DRUG TESTING ADVISORY BOARD

Exploring the Science and Experience of Testing for Prescription Drugs in the Non-Regulated Workplace

August 20, 2008

Sugarloaf and Seneca Conference Rooms
One Choke Cherry Road
Rockville, Maryland 20857

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Proceedings (8:31 a.m.)

Call to Order

DR. BUSH: Welcome to the August 20th session of the Drug Testing Advisory Board where our topic is Exploring the Science and Experience for Testing Prescription Drugs in the Non-regulated Workplace. This is day two of a very exciting meeting.

I do have housekeeping announcements. For of those of you who were in the audience yesterday, you've already heard them. For those of you who weren't, you will hear them now. The doors still open into the same place; the doors to the hall are single doors while double doors lead into closets. Take your choice, depending on where you want to end up. I suggest the ones that go to the hallway, because the bathrooms are out here to the right, and there is a kitchen down the hall with vending machines for cold drinks and light snacks.

We thank those of you who called ahead with the information necessary to prepare a visitor badge. The sticky badge that you have on is a temporary pass that is good for today only. It will get you back into the building after lunch when you will need to go through the security screening process again. Please return that sticky badge to the guards on your way out at the end of the day, or if you do not plan to come back after lunch, then return the badge before you leave this morning.

There were several items of information at the sign-in desk. These include a roster of the DTAB members and a shuttle schedule. This shuttle circulates between the Shady Grove Metro Station and the SAMHSA building with a few additional stops along that route into the King Farm restaurant and business area during lunchtime. There is a

list of some local restaurants and a copy of the Federal Register Notice announcing this meeting.

When you signed in, you were asked to sign that you have received or had read the Federal Register Notice announcing this meeting, which includes standards of conduct. I will read it now for the record. SAMHSA would like to ensure that Advisory Committee Meetings proceed in an orderly fashion, are conducted in a safe and secure environment, protect the right of free speech, and permit the ability of SAMHSA Advisory Committees to accomplish their objectives. Therefore, the following procedures will be followed by DTAB. Attendees may be subject to the security screening that you have already experienced on your way into this room. Any interested persons who wish to be assured of the right to make an oral presentation must register with Mrs. Giselle Hersh before the meeting. Those who have not registered before the meeting will only be invited to speak at the discretion of the Chair, Mr. Stephenson, and should submit their request to the Designated Federal Official, that would be me, Donna Bush, on the day of the meeting. Open public hearing participants who are designated to speak may be questioned only by the Chair or other DTAB members. Audience members may not present comments or questions to the committee unless recognized by the Chair. Attendees at the meeting are asked to maintain order and not display behavior that is disruptive to the meeting, such as shouting from the audience or loud outbursts. We ask that attendees not approach the DTAB table area during the meeting without permission from the Chair or the Designated Federal Official. The DTAB Chair or Designated Federal Official will note for the record any disruptive behavior and will ask the person to cease the behavior or else leave the meeting room.

For those of you who've worked with us over the years, you will note that this is an expansive meeting topic for us. We wanted to use the model that our FDA colleagues use at large public meetings to make our intentions for conducting this meeting clearly known.

Anyone who would like to make an open public comment at today's session please let me know at some time during the day. The public comment period, according to the agenda, will be from about 4:30 to 5:00. It may be adjusted slightly should we finish early or need to stay late.

That is all I have for my housekeeping notes, Bob. I will turn the welcome and opening remarks for this morning over to you.

Welcome and Opening Remarks – Robert Stephenson

MR. STEPHENSON: This is day two of a rather ambitious meeting agenda. We've had wonderful collaboration and cooperation. I want to thank everybody who is in the room. I want to thank the members of the Board for being here and for having great patience yesterday as we set the stage with the background information. We had to set the stage and present the background. Once we did that, we delved into the drug testing issues in the afternoon. Today, we will continue with the exploratory issues that are critically important.

Homework assignments for the Board members included thinking about what they heard and preparing to critically engage in the issues today. We welcome all of you that are here today.

We have a Master of Ceremonies and computers. Mike Baylor will be dealing with the presentations.

DR. BAYLOR: The first presentation is by John Mitchell. Dr. Mitchell is the Co-Director, Center for Forensic Sciences, RTI International. His presentation is on immunoassay as an initial drug test in drug testing.

Immunoassay as an Initial Test in Drug Testing

DR. MITCHELL: (Slide 1) Thank you, Mike. We, as scientists or technical individuals, often forget that there are people in the audience who do not understand the issues that we take for granted. (Slide 2) Today, we will provide some of that background and discuss the immunoassay, its importance in drug testing, the importance in understanding it, and the review of immunoassay data. The goal is to enhance the understanding of the immunoassay test for the detection of drugs and also to enhance understanding of the results that are reported by that testing.

(Slide 3) Briefly, there are two major schemes that are used in testing for drugs in human matrices. The first is the one-test system, which usually is an immunoassay that is used to detect the drugs in a particular matrix. It is most often used for medical purposes in clinical and rehabilitation settings. The second is the two-test system, which has become the basis for workplace drug testing and also forensic testing. It begins with an immunoassay, which is used as an initial screening test to identify specimens that may have a drug present, followed by a more specific confirmatory method. The initial test, especially with expanded panels, is not always an immunoassay. For instance, GC-MS may serve as the initial screen. These two-test systems are commonly used to

produce results that require a high level of certainty, such as in the forensic workplace arena.

(Slide 4) What is an immunoassay? It is a biochemical test that measures the concentration of a substance in a liquid, such as blood, urine, oral fluid, or an extract of a biological specimen. Its basis is the reaction of an antibody or antibodies with an antigen, which in the case of drug testing, is the drug. (Slide 5) Antibodies are proteins that are produced by the immune system in response to a foreign substance, the antigen. These antibodies, directed towards an antigen, form the foundation of the immunoassay and permit the detection of the foreign substance, which is the drug that we are looking for. The basis of the reaction is that the antibodies bind to the antigen that is responsible for their production.

(Slide 6) Antibodies, usually harvested from sheep or rabbits, are proteins known as immunoglobulins (Ig), which are represented schematically by the figure Y. These IgGs, developed against classes of drugs, recognize their antigen by its shape and interact with the antigen through certain sites on the immunoglobulin.

(Slide 7) Immunoassays detect the binding of the drug to the antibody through tagged drug targets, which consist of an indicator bound to the target drug. This tag, which could be an enzyme, a fluorophore, or a radioactive material, signals the binding of the antibody with the drug target. The detection is typically based upon competitive binding, whereby the antibody can either bind with the drug or with a drug target in the specimen.

(Slide 8) In the scenario when drug is present in a specimen at high concentrations, antibody is first added to the specimen followed by an incubation in

which the antibody binds to any drug that is present. (Slide 9) The tagged drug target is added, but since most of the antibodies are bound to drug present in the specimen, there is little or no antibody binding to the tagged drug. As a result, there is little or no change in the signal that is monitored for reaction detection.

(Slide 10) If we take a specimen without drug in it, there is no binding of antibody to drug because there is no drug there. (Slide 11) After incubation, the tagged drug target is added, antibody binds with the tagged compound, and the binding causes a change in the produced signal.

(Slide 12) Immunoassay tests are used to screen donor specimens for the possible presence of a drug or class of drugs, yielding presumptive positive results if drug is present. These tests may be conducted onsite as part of a collection process, in a laboratory, or in another facility. Onsite testing is normally conducted with a point of collection (POCT) device, which is also another type of immunoassay. (Slide 13) Most of the testing, especially workplace drug testing, is conducted in laboratories with validated procedures and validated analytical instrumentation. The advantage of the immunoassay initial test is that it allows the laboratory to screen a large number of specimens for drugs. Larger laboratories can screen over 10,000 specimens a day.

(Slide 14) Analytical specificity is the key to understanding the immunoassay test results. Specificity is the affinity of the immunoassay for the targeted drug. It is measured as cross reactivity, which is the response exhibited when an immunoassay reacts with a compound other than the target drug. Specificity determines the conclusions that are drawn from the results of an immunoassay.

(Slide 15) In an immunoassay with low specificity, antibodies react with many different antigens or drugs that have structures similar to the target drug. One example is the amphetamine immunoassay with a 300 nanograms/milliliter cutoff, which is quite commonly used in non-regulated testing. Per the manufacturer, this particular immunoassay is specific for D-amphetamine, the targeted drug; however, It has a great deal of non-specificity because it also reacts with L-amphetamine, the mirror image of the D-amphetamine, at the cutoff concentration. It will also react with phentermine, methamphetamine, ephedrine, phenylpropanolamine, and several other small amines.

If it reacts with these other unintended compounds to yield a positive result, what are you really measuring? Other means are needed for differentiation.

(Slide 16) The heroin assay, which is specific for the heroin metabolite 6-acetylmorphine, will be used as an example of a highly specific immunoassay. But first, I will review the metabolism of heroin. Heroin is nothing more than morphine with two acetyl groups added to it. In the body, heroin is metabolized to 6-acetylmorphine, which is further metabolized to free morphine. The free morphine is conjugated with the glucuronic acid to give the morphine 3-glucuronide. To calculate total morphine, morphine, morphine 3-glucuronide, and also 6-acetylmorphine are totaled, but the calculated total morphine concentration is dependant on the specificity of the particular immunoassay in use.

(Slide 17) A highly specific immunoassay will not react with structurally similar antigens or drugs, and therefore, may not detect their presence in the donor’s specimen.

One highly specific immunoassay for 6-acetylmorphine has a cutoff of ten nanograms per milliliter. Without 6-acetylmorphine present, it requires 9,000 nanograms per milliliter of free morphine to get a positive result from this immunoassay. In urine, free morphine is present in a user at a concentration that is 2 to 10 percent of the total morphine concentration. Therefore, for this test to give a positive result for morphine in the specimen, total morphine concentrations would range from 90,000 to 100,000 nanograms per milliliter. Thus, this test will not detect whether a person is using morphine. It will only determine, for the most part, the use of heroin.

(Slide 18) The specificity varies, depending on the manufacturer of the immunoassay reagent. To illustrate, data from the NLCP performance testing (PT) Program, as well as data provided by manufacturers, are presented.

(Slide 19) As an example, immunoassays for opiates and opioids will be examined. (Slide 20) Commonly, we use an opiate immunoassay, which has a cutoff of around 2,000 nanograms per milliliter of morphine, in regulated testing. The table illustrates the cross reactivity of this assay with hydrocodone. In the first column are listed the four different types of immunoassays that are used by the laboratories enrolled in the NLCP Program. In the next column, the reported cross reactivities as stated by the manufacturers are given. These cross reactivities are reported as the nanograms per milliliter of the concentration of hydrocodone that is required to give a positive result by the immunoassay. For these cross reactivities, the amounts required to give positive results range from 1,500 to almost 8,000 nanograms per milliliter.

The three PT sample shipments of one year contained challenges targeted at 1000, 1500, and 4000 nanograms per milliliter of hydrocodone. The data illustrate the

differences in the specificities of the immunoassays. For the EMIT (Enzyme Multiplied Immunoassay) EIA (Enzyme ImmunoAssay), at 1500 nanograms per milliliter, which is slightly below the cutoff for morphine, there was some reactivity with the immunoassay. At 2000 nanograms per milliliter for the EMIT EIA, 100 percent of the laboratories that tested this sample found it to be positive. With the CEDIA (Cloned Enzyme Donor Immunoassay) at 4000 nanograms per milliliter, all results were positive. Because the stated cross reactivity is 2000 nanograms per milliliter, we expected at least 50 percent to be positive at that level, and it did not happen. The cross reactivity that is reported in the insert appears to be too low. The other two reagents, DRI (Diagnostic Reagents Inc.) EIA and KIMS (Kinetic Interaction of Microparticles in Solution), did not give any positive results at 4000 nanograms per milliliter level. According to which immunoassay you are using, whether hydrocodone will be detected and at what concentration is determined by the concentration of the hydrocodone in the urine. For the last two immunoassays, hydrocodone must be at least 8000 nanograms per milliliter before it would be detected.

(Slide 21) Hydromorphone is a drug in itself, is biologically active, and is also a metabolite of hydrocodone. The hydromorphone immunoassay has a 2000 nanograms per milliliter cutoff. The manufacturer’s stated cross reactivities range from 2000 to 11,000 nanograms per milliliter. With these PT challenges, positive results are not prevalent until the 4000 nanograms per milliliter level. Some of these immunoassays have little cross reactivity even at 10,000 nanograms per milliliter. To detect hydromorphone, the first two assays are logically the best.

