hours; thus, this medication should have been finished long before now. Non-compliance with drugs is common. In fact, it is probably the number one reason why we have untreated disease.

What about a medication that is legally prescribed for an active condition but used by other than the prescribed route? For example, a person noted in the parking lot, sniffing white powder. Testing under reasonable suspicion, the test comes back positive for amphetamine. The donor admits to ADHD and provides a valid prescription. But the donor was crushing the pills and snorting it. MRO-verified positive or negative? It is a legal prescription, prescribed for that individual. Does the donor have a problem since he is snorting his medication? Is that a safety hazard? Do we ignore that, or is there some mechanism to take action? These are some scenarios that I want to convey to you.

One more case about prescription labels. A person allegedly has a back problem and is on opiates. You call the pharmacy. Pharmacist says the prescription was written for Jack Burns. Who is the doctor? The prescribing doctor is a veterinarian. The guy gave his dog, Jack Burns, his name. This is a fictitious name, but he acquired medications for himself from a vet.

To report a result as positive, it has to be a verifiable illegal use or the MRO must be unable to verity that the medication has been legally obtained. The MRO is unable to determine polypharmacy. People go to multiple pharmacies and multiple doctors. They test positive, they have got a prescription, but do they have an addiction? Again, I still do not know that.

Another example is evidence related to a post drug collection doctor visit. A donor tests positive on a specimen collected on a Friday. The following Monday, the donor goes to his doctor. During the interview, the doctor says that the donor is his patient and complained of an upper respiratory infection at that time. The use of the codeine was appropriate. The person doesn't have any symptoms now; he is healed by Monday and his cough went away. What does the MRO do? Tell the doctor he is a liar? This is an after-the-fact, physical findings report.

What about the age of prescription? What about the quantity dispensed? Both of these topics were discussed a little bit earlier. What about when the prescribing provider is unavailable or has moved away? What about the loss of privacy? For example, the donor leaves his phone number on the form. Because you cannot get in touch with him, you call his employer for more contact information. As soon as you tell the employer that this is Dr. So-and-so calling about an employee who had a drug collection last Wednesday, the employer knows that this person tested positive. There is no privacy at that particular point. I don't know exactly what to do about that, but I wanted you to be aware.

Requirements to divulge medical information represent a safety hazard. For example, you contact the treating physician to inquire about the donor's response to the medication. Is he having any side effects or problems? What doctor will admit that he is prescribing medication to his patient that is causing side effects?

We have covered post-test diagnosis and documented family use, for example, between a husband and wife, who use the other's medication. Is it reasonable to ask the doctor if he had seen the wife before? I had one individual claim that he took his wife's medication. I requested that the donor ask his doctor, if it was his wife's medication, to provide me with the information about how he prescribed the medication to her. The donor could not produce it. Then, the doctor was out of town, and so on and so forth. Ultimately, I declared him positive. His was a morphing story.

I have also seen MROs exercise what I call transference. Billy Bob is a good ole boy. The MRO called the supervisor who declared Billy Bob as one of his best employees who has a soft condition. The MRO downgrades the test. There are cases of a dual diagnosis, a substance abuse disorder and pain syndrome. One donor had an opiate addiction and was seeing a physician. His doctor worked, oddly enough, in a pain clinic. He does not treat addiction, but he was prescribing buprenorphine, a schedule III drug, for the individual. It could cause some impairment in a safety-related job. The doctor was prescribing buprenorphine under the guise of treating the pain syndrome, and yet, there is no way to test for it. Fortunately, because we have medical standards, we were able to test for that drug under that program and found that the person was using it.

What can MROs not do? MROs are unable to verify abusive use of legal prescriptions. The MROs are unable to verify impairment. They have the information given to them by the donor. You might be able to get some secondary information, but that may be unreliable, given the fact that other people may try to enable and cover up for other folks. MROs are unable to verify whether or not someone is fit for duty, simply on the basis of the drug test.

One of our neuropsychologists did a study with Benadryl and one of the drugs used for bladder control, comparing the subjects' cognitive functioning on the drug and their subjective views of themselves in terms of impairment. There was a huge difference. All subjects reported no impairment with these drugs. Yet, from cognitive testing, they were all impaired. Thus, a donor may admit that he is fine on that medication; he is not lying. But the fact is he is impaired because he does not have self-awareness of it. The MRO must make a judgment of whether this is impairing or not. How do we do that, if we really want to be honest with ourselves?