(Slide 22) In non-regulated drug testing, quite commonly the laboratories use immunoassays with a cutoff of about 300 nanograms per milliliter of morphine, which is about three times more sensitive than the immunoassay used in regulated testing. With hydrocodone, at 300 nanograms per milliliter, the EMIT EIA shows good cross reactivity; at 247 nanograms per milliliter, it would give us a positive result for hydrocodone. The cross reactivies reported here range up to the DRI EIA parent cutoff of about 1700 nanograms per milliliter for the hydrocodone, which is at least five times the cutoff that we would expect.

For hydromorphone, the pattern is the same. Because of its structure, oxycodone is quite different from morphine, and therefore, the specificity is much less. In fact, with this reagent, the KIMS, the reported cross reactivity of oxycodone is greater than 75,000 nanograms per milliliter. With oxymorphone, increasing amounts of the compound are required to yield a positive result. With oxycodone and its metabolite oxymorphone, which are synthetic opioids, using antibodies directed against morphine is not an appropriate immunoassay to detect oxycodone.

(Slide 23) Another aspect of the immunoassay is the cross reactivity of the immunoassay with other forms of the compound of interest. For morphine 3-glucuronide, these are data were obtained with a 2000 nanograms per milliliter morphine cutoff assay. The manufacturer-stated cross reactivities vary about threefold. In a PT challenge that contained morphine 3-glucuronide at 2500 nanograms per milliliter and free morphine at 500 nanograms per milliliter, which is far less than the free morphine cutoff of 2000 nanograms per milliliter, the total exceeded the 2000 nanograms per milliliter cutoff by about 1000 nanograms per milliliter. With the CEDIA

and DRI EIA assays, 100 percent of the samples tested positive. This indicates, at least in this assay, that there are some synergistic effects between the combination of morphine and morphine 3-glucuronide. With morphine 3-glucuronide itself, the cross reactivity is rather low. With many of these assays, similar cross reactivities are evident with the free morphine as well as the morphine 3-glucuronide. This would be advantageous for detecting morphine in the urine.

(Slide 24) The NLCP presented the laboratories with PT samples containing 75,000 and 100,000 nanograms per milliliter of oxycodone to determine how well the oxycodone-specific assays performed. The EMIT assay was about 80 percent positive at both concentrations, but 100 percent positivity was expected. With CEDIA, the positivity rate was 100 percent. The other assays, DRI EIA and KIMS, did not produce any positive results at 75,000. Of course, the KIMS assay yielded no positive results, which is consistent with the data reported by the manufacturer.

Before selecting a particular immunoassay, it is very important to inspect the cross reactivity data to determine whether the results obtained with a certain compound are significant or not. For instance, the KIMS immunoassay would not be selected to detect oxycodone.

(Slides 25-26) The DRI oxycodone assay, with a cutoff of 100 nanograms per milliliter for oxycodone, is an example of a highly specific immunoassay. It will react with oxymorphone, which is its metabolite, and it gives essentially equal reactivity with oxymorphone and oxycodone. Detection of any of the other opioids compounds, such as hydrocodone, morphine 3-glucuronide, morphine, codeine, or 6-acetylmorphine,

would be unsuccessful because of the assay's high specificity. This is desirable for the detection of a particular compound.

(Slide 27) Benzodiazepines are important because their prescription use is high. Alprazolam, lorazepam, and clonazepam are among the top 25 generic prescriptions issued in the United States in 2007 and are also among the top 25 seizures by U.S. law enforcement.

(Slide 28) There are at least four immunoassays that are available for benzodiazepines. Many of these immunoassays have very good cross reactivities with all four drugs, but some do not. In selecting an immunoassay for the benzodiazepines, the desirable method would cross react with alprazolam, clonazepam, diazepam, and lorazepam.

(Slide 29) There are other immunoassays available for other drugs, such as propoxyphene, methadone, and ecstasy, and these have all been FDA cleared. There is an assay for buprenorphine, which is in the clearance process at this time.

(Slide 30) I'd like to summarize very quickly the presented information. One, a positive immunoassay is only a presumptive positive test. If an assay has low specificity, it may be positive for one of a half a dozen compounds or so. If it is a highly specific, there is a higher degree of certainty as to what it is reacting with, but it is not necessarily 100 percent.

The drugs that are detected by the immunoassay are limited by the antibody specificity and the cutoff that is used. That is, the detected concentrations for a particular drug, whether it be the target compound for the immunoassay or one that cross reacts, are limited by these two factors.

Also, the specificity cutoff may vary by the manufacturer of the immunoassay reagent. Many of the immunoassays that are provided allow cutoffs lower or higher than the standard one that is used in the industry. It is important to know what the cutoff is for the immunoassay used when interpreting results.

(Slide 31) Even with the two-test procedure, the number of positives is limited by the analytical specificity and the sensitivity of the immunoassay. In using an immunoassay to identify the presumptive positives, drugs cannot be found that are not detected during screening, so its utility is limited. All data concerning drug prevalence, particularly in the case of opiates, must be interpreted with the understanding of the immunoassay used in the test.

(Slide 32) The immunoassays used in current workplace testing do not appear adequate to detect of many of the abused synthetic opioids, particularly oxycodone. There are some limitations with drugs like hydrocodone, which was the number one prescribed generic drug.

Also, there are immunoassays currently available or in development that allow testing for some of the more commonly abused pharmaceuticals. In this industry, assay development and approval takes time. An immunoassay can be expected to be developed for a particular drug if there is a market for it. Thank you.

DR. BAYLOR: The next speaker this morning will be Barry Sample. Dr. Sample is the Director of Science and Technology for Quest Diagnostics in Atlanta, Georgia. The title of his presentation is: Statistical Trends in Workplace Drug Testing: 2003-2007. Barry?

Statistical Trends in Workplace Drug Testing: 2003-2007

DR. SAMPLE: (Slide 1) Thank you, Mike. I want to summarize workplace drug test data that we have collected over the last five years between 2003 and 2007.

(Slide 2) First off, here's the agenda. I will be talking about the Drug Testing Index (DTI), which is updated semiannually. Overall positivity, that is, all non-negative test results, which include results that are non-negative for a drug and/or a failed specimen validity test, will be presented. Positivity by drug by testing reason will be discussed, with a focus on the pre-employment and post-accident testing. Finally, any questions and comments from the Board will be addressed.

In the Drug Testing Index, the data are separated into two main groups. There is the Federally-mandated safety-sensitive group and the general workforce. The majority of the Federally-mandated safety-sensitive group testing is for DOT. Others in the Federal group include testing mandated by the Nuclear Regulatory Commission as well as the testing-designated positions for Federal employees. The general workforce is the private sector tests that are done pursuant to a company's drug testing policy. Many of these company drug-free worker programs are established in response to incentives from various states for reduced worker's compensation rates.

The data source for the DTI is solely workplace. The data are continually scrubbed to exclude rehabilitation clinics, criminal justice, family court, and known POCT confirmation specimens. Suspicion is aroused regarding those client accounts with 80 or 90 percent positivity rates. Whether these clients are known POCT accounts or not, high positivity data are also excluded from the DTI.

(Slide 4) This slide presents the overall drug positivity. While the data go back further than 2003, it gives the long-term historical trend from 1988 to 2007. We were initially at 13.8 percent overall drug positivity in 1988 when we first published this data and are now down to 3.8 percent in 2007. While this certainly encouraging, it does not necessarily mean that drug use in the workplace has declined. This is a reflection of data from those employers that include drug testing as part of their employee screening process. It is reflective, though, of what is happening in those workplaces where drug testing occurs.

(Slide 5) In 1995, we began breaking out overall positivity by the two major groups – Federally-mandated and the general workforce. The key message here is that the general workforce has roughly double the positivity rate that the Federally-mandated safety-sensitive group. In 2007, positivity was down to 1.8 percent in the Federal group and 4.4 percent in the general workforce.

(Slide 6) For overall positivity by testing reason for all non-negative results in 2007, we were at 1.8 percent for Federal and 4.4 percent in the general workforce. Generally, the pre-employment mirrors or is slightly lower than the overall positivity rate.

(Slide 7) What is a little more interesting is when we focus on two of the other testing reasons. In the Federal group, the random reason for testing positivity rate is lower than the overall as well as the pre-employment rates, whereas in the general workforce, the random positivity rate is higher than the overall and the pre-employment rates.

(Slide 8) In the post-accident tests, there are slightly higher positivity rates in the Federal group for post-accident and much higher positivity, about 50 percent higher positivity, in the general workforce group.

(Slide 9) What do we think may be going on here with these tests? This summarizes results of all the specimens between 2001 and 2007, including 9.1 million Federally-mandated safety-sensitive tests and 39 million general workforce tests in these data sets. In this Federal group, there are roughly equal numbers of pre-employment and random tests. Post-accident accounts for about four percent and the other testing reasons are seven percent.

In contrast, in the general workforce, there are 39 million tests; 78 percent of the tests were pre-employment, and only 10 percent were random. Perhaps that is why there is a much different positivity rate in the random test between the Federal and the general workforce groups. The Federal group knows there is a higher expectation of being tested randomly. In hiring those who pass that first gate with the pre-employment test, most likely the drug users have been weeded out and those hired are people that are more likely to remain drug free. In the general workforce with a lower frequency of pre-employment testing, job applicants may stay off drugs for the pre-employment test, but then go back to their drug using ways, and they'll get detected in the random test. Post-accident tests account for about six percent of the tests in the general workforce, and the other testing reasons for about seven percent.

(Slide 10) For amphetamines 2002 and 2003, there was much variation. There was a large increase between 2002 and 2003, about 44 percent, followed by a decline in the amphetamine positivity rate with perhaps a slight up-tick back up in 2007. There

are higher positivity rates in the general workforce than in the Federally-mandated safety-sensitive testing group.

(Slide 11) For amphetamines and methamphetamines in the general workforce, positivity increased in 2003 and 2004, with both amphetamine and methamphetamine tracking together. There was a slight decrease in 2005; again, they tracked together. There was a continuing decrease in 2006, although methamphetamine is dropping more than amphetamine, and in 2007, for the first time ever, we have those two drugs diverging. Where they used to track together, in 2007, there was a big decrease in methamphetamine and a large increase in amphetamine. That is not necessarily out of the data we saw yesterday with the increasing prescription rates, but may possibly be related to the MRO data which will be discussed later.

(Slide 12) Overall opiate positivity includes the codeine and morphine specific data as well as the expanded opiates. Positivity is fairly constant at about 0.3-0.35 percent in the general workforce and about 0.15 percent in the Federally-mandated safety-sensitive group. This is a large amount of data and in 2007 that equated to nearly 7 million tests in the general workforce and about 1.8 million in the Federal group.

(Slide 13) In this slide, which depicts the overall opiate positivity by testing reason, these two bars represent post-accident and these two bars pre-employment. The darker bars are the Federal group, and the lighter bars are the general workforce. Not surprisingly, the general workforce has higher positivity rates than the Federal group. What is of note is that post-accident tests have two to three higher positive rates for opiates than the pre-employment tests. There appears to be a much larger indication

of opiates being on board when a donor is tested following post-accident or post-incident.

(Slide 14) The expanded opiates are tested at a lower cutoff. This opiate screening assay has good cross reactivity, not just with codeine and morphine, but also with hydrocodone and hydromorphone. There are very good detection rates from a screening perspective with the immunoassay that is used for this expanded opiates testing. We seen increasing numbers and frequency; in 2007, we had nearly half a million, 466,000, tests. While codeine and morphine stay relatively constant, notice the big differences, particularly with hydrocodone. Hydrocodone went from 0.57 percent in 2003 to 1.23 percent in 2007. Consistent with the prescription data and the National Survey of Drug Use and Health, there is increasing use of some of these prescription opiates.

(Slide 15) While we were testing for oxycodone in 2003 and 2004, these data are excluded from this slide because in the middle of 2005 the screening technology was changed to an oxycodone-specific screening reagent. If these data were included, there would have been a big jump because it used to be about 0.35 percent, and with the specific reagent, it was nearly 0.6 percent in 2005.

In 2007, we had about a 0.85 percent positivity rate for oxycodone. The number of observations for the oxycodone mirrors the expanded opiates. The expanded opiates in our system include two different immunoassay-screening tests - one for codeine, morphine, hydrocodone, and hydromorphone and then the second immunoassay specifically looking for oxycodone.

(Slide 16) The oxycodone positivity rate was evaluated by testing reasoning: pre-employment and post accident. Once again, there are two to three times higher incidents of oxycodone positives in post accident testing versus pre-employment testing.

(Slide 17) Barbiturates have been relatively flat over the course of this time period, around 0.25 percent or so. No large movement in the barbiturates was seen in this time period. (Slide 18) For the barbiturate positivity by testing reason, it is only about 50 percent higher in a post accident test versus a pre-employment test. We are not seeing those two- and three-fold differences in positivity in the barbiturates as seen in the opiate class of drugs.

(Slide 19) Benzodiazepines are relatively flat with no major changes in this time period. Roughly, the same type of pattern as seen with the barbiturates is evident. (Slide 20) There is perhaps a slight increase in positivity in the post accident setting between 2003 and 2007 for the benzodiazepine class and about a 50 percent higher positivity post accident versus pre-employment.

(Slide 21) There was an initial increase in methadone positives that started between 2000 and 2001, which is now relatively flat.

(Slide 22) Some sharp increases in methadone positivity are noticeable when reasons for testing are separated into post accident versus pre-employment. There was a very small difference between those two groups in 2003, and roughly about 50 percent higher incidents in 2007 for the post accident versus the pre-employment test. This may mirror some of the data that was presented yesterday that showed the significantly large increases between 1998 and 2007 in the methadone prescriptions. I

do not think this means that we are seeing more heroin users in the workforce and in rehab, but it is probably a reflection of what is going on in the pain clinic.

(Slide 23) For propoxyphene, it is relatively flat for overall positivity. (Slide 24) There are some large differences in post accident versus the pre-employment positives for propoxyphene. There is a little dip here in the middle, but differences between the post accident and pre-employment settings remained rather significant over that entire time period.

What is interesting as this data is divided by the testing reason is that there are some significant differences, at least for certain drugs, in a post accident setting versus the pre-employment setting. While we do not know whether or not having these drugs on board contributed to the accident or was the cause of the accident, there seems to be a relationship between positives for certain drugs in these testing situations.

There are some employers that we service who deal with these drugs from a fitness for duty perspective. This will complicate how employers and MROs are going to deal with these data and would complicate matters for the programs as well. It will require more than just looking at whether or not there is a valid prescription. Perhaps it needs to be dealt with from a fitness for duty, safety-sensitive perspective. (Slide 25) I will open it up for any questions from the Board.

DR. SHIPPEE: Most of the people on the Board realize it, but I think people in the audience do not. This is not MRO data but is laboratory data. Everybody has to be careful with that. The reason I am sensitive to it because Congressional staffers dig down into the weeds of my data, so I have to be an honest broker when I send data, including my Annual Report, to Congress on what is going with DoD. I provide data to

people, such as General McCaffery, who receive media attention on national news. You make no attempt to derive unique results. Your data represents the total positive tests divided by your denominator of total tests.

DR. SAMPLE: That is correct.

MR. SHIPPPEE: We made a big adjustment two years ago. For the five year rolling data, I had DNDC go back and adjust. We give unique numbers because this underestimates the positive rate. During a time period, like a year, when you find someone positive, do not count him or her again. You're going to come up with a higher percent positive, which we feel is a true indication of your positive rate in our data set. You have got to be careful when with laboratory data. It also creates a problem for me. I have talked to your statistical people because Congress asks me how we match up against other industries. I can't compare. I give them the graphs and charts with a caveat that you can't compare us because I can't get at MRO data and I can't get at a unique positive. Again, be careful how you use the data. The post accident data I think is really useful. Nice presentation.

DR. SAMPLE: Thank you.

DR. TURK: For your amphetamine class, do you look at MDMA and MDEA (3,4-methylenedioxy-*N*-ethylamphetamine)? Is that included or not?

DR. SAMPLE: It is not included. For MDMA, we use a specific screening immunoassay test. There is a very small number of tests, maybe a quarter of a million, that are performed, and our overall positivity rate for MDMA is about 0.02 percent, which is on par with PCP.

DR. TURK: You do not look for it with the amphetamines?

DR. SAMPLE: No, not with that class.

MS. GORDON: I have a question about the post accident data. Are any of those collected after they receive treatment? Could that account for some of the elevated opiates?

DR. SAMPLE: We do not really have that data of when it is collected relative to treatment. Certainly, some of them could be coming from hospitals but I would expect many of them are coming from a more traditional collection site. As to whether they have been treated or not, I have no way of knowing and no access to any of that data.

DR. TURK: For the post accidents, is testing performed for caffeine? Truck drivers, especially, use high doses of caffeine. Is that included in any of your data? Do you look for it?

DR. SAMPLE: Not in the work place.

DR. TURK: Thank you.

MR. STEPHENSON: Barry, thank you very much for the presentation. This is a data set that is a very important national treasure. Are there any caveats, limitations, or special aspects of how to interpret the data?

DR. SAMPLE: I have two caveats and I thank COL Shippee for pointing them out more explicitly because I meant to provide them in my overview. First of all, this is just laboratory data; they have not been MRO verified. It does not include post-MRO reviews, so I want to clearly indicate these are laboratory positives. The other is that these data are not reflective of all work places. The data only reflect of what is going on in those workplaces where the employers include drug testing as a part of their employee screening process. There may be something else going on in other work

places. Certainly, data from the National Survey on Drug Use and Health show that people that have used illicit drugs in the previous 30 days have a 50 percent higher self-report positive rate when they work for employers that do not include drug testing versus working for employers that do include drug testing. Because the data represent eight to nine million tests on an annual basis, it is very much population data among only a certain subset of employers.

DR. NIPPER: Barry, you mentioned earlier that your positivity rate included specimens that failed specimen validity testing (SVT), so you had non-negatives in there as well. What is your rate of non-negativity or failed SVTs?

DR. SAMPLE: Failed SVT tests account for 0.15 percent plus or minus 0.01, or about 15 out of every 10,000 specimens, in the general work force. It varies a little from year to year, but it is been very constant. Those data that failed due to invalid pH, the incongruent or abnormal creatinine or specific gravity, substitution, adulteration, et cetera, are all failed specimen validity tests.

DR. GUTIERREZ: Do you include any school testing in your workplace data?

DR. SAMPLE: In this data set there should not be any school testing. Quite frankly, we do not do much school testing. Our business is predominately workplace testing.

DR. GUTIERREZ: Regarding the workplace data, do most workplaces test for all drugs or are there large variations between those that just test for the NIDA (National Institute on Drug Abuse)-5 and those that test for other drugs?

DR. SAMPLE: The majority of the employers are testing for the minimum five drug panel. Some employers may use slightly different cutoffs than the Federal

program, but the majority of tests are still done at the standard cutoffs. For the prescription drugs, their testing rates are about half of that. Considering the overall testing volume in the general workforce is about six to seven million, the tests for barbiturates, benzodiazepines, methadone, and propoxyphene are about three to three and a half million tests. Those volumes have been fairly constant over time.

DR. BUSH: Barry, your workplace drug testing results are not MRO-verified, but does this laboratory positive and negative database also include blind quality control samples?

DR. SAMPLE: Yes. This is more of an issue in the Federal program. While there certainly are some blinds that are done as part of company policy tests, by far, the majority of blind quality control samples are in the Federal program. The utilization of those blinds is more likely to impact some of the low incident positives, like PCP or substituted urine in the case of the other non-negatives. In the general workforce, the impact is minimal.

DR. GUTIERREZ: For barbiturates, benzodiazepines, and the other drugs that are not part of the workplace five-drug panel, are those tested by just screening or screening and confirmation?

DR. SAMPLE: All of these data are derived from immunoassay screens followed GC-MS confirmations for forensic defensibility.

DR. NIPPER: In Dr. Mitchell’s presentation, we saw that immunoassays for benzodiazepines vary widely in their cross-reactivities. Which benzodiazepine assay are you using, a very cross-reactive one or one that is primarily detecting alprazolam or diazepam?

DR. SAMPLE: For benzodiazepine screening, we use a widely cross-reactive immunoassay. However, the majority of those tests only involve the confirmation of oxazepam. Considering the metabolic pathway, the lowest common denominator for many of the benzodiazepines is alprazolam and oxazepam. We have a certain subset of customers that are interested in the expanded benzodiazepines, including lorazepam, triazolam, and flurazepam, which are typically only done as part of our medical professional testing. If it would be helpful to the Board, I could perform additional data analysis to differentiate positivity for some of those expanded benzodiazepines requested by employers.

MR. SWART: Are there any data on prescription medications that would give an MRO or a review official any information as to whether one could imply impairment from any of these results?

DR. SAMPLE: No, we do not have any information in our database with respect to whether or not the person was impaired or appeared to be impaired.

MR. SWART: Or as a causative factor?

DR. SAMPLE: No, we do not get that feedback information. That would be more of an MRO question.

DR. TURK: For the post accidents, are you doing blood, serum, and urine testing or are you just doing urine? Did the data you just presented represent just urine?

DR. SAMPLE: Urine only. The results are all from urine workplace drug tests with no oral fluid or hair data included.

DR. TURK: For post accident testing, are you testing for specific benzodiazepines, such as oxazepam?

DR. SAMPLE: What is tested is a function of that employers' drug panel, which is commonly a ten, six, or eight drug panel. Most often, the included analyses are the same whether it is for pre-employment or post accident testing. I am not aware of many employers who would request a five drug panel for pre-employment but for post accident testing would request expanded benzodiazepines and opiates. A post accident expanded panel would make more sense, but I am not sure how often that occurs.

DR. TURK: For clarification, are the post accident data only urine results?

DR. SAMPLE: All of the data that I presented is only urine.

DR. TURK: Thank you.

DR. KUNTZ: Do you have the ability to break out drug concentrations? Can you determine normal concentrations? Can you calculate the percentage of drug concentrations that are within certain concentration ranges? For instance, a very small percentage is expected to be over 50,000 nanograms/milliliter.

DR. SAMPLE: We do have the ability to do that, but I have not done so. If the Board would have some interest, please let me know.

DR. GUTIERREZ: In the workplace database, is the data set fairly robust considering it contains results from client-specific, custom-tailored expanded panels? Are there major differences in cutoffs, for instance, that that would make it difficult to compare one to another?

DR. SAMPLE: The majority of the specimens are tested at standard cutoffs for both the screening and the confirmation. Yes, there is some number of tests, but it is a much smaller portion, that will have custom cutoffs on the confirmatory tests, but not for the screening tests which are all following FDA-cleared cutoffs. Opiates would be 300 or

2000 nanograms per milliliter. Benzodiazepines, all the so called non-NIDA's and prescription drugs are all at 300 nanograms per milliliter, and the oxycodones are at 100 nanograms per milliliter because that is the FDA-cleared cutoff.

DR. COLLINS: The screening cutoffs are standard, but we find that different customers want different confirmation cutoffs so you probably have a mix of people that are confirming at 300 or confirming at 100 nanograms per milliliter, but I would say that the majority are probably standard.

DR. SAMPLE: Yes. There is more flexibility in those GC-MS confirmations cutoffs, but the majority is all at a fixed, standard cutoff. For us, the standard cutoff for the prescription drugs, including barbiturates, benzodiazepines, methadone, and propoxyphene is 200 nanograms per milliliter.

DR. SHIPPEE: What percentage of your total workload request is regulated work?

DR. SAMPLE: In 2007, we reported on 6.9 million general workforce tests and 1.5 to 1.6 million Federally-mandated safety-sensitive tests. The percentage of regulated workload to our total workload is relatively constant.

MR. STEPHENSON: My mantra is do not ask a question you do not already know an answer to, but I will ask anyway because it is one of the challenges that we are facing today with the expanded testing for prescription drugs. The issue is the differences between different assay types and their cross-reactivities. With a well defined target analyte, the ideal is a rather clean assay that does not cross react. Alternatively, a non-specific screening immunoassay permits the detection of structurally similar analytes and yields more presumptive positive results that are sorted

out later, whether it is through confirmation testing or MRO differentiation. How do you sense the market in that? How do you sense your interest in this as a laboratorian and as a person in a corporate environment? What would you expect to have come from the government or from other standards to help guide this future direction?

DR. SAMPLE: Well, I would say we currently leverage those differences and those immunoassays today. When we are screening for opiates at the 2000 nanogram per milliliter cutoff, we use immunoassays that are much more specific for codeine and morphine and have much lower cross-reactivities for hydrocodone, hydromorphone, and oxycodone because that is more efficient and more cost effective both for us and the customer. For the expanded opiates, we use a different screening reagent to take advantage of its broader cross-reactivities.

Perhaps as regulations change, if they change, testing strategies will evolve to leverage the various capabilities that the reagent systems afford the laboratory and ultimately the end user to test in the most efficient and cost effective manner.