Most MROs do not have an understanding of all the tests. In Federal employment, the imposition of medical standards requires a job task analysis using uniform guidelines. What does this person actually do, and how does that relate to the particular medical standard in order to meet the qualifications of that job? That is accomplished through a scientific study. The alternative is to make the case about business necessity and safety. How do you make that argument so that it can withstand third party scrutiny? Do you think a simple call from an MRO trying to assess what that person does will suffice? Are we making a good assessment or are we just turfing the issue? If the MRO calls the employer to say that this person is taking a medication or has a condition that I think, in my clinical judgment, can adversely impact safety, what happens next? If there are no medical standards for the employee, what does the employer do? They might call someone else or call me back to ask what to do about it. If there are no medical standards, given the protections of the Americans with Disabilities Act, how do you defend that this person is no longer qualified for his job? It sounds good because we put something on paper, went through the notice, did our due diligence, and protected safety. But at the end of the day, what happened?

Another issue is foreign acquisition of drugs. People can readily cross the border into Canada, where opiates are readily available, or Mexico, where amphetamines are readily available. In Canada, codeine can be obtained over-the-counter. For a donor who tests positive for codeine obtained in Canada, I read them the riot act and say, okay, I will downgrade it this time. But I am putting you on notice that you cannot import drugs. If you come up positive again, I will verify the result as a positive. The Tylenol with codeine equivalent is over-the-counter in Great Britain but was taken here in the U.S. It was a legal acquisition, and the donor could probably produce a sales receipt from a pharmacy.

The Privacy Act applies to Federal physicians, thus, I am constrained by the Privacy Act, but I am not constrained by HIPAA, which does not apply in my world. But the pharmacists I interview might have to comply with HIPAA. If I ask them information about a Federal employee, they can respond that that information is covered by HIPAA. Some of our doctors require the donor to sign a release. I am not quite sure about when to require somebody to sign a release and whether it signifies consent in any way.

Here are some of the phrases that I want to sensitize you to: likely to pose a significant risk to safety, safety risk, reasonable medical judgment, MRO must attempt to release as little specific information, a significant safety hazard, diagnoses or other specific details of medical information do not need to be provided, the essential government functions, etc. If, as an MRO, you receive such information from the prescribing physician, you must transmit this information to a third party to whom you previously provided information about the safety risks of the employee's other medications. These are statements that are in all of the regulatory language.

Let's talk about employer behaviors. I called up an employer and stated that I need to speak to so-and-so right away. The employer believes that Bobby must have come up positive on a drug test. Though I could verify it as a negative result, but in his mind, Bobby was positive in a drug test and things happened to him. Must employers document the nexus of drug testing to employment duties? Is it reasonable enough to say that it will impact safety? It speaks for itself. Or do I have to show some assessment about how, in fact, it does affect safety? They must be able to provide documentation for fitness of duty evaluation. When I was in private practice, the employer would ask if the donor is fit for duty. But there were no standards about what constitutes their job. How do you do that? Through clear guidance on reasonable suspicion testing, observable behaviors, or reliable information.

I will give you an example. Somebody calls up and says, we just arrested your employee because we found 1.2 kg of cocaine in his car when he was stopped in Texas while driving from California to New Jersey. Is that a reasonable basis to test that individual? These are debates that happen. If the attorneys cannot figure that out, how do we, as MROs, advise whether or not a drug test is appropriate? Furthermore, the employee wasn't observed being under the influence of the drug; he was found transporting a chemical.

Let's talk about donor behaviors. I have discussed borrowed medications, self-prescribed, old medication, different medical problem, foreign drugs, and drugs taken in excess. What about an old prescription bottle filled

with a new drug supply? This could be another cover-up. What is a reasonable lifetime for a prescribed medication? Couldn't we have a standard that says prescriptions cannot be more than three months old? Or could we look at how much was dispensed, because in chronic conditions, people are often prescribed three months at a time?

I am held to privacy laws, whether by giving up information or pretending that I have authority to receive information. The MRO Manual says that MROs must send the report using one of the following methods, in a manner designated to ensure confidentiality of the information. Information provided by the donor, such as the donor states he has a seizure disorder, especially if it is at the donor's request to report this, must not include specific medical information. How do I convey a safety hazard without describing what the issue is? If someone might lose his job because he may not be qualified, the people who are going to take adverse employment action are going to need to know specific information, in order to take that action. What are the conflicts with other laws with respect to employee protections and so forth? I think these things need to be resolved.
How is it best to maintain the confidentiality of information received during the review process? Again, if this is what we are supposed to not tell, how do we tell? If there is a significant safety hazard, someone needs to describe what is significant in any particular context. If I give you a scenario and ask everyone here to line themselves up on a line from most significant to least significant, I guarantee that I will have every spot on that line filled.