DR. COLLINS: Regarding specificity, there a difference between what the manufacturers publish in their package inserts and what the laboratories find in real life The manufacturer’s stated specificity may guide in the decision about which immunoassay to use, but in reality, the cross reactivity you experience in real urine specimens is quite different than what is printed in the package inserts.

To obtain that data, and the laboratory looks at confirmation rates using a particular cutoff, whether or not it is confirming for just codeine and morphine or confirming for the other opiates. Those things vary quite a bit. Information from the

manufacturers is good, but your real life experience is going to provide a better feel for how you can use those assays effectively.

MR. STEPHENSON: Questions from the Board?

DR. BAYLOR: The next presentation is Dr. Edward Cone from ConeChem Research, and the title of Dr. Cone's presentation is Urine Drug Testing of Pain Patients: Licit and Illicit Drug Patterns and Prevalence.

Urine Drug Testing of Pain Patients: Licit and Illicit Drug Patterns and Prevalence

DR. CONE: (Slide 1) Mr. Stephenson, Dr. Bush, and DTAB, it is a pleasure to be here. Thank you for inviting me. This is a project that Yale Caplan, I, and Dave Black began in 2007 when we thought it would be interesting to evaluate the drug testing information on pain patients, a population that we really do not know much about. There was tremendous interest and information available. This project was fun, as we coordinated the data and separated it out in different ways. I will share our overall findings from this large body of data on pain patients. The data represent not only a forest but individual trees. You will see the forest data, and I will show you a little bit of the tree data as well.

(Slide 2) Briefly, I will talk about pain management monitoring and why we do it. It is almost exclusively urine drug testing. I am confident that this very rapid growing area will encompass other specimens, particularly oral fluid, in the future. The data are from a fairly large database. Our interest included defining the results from pain patient testing and the associated licit and illicit drug patterns.

(Slide 3) Chronic pain is a very important health issue because it is highly prevalent. It is difficult to get exact estimates, but clearly, chronic pain is with many of us. About 20 percent of all adult Americans have chronic pain. Treatment varies, but opiates and opioids are the primary therapeutic tools for the treatment of chronic pain because they are very effective. A patient who is in a pain program typically receives a number of other drugs as well.

Pain patients may also be drug abusers. One issue in monitoring pain patients is whether they using their medications appropriately. Hopefully, they are not developing the disease known as addiction. That is to be distinguished from the expected outcome of chronic treatment with opiates, which would be physical dependence and tolerance. Those are natural phenomena that are associated with the use of these drugs, but addiction involves some maladaptive behavioral changes. Those are certainly some of the problems that the physician who is prescribing wants to monitor.

(Slide 4) The rate of addiction in the pain population is very difficult to determine. Addiction in the pain population has been estimated to range anywhere from 3 almost to 20 percent. Drug testing cannot resolve or solve the problems, but it can help the prescribing physician determine whether the patient is taking what he is supposed to be taking or if he is a taking drug he is not supposed to be taking. Drug testing is a valuable tool in lieu of all the other evidence, including clinical evidence. Urine drug testing brings some objective information to that milieu of information.

(Slide 5) There wasn't much information that we could glean from the literature on broad-base population studies when Yale and I, and Dave Black started this study. We looked at an entire year of data from the Aegis Laboratory to determine the specific

prevalence and exact demographics of drug use in this population. This was fun to undertake because in the workplace setting we deal with a restricted number of drugs.

(Slide 6) We began with almost 14,000 specimens collected from 31 pain clinics in 6 primarily southern states. Of those, about 11,000 were confirmed GC-MS positive results. We restricted our analysis to those 11,000 confirmed positive results to characterize and look at the forest and the trees. Each and every specimen was screened by immunoassay and confirmed by GC-MS. The confirmation assays detected 39 different analytes, of which 32 were detected in the process of the study for that one year. There were a few analytes that were included but were not detected.

(Slide 7) This is the overview. We started out with 10,922 specimens. The analytes were divided into eleven general drug groups. From almost 11,000 patients, we had 15,859 positives within those drug groups. Each drug group may be a single analyte, such as cannabis or cocaine, or multiple analytes, such as in the amphetamine category, which is shown here broken down into the components of the amphetamine category. 3,4-Methylenedioxy-*N*-ethylamphetamine (MDEA) and para-methoxyamphetamine are two drugs that were included but for which we never saw a positive.

(Slide 8) This is the forest of the 10,922 specimens and 15,859 positives. The numbers for the positives are represented in this very complex pie chart. As you would expect, opiates are the biggest piece of the pie – 8,996 positives in the opiate category for these specimens. The other bigger piece of the pie is the benzodiazepine category - 2,397 specimens were positive for benzodiazepines. In addition, methadone was big. There was some significant use of the illicit drug cannabis by this population. There was

also a smaller but somewhat significant amount of cocaine use. This was surprising for this population, but never the less, it was there.

(Slide 9) Focusing on the opioids, including all of the natural opiates, the semi-synthetic opiates, and the synthetic derivatives, hydrocodone was the most prevalent, followed by hydromorphone and hydrocodeine. These three analytes are primarily a result of hydrocodone prescription use because both hydromorphone and hydrocodeine are commercial drugs as well as metabolites of hydrocodone. This breakdown was a surprise, though, considering the publicity associated with oxycodone use. Oxycodone use was a very small second to hydrocodone in this population. In the statistical data from yesterday, it showed that hydrocodone was very prevalent, especially in the South. This may explain why hydrocodone is so prevalent relative to the other opiates and opioids.

(Slide 10) How many people were using or had evidence of a single opioid versus multiple opioids? For example, for hydrocodone and hydromorphone, since it cannot be determined whether that is one drug or two, it is classified conservatively as one drug. For those drugs that produce common metabolites that are also commercially available, those are counted it as one drug. Using this conservative estimate, about 85 percent used a single opioid while 12.5 percent had clear evidence in their urine of having used two opioids, 1.2 percent used three, and surprisingly, there was a small percentage that used four opioids.

(Slide 11) This slide presents the individual combinations or common combinations of opioids for individual specimens, which should depict those combinations that are most prevalent. “HydOp” refers to hydro-opioids, such as

morphine, codeine, hydrocodone, hydromorphone, and “oxyop” refers to oxycodone and oxymorphone. The obvious combination of two opioids was hydrocodone and oxycodone together. There was a good number of hydrocodone/methadone combinations and any number of dual uses of hydrocodone, oxycodone, and benzodiazepines. A two opioid combination is not too surprising because frequently chronic pain patients are prescribed a continuous release medication and also different medication for breakthrough pain.

(Slide 10) Interesting combinations are oxycodone, methadone, propoxyphene, Fentanyl, and cardisoprodol. Some of the other interesting combinations include methadone, Fentanyl, oxycodone, and hydrocodone, et cetera.

(Slide 13) This slide presents an interesting look at what people took in combination with opioids from the other drug classes. Benzodiazepines were very prevalent.

(Slide 14) This slide presents an overview of the prevalence of illicit drug use in this unique population. All of the positive cannabis specimens were categorized as most likely representing illicit drug use, although the use of Marinol cannot be ruled out. That was also true for cocaine because there is some possibility that a few of these were legitimate cocaine use. Methamphetamine could potentially represent illicit drug use, but the distinction is even grayer. There were only four positive ecstasy specimens. The cannabis is not unusual, having been reported in previous very small studies. This large study reproduces what the small studies have shown: 8 to 10 percent of the pain population is using cannabis. One reason for cannabis use in this population includes self-medication.

(Slide 15) Other interesting prevalent illicit drug combinations include 196 positive results for hydrocodone and cannabis, 193 for cannabis only, and 24 for cannabis and cocaine only.

(Slide 16) This slide presents really bizarre combinations of benzodiazepines, cannabis, cocaine, hydrocodone, oxycodone, methadone, and carisoprodol.

(Slide 17) The next series of slides presents drug group patterns.

(Slide 18) Within the amphetamines group, only 160 specimens were positive for amphetamines. Out of those 160 specimens, there were 204 positives because of multiple analytes, including amphetamines, methamphetamines, phentermine, MDA, and MDMA. The specimen numbers and the mean concentrations are given in the table. The paper that summarizes all these data will be published in the special issue of the Journal of Analytical Toxicology (JAT). In that article, we present much more detailed information on the mean, median, range, and so forth, for all of these drug concentrations. This pie chart displays the breakdown for amphetamines. Amphetamines represented the largest percentage of positives, followed by combinations of methamphetamine and amphetamine, phentermine, and so forth.

(Slide 19) Three hundred and eight specimens were positive for benzodiazepines. Within the benzodiazepine class, butalbital had the highest prevalence, with very few other benzodiazepines being detected. In researching this, I learned that butalbital is frequently prescribed for headaches in pain patients.

(Slide 20) The benzodiazepines, as you would expect, were very complicated. We tested for oxazepam, temazepam, nordiazepam, alprazolam, clonazepam, and lorazepam. The detected combinations were often immense and bizarre. Many of the

patterns could be accounted for by diazepine-type benzodiazepines. Alprazolam was the second most frequently encountered, but there was clear evidence of multiple other benzodiazepines in this group.

(Slide 21) Cannabis is very simple because it is a single analyte. The range and the median are given in the table. The range for cannabis was from 2, which was our cutoff, to the reporting cutoff to 11,554 nanograms/milliliter.

(Slide 22) This slide illustrates the importance of testing for carisoprodol and meprobamate. If you only test for carisoprodol, almost half of the positive specimens would be missed. Meprobamate only was present at around 60 percent of the specimens.

(Slide 23) Benzoylecgonine (BZE) is also a single analyte. The range is from 50, the lower reporting limit, to 425,000 nanograms per milliliter. There were a few heavy-duty users of cocaine in this group.

(Slide 24) Fentanyl is a single analyte with a range from 1 to 2382 nanograms per milliliter.

(Slide 25) It is important to test for both meperidine and normeperidine, or some of the specimens will go undetected.

(Slide 26) For methadone, both EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) and methadone should be tested, or again, a few will be missed.

(Slide 27) The opiates were already discussed in detail; this slide presents a breakdown of the opiate category. Opiates are very complex because of the multiple uses, metabolites, and crossovers from metabolic patterns.

(Slide 28) For propoxyphene, it is important to test for both propoxyphene and norpropoxyphene.

(Slide 29) In conclusion, it requires many different assays to do comprehensive drug testing for prescription drugs. You see many, many, different patterns of both opioids and other drugs. (Slide 30)There was evidence of significant illicit drug use, based on cannabis, cocaine and ecstasy data, nearing about 10 percent in this population. This is a new world of prescription drug testing, specifically in terms of the complexity, the need for additional technology, and so forth. All our data from 2006 were immunoassay screened and GC-MS confirmed. To some extent, that technology is outdated, and we are no longer using GC-MS. There is a better, simpler, easier way to do it, which is LC-MS-MS. It is also environmentally nicer to use. I hope that these data have shed some light on this unique population. We had a great time looking at this data and exploring. Thank you.

DR. BUSH: When I do medical review officer training with the American Society of Addiction Medicine, I run into different doctors in different lines of work in their medical profession. I have met increasingly larger numbers of pain doctors who tell me there is really no text book on how to treat pain. Many doctors are learning as they go and trying to share within the literature and develop a practice.

Looking at some of your slides on the bizarre and illicit combinations of drugs and then the interesting licit and illicit drug combinations, is there any way that you could outreach back to the pain clinic doctors and try to share your wisdom and have them share their wisdom with you and develop a different facet of a presentation for this kind of work?

DR. CONE: The relationship with pain doctors is always a challenging one. We are involved in establishing closer ties with what they are doing, but we view it as a two way street. We can provide some information to them, but they can provide us with so much more information and guidance in what they are seeing, what they are doing, how they are utilizing the results that we are presenting to them, and how we help them if they need in interpretation.

It is an evolving process. This strikes me as being a very early step in just defining what is out there in a database larger than 100 patients. It was rewarding to play with the data and see what really is out there without the confines of a very structured program. These doctors are looking for help. Every time we talk to them, they are hungry for information on how something is done and what does it mean. The laboratory and the treatment specialists have a long way to go to understand how we should get together.

DR. TURK: You indicated that hydromorphone and hydrocodone were more prevalent in the South.

DR. CONE: Yes, that was indicated by yesterday's statistics and certainly from our data.

DR. TURK: Since your data has two northern states, Indiana and Ohio, how did you break it out?

DR. CONE: We did not break it out. I have been puzzled, and in the publication, I did not speculate. I raised the issue of why hydrocodone seems to be so prevalent and cited other references. In any number of references on prevalence data within the pain population, they all clearly indicate oxycodone as the big winner; it is the most prevalent

prescribed opioid for chronic pain. We referenced those citations, and say our data digress from that conclusion at least within the context of what our data are. It certainly doesn't say that oxycodone, at least within this population, is as prevalent as hydrocodone. Some of the data that were shown yesterday support that. I learned from yesterday's presentations about hydrocodone being more prevalent in the southern states, but we did not break it down by state.

DR. TURK: Usually there is a pattern of abusive drug traffic, from one part of the country to another. Do you see any kind of pattern in that right now?

DR. CONE: Since we were dealing with only one laboratory with very regional data, maybe Barry could look much more effectively than we could because he access to zip code data. We do not have zip code information so that would be a very good question to ask Barry.

DR. KUNTZ: My experiences are not so much with pain management as with medical professional monitoring programs. Tramadol has always been an issue within that group. Urine levels can get very high. Did this study examine tramadol?

DR. CONE: It was not included in the 2006 test panel, but it is included in the current test panel. Our data reflect what was going on two years ago, and the field is changing. About ten new drugs were added to produce a 39-test panel.

MS. GORDON: Do you have a sense for how many of the prescription medications in this population were not their personally prescribed drugs but were non-prescribed medications?

DR. CONE: No, I do not. That is our next study. In this 2006 study, we did not have access to the prescriber information. As of 2007, we can do the same study and ask, “Were these drugs supposed to be there?”

MS. GORDON: In the death investigation world for opioid-related deaths, other opiates or opioids are commonly co-ingested. There is no evidence of any prescriptions for some of the other opioids. They get them by whatever source they can.

DR. CONE: I was unhappy that we did not have prescribing information, but if I did have prescribing information, my publication would have been rejected because it would have been 20 pages longer than it is now. That is certainly the place we want to be to understand what these data mean.

DR. BUSH: Thank you, morning speakers. I want to remind the audience that there are index cards and sheets of paper for writing down questions. Please do so and submit them either at the front table or at the back registration table. I have three that I received after the close of the meeting last night. They will serve as interesting questions to launch discussion.

It is about 10:21. Let’s take about a 10 to 15 minute break and then we will reopen the session. Thank you.

(Break)

DR. BAYLOR: Next speaker is Dr. David Kuntz. He is the Executive Director of Analytical Toxicology at Clinical Reference Laboratory. He has titled his presentation: Laboratory Perspective on Additional Drug Testing and Associated Costs.

Laboratory Perspective on Additional Drug Testing and Associated Costs

DR. KUNTZ: (Slide 1) Thank you, Mike. I will provide a high level overview as it relates to laboratory.

(Slide 2) Clinical Reference Laboratory, or CRL as it is generally known, is a privately held Category 5 laboratory. We do testing in urine, oral fluids, and sweat patches and provide some broad-based medical/professional panels. Unlike some of the other talks that have been given, we are not involved in pain management programs at this time. With these broad-based programs, you use any available tools in your laboratory to reach those target analytes, including the homogenous immunoassays from the standard Hitachi/Olympus types of platforms. We do ELISA (Enzyme-Linked ImmunoSorbent Assay) for more of the therapeutic drug monitoring type of drugs. We also are doing some screens by LC-MS-MS. Confirmation testing is either by GC-MS or LC Tandem MS.

(Slide 3) The panel selections are a dilemma for laboratories. We have the problem that Donna Smith talked about yesterday. You deal with programs in which everyone wants a unique panel for their people. Extended narcotic panels mean ten different things to ten different people.

We are breaking into some other testing within the transportation industry. Under its corporate program for pre-employment practices, an airline requested nicotine testing, which was the groundbreaker for us.

Laboratory efficiency on the screening and confirmation methods is the cost driver for the price of a testing panel. It becomes especially difficult to correlate categories of drugs and making those an efficient system for the laboratory. For

instance, in screening for expanded benzodiazepines, including midazolam, flunitrazepam, et cetera, LC-MS is used with sensitivity as low as one nanogram per milliliter.

The complexity that you create when drugs are added and subtracted from panels is there literally hundreds of possibilities for panels produced. There is little financial gain typically for the contracting company or agency when they say, “I do not really care about oxymorphone, but I want all the other ones.” There is not a financial advantage because the laboratory will screen for all of those and confirm simultaneously. It can actually be detrimental to the laboratory if panels are not set up precisely because results can sometimes be inadvertently released. When a compound is reported that is not authorized under a program, a whole flurry of unpleasant events ensues.

In data review, all kinds of documents are needed for that final certification. You have your automated chemistries with your ELISA result for Fentanyl and other ELISA results for alfentanil, Tramadol, meperidine, et cetera that are tested in batches rather than in a random access type of analyzer. There are mounds of paper along with your LC-MS screening data.

(Slide 4) For panel selection, typically the laboratories perform a SAMHSA DOT 5 panel. Common variations are the seven, nine, or ten drug panels. It is bewildering, but we are still testing for methaqualone because it is in corporate programs. Since clients will not revisit their drug-testing programs, it stays. Urine alcohol is tested along with expanded synthetic opiates in the seven, nine, and ten drug panels. With the

addition of nicotine, we confirm for hydroxycotinine, which is either done in urine or in separate oral fluid collection as a pre-employment test.

The larger panels that we are using for medical professionals are really directed towards pharmacists and anyone with access to specific drugs, especially narcotics. Some of the big national chains are pulse testing pharmacy personnel only. When there is theft, especially if they believe the narcotic counts are low or there is a shortage on the floor in a hospital, testing is conducted. There are some pre-employment tests occurring for hospital personnel that years back were not included. Typically, nurses went from hospital to hospital even though they had a narcotic or meperidine addiction.

(Slide 5) This is a typical broad-base panel with all the drugs listed. Fentanyl for anesthesiologists can be important; they are also using alfentanil and sufentanyl, which I did not include because they are part of the Fentanyl family. The Fentanyl ELISA Kit is specific for Fentanyl; there are assays for alfentanil and sufentanyl. The costs for doing these assays are pretty high. For a Fentanyl assay on single specimen, $20 is invested in reagents only to get a single test because of the included calibrators and controls. It is important that you have a critical mass of specimens or convince anesthesiology groups to collect them in batches.

Tramadol has been excluded, and I made a comment earlier that tramadol addiction and theft is significant. With the pharmacy groups that we are doing, tramadol is very prominent, as much as hydrocodone in most of those cases.

We had a discussion earlier this morning about benzodiazepines and cross reactivaties. Certain groups have access to injectable benzodiazepines, such

midazolam or versed. Many of these do not cross react well in immunoassays and that is why we screen the benzodiazepines panel by LC-MS to detect all of these products.

Zolpadem or Ambien are often added. Meprobamate is common along with carisoprodol. Of course, we have the standard barbiturates, stimulants, and methylphenidate, Ritalin is very common, and so ketamine is included. When we are testing in the medical professional group, ethyl glucuronide and ethyl sulfate are often added.

(Slide 6) Obviously, the biggest category to add is oxycodone, hydrocodone, oxymorphone, and hydromorphone. Other narcotics to consider adding include the butorphanols, the buprenorphines, and so forth. For the expanded benzodiazepines, especially with date rape panels, flunitrazepam and clonazepam are included.

Some of these drugs do not react well with the immunoassays, others do. Stimulant levels, such as for diethylpropion, and phentermine, get to be very high. Trying to screen for these can be a challenge. I have done some of these by LC-MS-MS.

In a big panel screen for ten different drugs with a phentermine result of 50,000 nanograms per milliliter and phendimetrazine at 200 nanograms per milliliter, it does create analytical challenges. For instance, detuning the LC-MS to keep detections on the level playing field allows for accurate quantitations.

(Slide 7) Urine alcohol by itself confirmed by FID (flame ionization detection) is probably not conclusive evidence of alcohol ingestion. Breath alcohol is the preferred mechanism for determining impairment.

The health professional groups insist on continuing with ethyl glucuronide and ethyl sulfate. It is still the best test to detect previous alcohol consumption within the last two to three days. However, inadvertent use of mouthwash and so forth can lead to positive tests. We continue to counsel clients who want to do this type of testing that they have to use a medical review officer. The policy of the laboratory is not to release the results of a health professional monitoring panel to any client that may have an administrator making determinations; it has to go through an MRO. Use of an MRO's services is appropriate for monitoring unless the donor is in a total abstinence program, where extensive rights are signed away.

CRL has developed a requirement for ethyl glucuronide testing. We use a 500 nanograms per milliliter cutoff for ethyl glucuronide (EtG) with an ethyl sulfate (EtS) at least at 100 nanograms per milliliter. My experience with EtS is it may or may not be present in every specimen, but this reporting criterion is a safety net to avoid inappropriate reporting that may be taken to the next level with disciplinary action.

We can have further discussions on EtG and EtS, but it is still out there. Clients are clamoring for it, and they request the lowest possible detection level that you can provide them. They say, "We will take it from there. We want to be able to confront this dentist, this physician, or this nurse and their claims." At least half the time, they get the recognition that alcohol had been consumed. They have no problem with that 50 percent but it is the other 50 percent that you have to really be careful with.

(Slide 8) Part of Clinical Reference Laboratory's work is providing testing for the life insurance industry, and of course, nicotine is a health risk. It affects insurance rates, and so we have been doing nicotine analyses for many years. We are starting to add

nicotine to panels both as urine and oral fluid specimens for pre-employment purposes. The employers refuse employment if an applicant has a positive nicotine test. The goal is to maintain or decrease the healthcare costs for their corporate premiums. We perform cotinine and hydroxycotinine analyses both by LC-MS-MS and GC-MS.

(Slide 9) Almost every laboratory has a program to provide onsite devices to clients. There is less pressure recently to move to onsite testing because the driving force from several years past was an ability to hire people quickly. It is receiving attention again because it can possibly save money. Employers test on-site for a few dollars and not have the costs associated with sending that specimen to the laboratory just to get back a negative result. It continues to be a big marketplace and driver for laboratories and how they price their drug testing going forward.

We have onsite testing, and onsite testing is commercially available for both urine and oral fluids products. The positive screens still need to be confirmed, but the specificity is not great for all these tests. The monitoring for SVT can also be problematic.

(Slide 10) Oral fluids are another matrix that we are involved with as a way to avoid the issue of dilute urines. We do provide a 7-drug panel that includes a portion of the benzodiazepines, and now we are also offering the oxycodone, hydrocodone, and morphine-type products in the opiates. There is a movement into more automated chemistries, but we are still using the ELISA-based testing for screens. Confirmation testing is done by different techniques, including GC-MS 2D, GC-MS, or LC tandem MS.

Sweat patches are probably not associated at this point with workplace drug testing as much as with probation. There is no reason not to believe that you can't do all the drugs that we are concerned about now using the sweat patches. Certainly, sensitivity is not a problem when you have high performance LC tandem MS. There is certainly enough specimen volume to extract that sample, so analytes that can be tested in urine can theoretically be performed with sweat. At this point, we really do not have any workplace-related or follow-up testing using sweat patches. It is limited to probation and family court-related testing.

(Slide 11) In summary, we do see a trend to adding more drugs to the panels than we have had in the past. When I began drug testing in 1988, everything was a 10-panel or more. With the DOT and SAMHSA regulations, everyone defaulted back to a five drug panel, and now they are expanding again.

Insurance companies are targeting medical staff for theft of drugs and for impairment in judgment and medical malpractice in an effort to decrease insurance costs. We are seeing nicotine for controlling healthcare costs. Certainly, drug testing is involved in holding down workman's compensation costs. The major drug testing cost is associated with ultra low detection levels, such as in LC-MS-MS. LC-MS-MS requires 100 microliters or less of sample for whatever work that you need done. The trade off is that better trained, highly technical staff are needed to keep that equipment operational 24 hours a day because it is much more complex instrumentation that GC-MS.

Bigger panels cost more. The laboratory has a lot of investment in the data review and in the instrumentation to achieve the testing that these companies want. Thank you.

DR. SHIPPEE: With expanding the screening with chromatography and MS, do you have any experience with the Symbiosis Automated Extraction as the front end for the LC-MS?

DR. KUNTZ: I do not.

DR. SHIPPEE: Dr. Paul Robandt in my San Diego lab has done work with it. We are thinking about certifying him for some drugs and the obtaining production and case log information.

DR. GUTIERREZ: I thought including nicotine was interesting as an abused drug. Do you have any feeling whether most people treat is as such?