Diagnosis of other specific details and medical information need not be provided. HIPAA is interesting; it discusses public interest, public interest purpose, and essential government functions, specifically making medical suitability determinations for the U.S. Department of State Employees. I remember testifying in a cocaine case in which person was tested under state regulation, not a Federal regulation. We did not use the regulation that talked about testing positive under the DOT program, but we used Misuse of a Substance, because it was a state law and not a Federal law. The attorney started to attack me, saying if they wanted you to use the state regulation, they would have written that. But they did not write that, and you went beyond the regulation. And it is the same kind of logic here. It specifically said in making medical suitability determinations for these State Department employees. If you meant transportation workers, how come you didn't write that? I can hear this happening. So which one do you use, public interest, or does this somehow constrain our ability in those other cases?

I am not throwing a stone at this; I want you to understand that. As we move forward, especially with prescription medications, we need to make sure that the laws are in place, so that we can get to the desired endpoint, which is to identify the person that has an addictive or substance use disorder, get them treated, and get them back integrated into society.

The end game, I would tell you again, is to eliminate the negative effect of the use of drugs on society. The process should be one of inclusion, not disenfranchisement, and mandated rehabilitation with effective monitoring and effective standards for rehabilitation. For fitness for duty, I would encourage employers to develop standards for people who are subject to testing. If you are going to subject somebody to testing, it is reasonable to be able to define what constitutes fitness for duty. Also needed are a restatement of program objectives, definitions of substance use disorders in the workplace and not DMS-IV, and rehabilitation standards. Another thing to consider is access to the state prescription databases, which will help us determine whether or not somebody is doctor shopping. The donor may provide one bottle, but they have actually seen five practitioners to get medication.

It is difficult to determine whether or not somebody is using drugs illicitly because drug users are exceedingly witty, smart, and clever. They all figure their way around the system. They are more motivated than any other player in the system.

Education of workforce employees is important. I have no problem calling a test positive if someone uses his/her spouse's medication. But I want the employer to put them on notice and to give them specific instructions, including what will happen to you if you use your spouse's medication again. I think that an education program needs to be mandated, especially with prescription medications. Otherwise, there is a

certain level of injustice. This is where my original statement of a clinician with a sense of social responsibility plays in.

And again, these are opportunities to educate all the players throughout the system. I think it is reasonable to talk to the pharmaceutical industry and even those that oversee the training of physicians. Doctors need to know that, even if you will not practice in the occupational environment but you are treating patients who are in the workforce, there are occupational requirements out there, including drug testing programs. This should be no more than an hour orientation program in medical school because they will encounter patients in the workforce and they need to be aware of that situation. And so that is it; I will get off my soapbox. I want to thank you for allowing me to address you.

Dr. Cook: Do any Board members have a question for Dr. Lomangino?

Mr. Bonds: Hi, Nick, thank you for your presentation. Not a question, a statement. I just want to say that you made it very clear to me how much more work we need to do in this aspect of the document, and I want to thank you for that.

Mr. Swart: As a Federal MRO, do you have responsibilities for determining fitness for duty?

Dr. Lomangino: Within the Federal program, we have responsibility for approving the rehabilitation program and determining when somebody can return back to duty. That is specifically defined in the order. And perhaps that is where my sensitivity to this comes in. Of course, I have my other role for airman medical certification, so I see the other side of that. But strictly from the MRO side, because I have those duties assigned, I am aware of those weaknesses in the present system. And what I am really concerned about is getting people to the right level of care and getting them back to work healthy.

I have to tell you, every time somebody loses his/her job, I actually hurt a little bit. To me, it is a loss. And if somebody is identified, gets into a program, and then at some later point, tests positive again, not only do they lose their job, but we also have an unperceived degradation in system safety during that time, from relapse to redetection. What did we do, from a systems safety perspective? And that is why, whenever I have an opportunity to talk about this, I try to raise that consciousness, because we all have an interest in it.

Mr. Swart: You are with the internal program at DOT with air traffic controllers. Do all medical review officers for the Federal program share your return to duty / fitness to duty requirements?

Dr. Lomangino: Jim, I don't know. All I know is the DOT order for employee testing.

Mr. Swart: As you know, MROs in the transportation industries do not share those types of responsibilities, unless indeed they would also happen to be fitness for duty physicians, issuing pilot certificates, mariner certificates, or commercial driver licenses (CDL).