DR. KUNTZ: They are not using it as an abused drug. They are testing it for healthcare cost purposes. If a donor has a positive nicotine result, they are excluded from employment opportunities.

DR. GUTIERREZ: Most of Barry's testing was being done with FDA-cleared screening devices. Are some of your assays FDA cleared?

DR. KUNTZ: I believe there are some that probably have not gone through that process yet.

DR. BAYLOR: The next speaker is Dr. Jennifer Collins. She is a Laboratory Director for MEDTOX Laboratories, Incorporated in Minneapolis, Minnesota. The title of her talk: is Laboratory Perspective on Additional Drug Testing and Associated Costs.

Laboratory Perspective on Additional Drug Testing and Associated Costs

DR. COLLINS: (Slide 1) St. Paul is where the Republican Convention is being held and MEDTOX is located in St. Paul as well.

You probably noticed that the title of my talk and Dave's talk are identical. That is not exactly a coincidence; we were assigned the topics. I did have the benefit of looking at his slide presentation before I assembled mine, which I appreciated very much. Though I tried not to restate what he said, there may be some things that I will say again, but sometimes things need to be heard often to sink in. We are presenting a laboratory perspective on what it takes to do some of these additional tests and our experience in that regard.

I have some statistics in my talk that are not as well scrubbed as Barry's data. It has been gratifying for me to learn how well the trends agree, even though the data are not specifically addressing the same age groups, et cetera.

(Slide 2) MEDTOX is a chemical and forensic reference laboratory located in St. Paul. Amongst all the services we provide, we perform drugs of abuse testing for both regulated and non-regulated workplaces, medical professionals, pain clinics, and some criminal justice clients. The latter is more of a newer group for us to test.

(Slide 3) How you perform testing and how you create the panels depends on what is being requested by the client and what types of drugs they are monitoring. The test panels range from discreet 5 to 10 drug panel immunoassays screens with chromatographic confirmation to more comprehensive screens that utilize multiple methodologies to look at a very wide range of prescription and non-prescription compounds. Other methodologies, which go beyond the scope of the discreet homogenous immunoassays combined with GC-MS confirmation, include other chromatographies and alternative immunoassay tests.

(Slide 4) I have divided this up by the way we approach the testing process in each of the specific customer groups that I am going to mention. The first is the non-regulated workplace testing. These groups tend to include, not just the standard 5 drug panel, but these additional tests as well. Testing utilizes homogenous immunoassays performed on laboratory automated analyzers. Typically, barbiturates, benzodiazepines, and opiates are at a different cut off than the 2,000 nanograms per milliliter. Specific tests are used for oxycodone, methadone, and propoxyphene. We also have clients request methaqualone, but we try to discourage it. The non-regulated workplace does test for alcohol, but not as often as it does for these other compounds.

On the non-regulated side, we confirm the results of the initial screening test by either GC-MS or LC-MS-MS, a technique that is seen more frequently. The components of the confirmation test vary because some groups ask to expand the confirmations to incorporate additional tests. For instance, the amphetamines can be expanded to incorporate the designer amphetamines. The specific opiates and benzodiazepines vary by the individual client.

(Slide 5) There are added costs that accompany additional tests. It is not so much the initial immunoassay reagent cost, which can usually be added without significant increases in costs and instrument overhead. The negative samples that are being tested for additional compounds do not cost much more. The financial impact is on the confirmation process. Results that are non-negative and proceed to confirmation can add to the cost of the process, including instrumentation cost, usage, and overhead. Looking at a typical cycle time for a standard SAMHSA panel from beginning to end, including a re-equilibration if using a temperature program, sample run or cycle times

are five to eight minutes for GC-MS. For some of these other tests, particularly those with expanded drug panels included in the confirmation, the cycle times are at least 25 to 50 percent longer and more sophisticated instrumentation is required.

We confirm all the benzodiazepines by LC-MS-MS because it works much better. We were repeating many benzodiazepines performed by GC-MS. Also, with LC-MS-MS, there is improved service to customers because turnaround times are better, but instrument cost is added to overall laboratory overhead.

Over the last four to five years, we have received an increasing number of requests from customers to test for additional opiates and opioid compounds. By GC-MS, which we were doing until probably eight months ago, the run times were two to three times longer than some of the SAMHSA run times. We transferred opioid testing to LC-MS-MS because we found that we were dedicating an increasing percentage of our GC-MS instruments to doing these expanded opiate confirmations. This impacts all the testing you are doing, not just for those customers who request these expanded confirmation tests.

With LC-MS-MS, we significantly reduced the sample run times, however, equipment cost was added, which increased overhead. Currently, the LC-MS systems or the LC-MS-MS systems that are utilized in most laboratories are about three to four times the cost of the GC-MS system.

(Slide 6) When you look at how we approach testing for some of the other impaired professional and the pain management panels, the screens include standard homogeneous immunoassay tests, with most of them using lower cutoffs on the initial

screening test if available. The expanded confirmatory testing is performed by GC-MS or LC-MS-MS.

In addition to the standard immunoassays, many of the esoteric compounds, such as the panels presented by Drs. Cone and Kuntz, require an ELISA or perhaps a chromatographic screen. This changes the dynamic of how you do the work in a laboratory. In this case, the additional costs incurred in the laboratory are not just instrument overhead. Added labor and reagent costs are increased for the entire process, but there is no adverse financial impact for those specimens that are non-negative.

We have taken a tiered approach for pricing in our laboratory. The Tier 1 or entry level, which includes a drug panel using standard testing on automated analyzers, is one level of pricing. For Tier 2, ELISA tests are added, which increases the cost to the laboratory per test. The cost per test for the laboratory is different than what we charge our customers. On an individual test basis, ELISA tests can be 5 to 10 times the cost of a homogeneous immunoassay for a standard drug testing panel. Tier 3 includes homogenous immunoassays, ELISA tests, and a chromatographic screen, the most expensive option.

Pricing determination is more involved than providing sales people with a price list. Laboratory infrastructure and overhead are different everywhere. Once more than five ELISAs are added to extended panels, extraction is a better alternative. Consider each individual panel because there are some very interesting drug combinations. It is better to cost and price them on an individual basis.

(Slide 7) Many of the ELISAs that are used for the more esoteric compounds are not FDA cleared. They are marketed for forensic or research use only. If utilized in a drug screen, how the laboratory approaches that validation is really quite different and should be quite different. There is additional work involved with validation. One reason why there are different thresholds and cutoffs in those panels is because the kit and its insert state the assay sensitivity, which is different than having an established cutoff supported by clinical data demonstrating precision around that threshold. The laboratories may end up with different cutoffs based on their validation data.

(Slide 8) Usually, the homogenous tests are less expensive than the ELISAs, but the newer homogenous tests tend to be more expensive than the standard tests. Because the comprehensive screens have longer run times and extensive data review, they are more labor intensive. From a laboratory perspective, you figure out how best to incorporate these tests into your routine workload because they tend to represent a smaller percentage of your overall test volume. We utilize homogenous immunoassays whose applications, when available, have already been developed for our automated analyzers. ELISAs should be automated as much as possible even though it is not the same. ELISAs are not as automated and the length of time to run them is definitely different than a standard immunoassay test. In our laboratory, we try to combine discrete assays into larger panels when possible.

(Slide 9) Historically, non-immunoassay, chromatographic tests originate from our background as a therapeutic drug monitoring (TDM) laboratory when requests were for the concentration of one specific antidepressant, for example. For efficiency, the laboratory tries to combine analytes into one large screen. At some point, there are

diminishing returns because the screening panel becomes so large that maybe only two screens are performed per hour.

What CRL, MedTox, and many other laboratories are doing for efficiency is to utilize more advanced instrumentation to minimize the amount of sample preparation and to reduce run times. Many compounds are amenable to LC-MS-MS, but unfortunately, these instruments are costly. The newer high performance liquid chromatography (HPLC) technology, ultra performance liquid chromatography (UPLC), utilizes different plumbing and different columns, which tend to be more expensive than a standard LC column, to reduce run times. UPLC is not familiar to the operators because the plumbing is different. It is not as easy to use a wrench to change a column because all components are internal. UPLC is a different, non-standard technology, which I expect will become more accessible with time.

(Slide 10) Our workplace testing demographics are about 30 percent regulated and 70 percent non-regulated. Of that non-regulated customer group, about 50 to 60 percent test for compounds beyond the standard 5 drug panel, with the average panel size being 7 to 8 drugs. For the most commonly added compounds, excluding the opiates, the positivity rate is about 0.5 to 1 percent.

(Slide 11) In our workplace population, the distribution of individual barbiturate and benzodiazepine positive results is as expected. For barbiturates, butabitol and phenobarbital are the most prevalent. For the benzodiazepines, alprazolam, oxazepam, diazepam, lorezepam, and some of their metabolites are frequently detected. Very little clonazepam is seen.

(Slide 12) For the non-regulated opiate screens, more than half of the clients utilize the SAMHSA panel with SAMHSA cutoffs, which includes screening and confirmation at the 2000 nanograms per milliliter cutoff for codeine and morphine followed by analysis for 6-AM when the morphine is positive.

In the non-regulated opiate group, our confirmed positive rate is 0.4 percent. About 35 percent of our non-regulated screens include expanded drug panels, with hydrocodone, hydromorphone, oxycodone, and oxymorphone being most frequently included. For the expanded drug panels, the confirmation rate is increased for two reasons. First, more compounds are being tested for, and secondly, screening is generally performed at a lower cutoff.

About 10 percent of the non-regulated drug screens include a directed oxycodone test, which has about a 1.7 percent positive rate. One obstacle we encountered was screening test cross reactivities because many clients wanted to detect some of these other opiates, oxycodone in particular. What is required is a specific oxycodone screen for detection which would increase the cost. Unfortunately, clients really do not want to do that; they want the regular opiate screen with an oxycodone confirmation.

One role of the laboratory is to help clients understand what they should be testing, usually because the solution costs more.

(Slide 13) In the non-regulated group, notice the spread in the drugs detected in the expanded opiate panel. Similar to the prescribing trends, the major drugs detected are hydrocodone and hydromorphone. Morphine is third in prevalence followed by

codeine, oxymorphone, and oxycodone. The data is probably skewed because only a smaller percentage of our customers are using that directed screen.

(Slide 14) In a data subset of the medical professional group, the positive drug detection profile is different than that of a regular workplace population where marijuana would account for about half of the positives.

The major drug positives detected in the medical professional group, even though the overall positivity rate may be low, are narcotic analgesics and benzodiazepines.

(Slide 15) Within the positive narcotic analgesic group, the drug profile indicates that the predominately detected opiates are hydrocodone, hydromorphone, oxymorphone, and oxycodone.

Though the number of propoxyphene prescriptions is decreasing, this is contrary to our laboratory statistics. Recently, we have seen a spike in propoxyphene positive results which may or may not be statistically significant.

(Slide 16) Testing for the pain management group requires a totally different mindset. There are some additional nuances that are important for the laboratory to consider when entering into this type of testing. Physicians are interested in both what patients are taking, what they are not taking, and what they might be taking in combination. The pain management testing perspective is the difference between a clinical TDM perspective and a workplace drugs of abuse perspective. On the clinical side, the drug is expected to be present while on the workplace side the drug is expected to be absent. Since the drug is not expected to be present, a set of criteria is

established that is directly applicable to that kind of interpretation within the laboratory as well.

(Slide 17) Our pain management data is mostly regional, mainly from local pain clinics in the Minneapolis-St. Paul and Greater Minnesota area, so it reflects regional differences. For pain management testing, comprehensive screening panels, which are a broader panel of discreet immunoassays, are performed. Specifically, the comprehensive screen involves an extracted broad spectrum GC-MS screen followed by confirmation through a variety of methodologies. As a result, many different drugs are detected, yielding interesting statistics. In this slide, only the top 20 drugs rated by incidence are listed so that you distinguish the bars on the graph. In this particular group, oxycodone/oxymorphone is the most prevalent, possibly because that may be a preferred compound in the Minnesota treatment philosophy. Benzodiazepines are the second most prevalent drug class followed by acetaminophen. The presence of acetaminophen may be related to combination drug therapy or possibly people self-medicating with acetaminophen for pain management. There is evidence of some illicit drug use, specifically, marijuana. Antidepressants are also present in this population, which is not surprising.

The interaction between the pain professional and the laboratory is significantly greater that the interaction between the workplace customer and the laboratory. Because pain management testing involves so many more drugs, there are many more nuances to the process for the laboratory.

(Slide 18) In the criminal justice group, we have one criminal justice client who is performing an onsite drugs of abuse screen combined with a modified drug recognition

exam (DRE). For this client, we established a comprehensive drug test to use when the results of the drugs of abuse screen were negative and the information from the DRE was inconclusive. Their comprehensive drug panel, developed without recommendations from the laboratory, was based on their experience and what drugs they expected to be positive. The result is an interesting group of drug classes, especially the anticonvulsants. To test for this group of drugs we utilize our comprehensive chromatographic drug screen, which includes an ion trap MS method. The confirmatory method depends on the compound and may be ELISA, GC-MS, or LC-MS-MS.

(Slide 19) The compounds in red represent the major positive drug testing results. Tramadol is by far the most prevalent compound detected. The major opiates that are detected, including tramadol and carisoprodol, are not those that expected in a standard drug screen. In the sedatives/hypnotics group, only butalbital is significant. (Slide 20) Antihistamines are found in significant amounts. Caffeine, if present, is only reported above a certain concentration, which is set above the incidental caffeine threshold. The cause of the positive gabapentin is either related to its use as an anticonvulsant or for pain.

(Slide 21) In summary, when additional compounds are added, the complexity of the testing process increases because of the use of multiple methodologies for the screen and the conformation tests.

The laboratories are going to incur added costs due to reagents, instrumentation, overhead, and labor. The magnitude of the cost increase depends on the make-up of

the drug testing panel. Because of the cost associated with some of this instrumentation, not all laboratories can offer all of these tests.

(Slide 22) Those laboratories with limited resources may choose not to enter into these esoteric drug testing areas. If you offer an extended panel, then clients will come and you will detect positive results for these additional drugs

The interpretation of the MRO is vital to these expanded profiles. The laboratories must learn as much as they can from MROs on their approach and interpretation of the screening process. The role that the MRO will play will become increasingly more important.

DR. BUSH: Any questions from the Board for Dr. Collins?

DR. BAYLOR: The next presentation is by Dr. Larry Bowers. He is the Senior Managing Director, Technical and Information Resources at the United States Anti-Doping Agency (USADA). His topic today is: “Drug Testing in Sports.”

Drug Testing In Sports

DR. BOWERS: (Slide 1) Good morning. Thank you for the invitation to speak today. We are in such a different testing situation representing the extreme. In particular, I will emphasize those things that either might be coming your way in the future or will have an impact in your laboratories.

Drug testing in sports has a number of unique considerations that are not generally present in the work place testing. Those unique features lead to differences in the programs, such as in collection procedures and the result management process, which in some cases are mandated by specific law.

The different aspects of the program will be highlighted. I will remind you that the testing program needs to fit the purpose. In our situation, deterrence is the main objective, but we need to be cognizant of the fact that we have health professionals and professional advisors who are knowledgeable about drug elimination, et cetera. In sport testing, it is difficult dealing with those athletes who are trying to actively avoid detection, something that hopefully isn't an issue in workplace testing.

(Slide 2) This slide presents USADA's vision statement. To familiarize you with sports testing, I will first discuss sports testing in general and then focus on some highlights.

USADA was formed in 2000 as an independent agency to do Olympic-level drug testing. As evident from our mission statement, it is not just about testing, but it is also results management research. USADA has budgeted $2 million dollars a year since the inception of the organization to develop new testing technologies, et cetera.

USADA has a fairly broad-based educational program that ranges from informing elite athletes about the program and how the program is managed so that they do not have inadvertent positives to impacting youth who might be making decisions about whether or not they want to use anabolic steroids and other substances.

(Slide 3) To understand how USADA fits in the grand scheme of sports testing, I have to talk about the organization of the sport. Most people wrongly believe that the International Olympic Committee (IOC) is in charge of testing all the time. That is not the case. The only time the IOC is in charge of the testing is a one month period around an Olympic Games. Because the Summer Olympics Games are currently in progress, right

now the IOC is performing all of the testing. No other agencies are testing the athletes who are participating in the Olympics.

In 2000, the (WADA), which is known as either WADA or AMA, the French organization, was formed as an independent body, in large part due to pressure from ONDCP and others in the U.S. The purpose of WADA is to manage drug testing and harmonize it worldwide.

The groups that control sport testing for most of the year are the International Federations; three examples, including track and field, cycling, and swimming, are given on the slide. These are linked to the U.S. National Governing Bodies. Each group has its own set of doping rules which incorporate the WADA rules. They also have interesting rules; for example, in Union de Cyliste Internationale (UCI), no matter who does the test or collects the sample, the case is referred to the country in which the athlete has his/her professional license. If you ever wondered why the Floyd Landis case came to USADA for adjudication, it is because the test was collected by UCI, which is a Swiss organization. The test was done in the Paris laboratory and the case was referred to USADA to adjudicate. This results in some interesting international interactions that we have to deal with.

Another piece of this puzzle that makes life interesting is that US sports testing has a national law called the Ted Stevens Amateur Sports Act. This law mandates that any decision regarding athlete eligibility must be heard by the American Arbitration Association (AAA). Thus, per USADA protocol, AAA must perform our adjudication process. However, we have incorporated an additional mandate that all of the AAA arbitrators must also be members of the Court of Arbitration for Sport, which is an

agency located in Lassen, Switzerland that has been put in charge of arbitrating any sports issues for both WADA and the IOC. These arbitrators have experience with sports and sports rules.

(Slide 4) The program that we operate under is the World Anti-Doping Program, which is comprised of five parts, including the WADA Code and four mandatory international standards. The World Anti-Doping Code was adopted in Copenhagen in March 2003. A major modification to the Code was approved in Madrid in November 2007 that will go into effect January 1, 2009. The Code addresses the rights and responsibilities of stakeholders, defined as athletes, international sports federations, and governments. Every process and every revision to the Code has comment periods for international input by all of those key stakeholders. Rules are only changed after the appropriate comment period has ended.

One of the international standards is the list of prohibited substances and testing methods that is published by WADA. This list is very important because that it defines what is tested for. That document is revised annually. Every January, potentially a few more compounds could be added to the list; I have yet to see anything removed. The WADA International Standard for Testing describes the procedure for collecting samples. The WADA International Standard for Laboratories describes the responsibilities and rights of laboratories. It also includes seven technical documents that cover specifics about particular issues. For example, one document provides guidelines for identification for compounds by GC-MS and LC-MS. The WADA International Standard of Therapeutic Use Exemptions is important from your perspective because lists many prescription drugs. The application for the use of a

prohibited substance involves a review by a physician or a team of physicians who are independent of USADA. If after medical review, a valid medical reason is accepted, the athlete is given an exemption. This is considered one of the very early steps in evaluating whether an adverse laboratory finding is doping or the use the approved therapeutic agent.

Because of the involvement of multiple governments in sports testing, there was a United Nations Educational, Scientific and Cultural Organization (UNESCO) International Convention developed in 2005. This was just ratified by the US Senate in July 2008 and signed by President Bush just prior to the Summer Olympic Games. This Convention does two things. One, it says that the government endorses the Code elements, and two, it states that we will enact national laws that subscribe to or at least are consistent with the Code. The long term implications of that are unknown but we are now one of the signatory members of that group. The most important aspect from the US standpoint is that Chicago would not have been eligible to host the Olympic Games because ratification is one of the stipulations in the host application.

Regarding the Anti-Doping Rules, there is a rule of strict liability, which means that there is no intent or no explanation for how it should not have been in your body. If you have a positive drug test, unless you can show a medically testified therapeutic agent that you did not get permission for ahead of time or can show that it came from something specifically, a positive drug test results in a sanction. Unlike the workplace program, we track down the athlete to collect a specimen for testing. About half of our samples are with no notice out of competition. Either we knock on somebody’s door or go to his/her training facility and collect the sample. If athletes are not available or they

are not where they say they would be, it is a missed test. Three missed tests is considered equivalent to a positive drug test result. Athletes are required to inform us where they are almost 24/7, and we hold them accountable for that.

(Slide 5) One of WADA's most important jobs is the recognition of the 33 laboratories in 29 countries around the world. This map depicts the locations of the 19 laboratories in Europe. Yes, the sports movement is definitely Eurocentric. There are six laboratories in the Americas, six in Australia, and two in Africa.

One of WADA's most important jobs is to regulate the laboratories and to ensure that the laboratory results are harmonized and consistent. This is done in two ways. One, every laboratory is required to be ISO 17025 accredited. Two, the international standard for laboratories is considered an expansion of the 17025 document. WADA has actively been working with the International Laboratory Accreditation Corporation to train individuals at that organization or in its member organizations on how to assess the laboratories against, not only 17025, but also the WADA International Standard for Laboratories. Secondly, WADA manages a proficiency testing program. Proficiency samples are shipped out to the laboratories quarterly. A significant issue for proficiency testing is the difficulty simulating a real specimen by spiking in metabolites. Frequently for steroids, there might be half a dozen metabolites of which only two might have been synthesized. Should the laboratory be testing for one of the metabolites that has not been synthesized, it is difficult to simulate that. About 80 percent of the samples for proficiency testing are administration studies, which are then handled and distributed amongst the 33 laboratories.

(Slide 6) Another important thing for WADA is its rationale for the inclusion of substances or methods on the prohibited list. To be included, two of these three criteria must be satisfied: medical evidence of enhanced performance, medical evidence of potential health risk, or violation of the spirit of sports.

(Slide 7) This is the WADA prohibited substance list, sorted by classes and compounds. Groups S.1. through S.5. and M.1. through M.3 are tests that are performed both in and out of competition. These include substances, such as an anabolic steroid, when taken during training would have a beneficial performance-enhancing effect and are therefore tested for out of competition. S.6. through S.9 are during competition as opposed to out of competition. The prohibited list is also an open list. For example, at the end of the S.1.1a steroid list, “related substances” is given. The reason for including this category is that substances that may be available in one country but not in another. If you remember, Bay Area Laboratory Co-Operative (BALCO) developed a designer steroid that was specifically designed to beat or be undetected the testing system. Through the collaboration of a number of experts around the country, the steroid was identified, its structure verified, and the compound was synthesized and produced as a reference material. The steroid was administered to a primate, its excretion profile was determined, and its biological activity assessed to prove its efficacy. Within 10 months after we received that drug in a syringe, we had our first case. This is an example of the research required to follow this kind of a list.

(Slide 8) When considering performance-enhancing substances, it is important to think outside the scope of just building bigger muscles. In fact, many substances are performance enhancing without building muscle mass, such as marijuana. Stimulants

give a euphoric feeling, improve focus and concentration, and alter the perception of fatigue, all of which could potentially help an athlete.

I will relate a quick story, which I always find interesting. An Outside Magazine writer, who is also an amateur cyclist, wondered if doping really worked. A physician placed him on a doping regimen, which included taking steroids, growth hormone, et cetera. Here is his comment about growth hormone: “I started to realize that my eyesight was really improving. I had been thinking about getting glasses to read fine print on maps, but now there was no need.” Even if growth hormone doesn’t build more muscle, being able to see the seams of a baseball at 40 years of age might be a performance-enhancing effect.

A drug side effect can promote the performance enhancement that the athlete is seeking. Pseudoephedrine was removed from the prohibited list because of outcry regarding the case at the Sydney Olympic Games where a medal was revoked because the athlete took an over-the-counter medication. Since that incident, we have seen pseudoephedrine concentrations in urine in the thousands of micrograms per milliliter. Pseudoephedrine is a fairly potent stimulant; athletes take it because they understand what they are doing and they do it with a reason.

It is difficult for us to verify the performance-enhancing ability of substances because of our inability to conduct the required research at the appropriate dosage and the combinations of materials. A substance is either proven to have performance enhancing effects, or it is logically extrapolated that it may possess performance-enhancing effects. For example, the group that sells steroids also markets aromatase inhibitors to enhance the effects of their compounds. It would be almost impossible to

obtain IRB (institutional review board) approval for that type of study. Approval was obtained, though, for a study of the administration of androstenedione to women at the levels found in over-the-counter supplements. Women in this study achieved testosterone levels in blood comparable to men. Even though this study was done at low doses, it was a very difficult study to get approved.

Athletes often state that they are using a natural substance; remember, many drugs are initially derived from plants. What is important is the effect of a substance, not its source. If an athlete took X root and a particular compound is in that root, it does not make any difference.

(Slide 9) One problem in sports testing is that some of prohibited compounds are present in the body as natural substances, resulting in not only testing issues for the laboratory but also producing programmatic philosophical issues. Steroids are metabolically interconverted. For example, testosterone is metabolically related to androstenedione and androstenediol. If testosterone is both an endogenous substance and a prohibited substance, how will the laboratory determine if it was abused and if so, how is it tracked?