Dr. Lomangino: That is an excellent point. I obtained a lot of this information from the course that I had to take. These points were highlighted in the MRO certification program. There was much in that certification program that did not overlap with my world or your world but were MRO responsibilities under the certification program.

Public Comments

Dr. Cook: We have now come to the public comment period. We will proceed alphabetically with our onsite commenters. We will begin with Bill Corl. Bill, I would suggest that you could come up front to speak from one of the seats up here.

Mr. Corl: Thank you, DTAB, for listening to my comments. My name is Bill Corl. I am the Chief Operations Officer for one of the major alternative testing laboratories. We have clients worldwide that test for government entities, national organizations, and many of the multi-national corporations that fall within your Guidelines and

outside in other countries. We manage to try and keep on top of all of the regulations, inside and outside of the United States.

We would also like to thank the DTAB for the accelerated process of approving oral fluid testing. We look forward to working with you on hair testing. The advancements of hair testing over the last five years have placed it as one of the most accurate and reliable drugs of abuse testing methods available. This can be evidenced by multiple accreditations available worldwide right now for hair testing and an international proficiency testing program that has over 50 laboratories worldwide enrolled in hair testing.

The main reason I am here is because of the regulated entities. Our clients keep requesting that we come to these meetings to voice our concerns and to state that we are testing for the regulated industries that are testing under company authority. They consider the urine testing program the minimum and outdated standard right now. They view it as an added expense, and that is why they keep pushing us to come here. Tell us when it is time for hair testing to be reviewed, and we will be here. We have statistics, and we have data. We also have a great deal of data with extended opiates. Many of the trucking firms have been testing for extended opiates for over two to three years. They perform urine and hair testing at the exact same time.

Hair testing has been shown to improve the success of drug testing programs because it increases the time period over which drug use can be detected, as compared to urine. Hair is easily collected, transported, and stored. It is less likely to transmit bio-organisms than urine and is much more difficult to adulterate. As I stated before, when you are ready, we are ready. We have statistics, we have plenty of data, and we will be there for you. Thank you.

Dr. Cook: Thanks, Bill. Our next public commenter, also here onsite, is William Ratcheck of the Neal R. Grossman Company.

Is there anybody else onsite who would like to give public comment, that has not registered?

Ms. Potter: Hello, my name is Abigail Potter and I am with the American Trucking Associations (ATA). ATA is the United Federation of Motor Carriers, state trucking associations, and national trucking conferences created to promote and protect the interests of the trucking industry. Directly and throughout its affiliate organizations, ATA encompasses every type and class of motor carrier operation.

ATA is pleased that DTAB is currently reviewing synthetic opioids and will be advancing recommendations on oral fluid testing. Since safety is our members' number one priority, improving Federally-mandated DOT testing programs is essential. Over the last 20 years, there have been many improvements to the Federal drug testing program that have helped to make our nation's roads safer. However, even with lowered threshold levels and improvements in detecting adulterated specimens, our industry's positive and refusal rates have stayed stagnant. ATA does not view these stagnant rates positively, particularly when random rates continue to have the highest numbers of violations. Our members strongly want to reduce the number of random rates but can only do that with a thorough pre-employment screening process.

Many of our members that have implemented hair testing have seen dramatic decreases in their random rates. I know you have heard this probably many times, but hair testing is also very hard to adulterate. Hair testing, particularly during the pre-employment screening process, is very helpful because it has a very large window. Some of our members who currently are doing hair testing have found that hair tests catch between 2.35 percent to 10.4 percent more drivers.

ATA's members have been leaders in improving Federal regulations. Our members were implementing drug and alcohol testing programs long before they were Federally required. DTAB should look to industry leaders for guidance in developing recommendations for drug testing programs. ATA recommends that DTAB bring in panelists from industry that are affected by the Federal drug testing program to review the new things and also review new research on hair testing that has been put out.

Another area of concern for our members is actually the rise of designer drugs. Some of the new drugs, including synthetic marijuana and bath salts, are some of our major concerns. These drugs are completely undetectable under the current Federally-mandated drug testing program and have caused problems for our members. ATA recommends that DTAB investigate ways that the Federal drug testing program can combat the use of designer drugs and find innovative ways for detection.

There was one instance that occurred at the beginning of the month. There was a truck driver who actually got 21 years for driving about 80 miles an hour on I-81. He ran into four cars and a police car. No one actually was killed in the incident, but he was on methamphetamines and also bath salts. To note, this driver had never failed a drug test. This driver had a valid commercial driver's license and was medically certified. That is one instance, and those types of instances are the ones that our industry wants to prevent because the employer, as has been stated by DOT many times, is responsible for the actions of their drivers, no matter what happens. So the company is responsible for the actions of its drivers, even if it can't prevent them.

As an industry, we are happy that DTAB is making a concerted effort to improve the Federal drug testing programs by reviewing synthetic opioids and advancing alternative specimens, like oral fluid testing. We hope in the future that DTAB will come to industry leaders for guidance on improving our Federal testing program. Thank you.

Dr. Cook: Thank you. We have one registered public commenter, who is joining us by webcast, and that is Mary Rush. Mary, if you would please press *1 to unmute yourself. Mary, are you there?

Is there someone who is joining us by webcast at this time who would like to give public comment? If so, please press *1, so that we could hear you. Ted?

Mr. Shults: Since the other public commenters did not show up, I will speak. I hope I am not a day late and a dollar short. My name is Ted Shults. I am the chairman of the American Association of Medical Review Officers. I always feel that I have to defend the MROs a little bit on a couple of issues. My colleague, Nick, raised a lot of systemic issues about protecting safety. Mr. Swart pointed out that it really is in the DOT world, and for many MROs, a very discreet function. That is what I want to come back to, just as a fundamental basis.

The essence of drug testing, as we know it, was originally designed as a deterrent for illegal drugs. It has morphed into a safety program because it was legally justified when the Federal government mandated it on public safety issues. That does not, by itself, make it a perfect safety issue. Whether you look at the DSM or at occupational medical standards, what is the magic bullet? Who is handing out the crystal balls to tell what the future performance of any employee will be with respect to their health conditions and medical services?

I have many MROs who refer employees for fitness for duty evaluations. They all come back fit. I have many MROs that say was this guy really in pain? They are all in pain. It really is an issue that, if you are looking at science to base your determination on, is very fragmentary. There is still a lot of information we do not know. We see a lot of tolerance with these drugs.

When we start moving into the issue of prescription drugs, we are talking about drugs that are essentially legal. Regardless of whether or not it is true that most of these drugs come out of the medicine cabinet, they all start their life as prescription drugs. The seminal events, looking back over the history of where we are today with the prescription drug program, are two things, the introduction of Oxycontin and the change in the standards of medical practice. The standards of medical practice were that you are limited to the amount of opioids for chronic pain. Now, you say, I am not for pain. I know MROs who are chronic pain patients themselves. There is no painometer or objective standard for determining what pain is. The fact is that these are euphoric compounds. There is lots of money associated with these drugs, which raises all the elements associated with illicit drugs. But they are framed as basically as legal issues. I do not want to discount that we are an aging population and people do use these drugs. It is a bigger social issue that is out there.

Finally, I hope I am not late with this recommendation. From the data presented this morning, one drug that has really taken off and the drug I have to deal with every day is methadone. It is the drug that we have seen the greatest increase. Looking at it in terms of patterns of prescription use, when Oxycontin got a black eye, pain doctors moved from prescribing it to starting to prescribe methadone. That has had its adverse impact, filling the morgues in many states. Many of my colleagues in the forensic community have seen the adverse fall-out from methadone because it is a very potent and very toxic drug. Most of the MROs who expanded testing in safety-sensitive environments were somewhat surprised when they noticed how many of their employees were on methadone. I think many doctors today, given the history of that drug, do not really realize that it is really a primary pain medication today. It is inexpensive, with a long action time. It is a drug that I think needs to be added.

If we start ratcheting down on these other drugs, even within the limitations that people have prescriptions and that we will miss some because of cutoff levels, the attractiveness of methadone as a drug of abuse will increase. Thank you.

Dr. Cook: We do have one public commenter joining us via webcast. Shannon Laley, are you there?

Ms. Laley: Thanks. I am with American Airlines. I am an in-house drug and alcohol program administrator. I have a very general question, which Dr. Lomangino launched into a little bit. Our concern from an employer perspective is, does a prescription guarantee safety? Regarding synthetic opioids, we are concerned about what kind of guidance MROs will be given on cutoff levels and reporting safety concerns to employers. What guidance will SAMHSA, DOT, and/or FAA give employers on handling prescription drug use in safety-sensitive positions? This is just something to think about; I do not expect an answer.

Dr. Cook: Thank you, Shannon. As mentioned previously, any questions brought up would be deliberated by the DTAB in closed session. We will take your questions under advisement. Would anybody else like to give public comment? If you are joining us by webcast, *1 please.

At this time, we have finished with the public comment period, and we have also finished with the open session of the Drug Testing Advisory Board. So, we adjourn.

(Whereupon, meeting was adjourned at 3:05 p.m. EST).