(Slide 10) The distribution pattern of urinary testosterone to epitestosterone (T/E) ratios for male athletes is presented in this slide. Though the quantities of the hormones are lower for females, the distribution pattern looks exactly the same and the ratios are similar between the sexes. In rebuttal to the Nature opinion piece arguing that not enough data exist for T/E ratios, presented here are 32,000 values that were accumulated over several years. Ninety-nine percent of the population falls below 4.56.

The threshold that was set by WADA is 4:1. Based on population statistics, a ratio above 4:1 is definitely in the abnormal or not usual range.

(Slide 11) Since there are a significant number of people who fall in that range, it is better to use the individual as his/her own reference point. Presented in this slide is historical data from a person over five years. Notice how invariable the values are for this ratio in urine for an individual.

(Slide 12) In this hypothetical historical T/E pattern, the spike above the threshold at about two years raises serious questions.

(Slide 13) Over the past year and a half, we have been investigating better ways to detect abuse of endogenous prohibited substances. This slide illustrates some of the models that have been used in the clinical field, including personalized reference interval and uniform standard deviation in the reference change limit model, all of which have been described by Gene Harris and Jim Boyd in their books. These models are predicting an individual's next value based on his/her previous values. With three or four historical values, I can predict with a certain degree of certainty what the next value should be. In this T/E ratio example, the result for the 18th assay at the cutoff ratio of four, which is the population threshold, is way above what you would expect for this particular individual based on modeling.

How do we utilize this kind of data? Can we only use it to focus our testing? Should additional testing be performed on this individual or is this enough information to document a violation?

(Slide 14) This is T/E ratio data from a different laboratory. Notice that the pattern looks just the same. On the left hand side of the distribution, there is a small population

of people that have ratios with a median value of about 0.1 as opposed to 1.1 to 1.2. Those individuals possess a deletion for the EGT2B17 gene, and they do not excrete testosterone in the urine as the glucuronide conjugate. Their blood levels for testosterone are comparable to rest of the population, but they do not exhibit the expected excretion pattern.

(Slide 15) Individuals who fall in that low T/E ratio range are particularly problematic because they never reach the upper end of the population statistics. A model is needed to evaluate these individuals. In this slide are the two lines for the reference change statistics. The line that originates from the top left hand corner, drops down, and then parallels the x-axis is based on Bayesian probability and predicts the upper limit of values expected from this individual. For the tenth result, the individual was administered testosterone. Though the result for this individual never approached the population threshold, he did exceed his predicted threshold. We are in the process of implementing these models to account for individual drug metabolism.

(Slide 16) I wanted to address erythropoietin (EPO) because of the number of surprising positives results detected during the Tour de France. EPO is an endogenous compound. The difference between endogenous and recombinant EPO is based on glycosylation. Whether a protein is expressed in a particular mammalian cell line changes the exact composition of the carbohydrates attached.

(Slide 17) The laboratory can differentiate between natural and recombinant EPO based on the charges on the carbohydrates. The amino acid sequence is identical, but the carbohydrates, and thus the charges, are different.

In addition, we are beginning to see genetically engineered substances like the so called Novel Erythropoiesis Stimulating Protein (NESP), which is a protein that has had amino acids changed in order to attach more carbohydrate residues because carbohydrates determine clearance for this protein. To be a more effective therapeutic agent, the protein was modified to retain it in the blood longer. This was great for us because it is detectable in the urine for a longer period of time.

This slide illustrates the patterns seen with EPO. Each one of those steps on the stepladder is a different charge state of carbohydrate. Band A is recombinant EPO, band B represents a normal person, while band C represents a person after administration of recombinant EPO. With the administration of recombinant EPO, endogenous EPO production is suppressed, but still detectable, thus making detection difficult. The three bands on the right are the NESP, which migrates at the opposite end of the gel. Its different charges make it very easy to detect that substance.

(Slide 18) Many of the substances that we see in doping control could not happen if there was not for assistance from health care professionals. (Slide 19) I excerpted two sections from a letter that was intercepted and forwarded to us. This letter provided instruction to athletes on how to beat the drug test. The first point is not to provide enough urine for confirmation so that a positive result cannot be reported. It instructed not to give any more urine than you absolutely have to. Interestingly, the letter discusses pharmacokinetics. For instance, if you know your urine sample will be collected at eight o’clock in the morning or four o’clock in the afternoon and it is not, take the next dose because by the next day when you are tested, it will not be in your system anymore. The more the laboratory codifies the way procedures are done, the

more likely it is that people will beat the system by taking advantage of that static unchanging process. As a result, we are very frequently changing collection procedures to ensure that does not happen.

(Slide 20) Remember the Balco scandal. (Slide 21) With the help of Congress, Balco was providing us with documents like this. This is the doping schedule from one of the athletes involved in the Balco scandal. L stands for the liquid tetrahydrogestrinone (THG), C is the cream comprised of testosterone and epitestosterone, and E is EPO. This doping schedule attempts to beat the test by suppressing endogenous steroids with THG and then deceiving the laboratory by absorbing exogenous testosterone and epitestosterone to produce normal patterns. These professional panels are created by people possessing the necessary knowledge to manipulate the tests.

(Slide 22) One of the objectives of USADA is to change the perceptions of the next generation of athletes. Shown here are a series of cartoons depicting doping. The one from Tank McNamara is entitled “A doping fantasy league”, where instead of choosing the athlete, you choose the compounds that you dope your athlete with. The bottom picture is an anti-doping fantasy league that started up and the last caption says, “Yeah, but the winner has to buy the loser a mass spectrometer for this Anti-Doping Fantasy League.” My personal favorite was Harry Potter on the lower left. Apparently, there is a doping problem in quidditch.

(Slide 23) Hopefully, we are changing attitudes. This is a social change as well as a drug-related change. Athletes need to do the right thing all the time.

(Slide 24) If you have some interest in this topic, there are a number of books here that I would certainly invite you to read and hopefully you will enjoy them. Thank you for your time. I would be happy to answer any questions you have.

MR. STEPHENSON: Questions from the Board? I feel your pain in terms of regulations and being proactive in advance of publishing it. We responded to this when we testified before Congress last November, and we addressed it with the General Accountability Office (GAO) analysts who had inquired and then subsequently wrote a report that outlines some issues within the Federal motor carriers arena. Why would you publish the rules by which you are going to test specimens? We have an issue in the Administrative Procedures Act and the process by which changes are made that affect the general public. In our case, we do not have the flexibility of making unannounced changes that are then immune from challenges in court or in subsequent hearings. It is more important for us to publish clear standards even though we are always in a cat and mouse game with those who try to beat the test.

There is some hope out there. There is a legislative recommendation that would ban the manufacturing, sale and perhaps even the use of these substances in the United States. We commend the support of GAO and the recommendation of Congress. Maybe your voice can be heard too because Congress is also interested in professional sports, including international athletics.

Thank you so much for sharing your experience and insights on this. Anybody else anymore comments?

DR. COLLINS: I know that we sometimes get questions from high schools and colleges that about testing for some of these compounds in their athletes. Our experience is that, though they would like to test for these substances, it is too expensive for them to do that. Do you have any comments in that regard?

DR. BOWERS: For us to test the entire competition list, which is that list of compounds that I showed you, costs about $230, with over $100 of that for steroid testing. The collection costs are also significant since we track down the athletes as opposed to having them come here. The cost per test for the program is well over $400.

DR. SHIPPEE: At DoD, we had units sending steroid sweeps into UCLA lab and the bill was expensive. We now have policy, and we do about 300 panels a year targeted at those who are building muscle quickly. The cost for us is about $280 for a limited panel. Do you perform the isotope ratio?

DR. BOWERS: Yes, we are performing GC combustion isotope ratio MS to detect very small differences in Carbon-13 and Carbon-12 ratios for the endogenous, normally present steroids. This test is very good if it is positive, but it is not so informative if it is negative. Athletes also take human chorionic gonadotrophin (hCG) to boost testosterone without changing the isotope composition.

MR. STEPHENSON: Anybody else?

DR. BUSH: Before we dismiss for lunch, I have the six submitted questions. I want to read them to give the Board time to think about them.

“Although drug test results do not indicate or correlate to level of impairment, is it scientifically feasible to associate results of the urine drug test with level of impairment in some way, such as the way a blood or breath alcohol level is associated with intoxication?”

“In workplace, does it really matter whether a substance is legal or illegal, therapeutic or not? Rather is not the concern one of whether or not it has an impairing effect and hence creates an unacceptable safety risk?” The last presentation of the day

will answer that for our Executive Order and the authority from whence this program derives its responsibilities.

"Dr. Clark spoke of efforts to train health care professionals in safe use of methadone and other pain management medications. Shouldn't such training also include focus on how to evaluate whether or not therapeutic drugs are compatible with performance of specific safety job functions?"

"Job hoppers are a growing problem for the non-transportation industry. Does HHS foresee adopting the same procedures as DOT with sharing positive drug tests, i.e., a national database?"

"NRC reports that MRO and substance abuse experts are trained to determine prescription drug abuse. They are making a joint determination. How does this process work? Is this correct? Laboratory, MRO, substance abuse expert to the agency, how does this chain go? How long is the process for reporting the results to the agency? NRC reported that they are utilizing saliva devices for alcohol testing, what is their accuracy rate? Is there a confirmation test?"

"If a doctor has a positive amphetamine and the donor provides medical documentation that he/she is taking a medication for weight loss which is described as phentermine, why does the MRO verify that as a negative drug test? Does the current drug panel eliminate these phentermine positives as explained in the MRO manual?"

At this time, 12:10 p.m., we will adjourn the Drug Testing Advisory Board. We will reconvene in an hour and 20 minutes at 1:30 p.m.

MR. STEPHENSON: This will provide time for dialogue this afternoon.

(Whereupon, a luncheon recess was taken at 12:12 p.m., to reconvene at 1:35 p.m.)

A F T E R N O O N S E S S I O N (1:35 p.m.)

DR. BAYLOR: The first presentation this afternoon will be given by Dr. Mike Baylor. He is the Co-Director at the Center for Forensic Sciences at RTI International. This is a joint project between RTI International and the Walsh Group, which is funded by SAMHSA. Thank you, Mike.

Analysis of Urine Drug Testing Results from a Medical Review Officer (MRO) Data Source, 2006-2007

DR. BAYLOR: (Slide 1) Today's presentation is the Analysis of Urine Drug Testing Results from a Medical Review Officer Data Source covering calendar years 2006 and 2007. (Slide 2) As a background to this study, drug testing indices, which are based only on laboratory-confirmed positive results, may not accurately represent illicit drug use rates because they inherently include blind quality control samples and also results that are later reversed after medical officer determination of valid medical explanations for the test results.

(Slide 3) The objectives of this study were to evaluate the relationships between laboratory-reported positive drug test results and the MRO-verified results reported to employers in Federally-regulated and non-regulated workplaces. Today with the expanded panel of prescription drugs, we will primarily focus on the non-regulated workplace data, specifically synthetic opioids and benzodiazepines positive drug test results.

(Slide 4) This project encompassed a review of the records from about 2.52 million urine specimens collected from January 2006 through December 2007. These

records were obtained from a large medical review officer data source. These specimens were from approximately 5000 companies nationwide.

(Slide 5) Virtually all of these specimens, about 99 percent, were analyzed by SAMHSA-certified laboratories. Approximately 40 percent of this data have a direct relationship to Quest's Drug Testing Index. About 98 percent of the 99 percent are derived from 10 SAMHSA laboratories. All blind QC samples were excluded from the analysis.

(Slide 6) Each of the records that were examined and downloaded from the MRO database contained 254 data elements, including donor demographics, employer information, collection site information, laboratory results, and the MRO determinations. HHS human subject protection criteria were adhered to for this project.

(Slide 7) This slide depicts a urine data summary from both the Federally-regulated and the non-regulated sectors for the two calendar years 2006 and 2007. In 2006, there were 223,000 Federally-regulated records and about 200,000 in 2007. Laboratory-positive rates were approximately 1.38 percent and 1.43 percent, respectively, of which 85 to 90 percent were MRO-verified. Remember, Federally-regulated is the five drug classes with opiates defined as codeine, morphine, and 6-AM.

In the non-regulated sector, there were a little over a million records examined in 2006 and a little over a million in 2007, with a laboratory-positive rate of about 4.19 percent and about 4.1 percent, respectively. The MRO-verified positives were approximately 80 percent in 2006 and 73 percent in 2007. The MRO reversal rates ranged from 0 percent reversal for PCP to 85.6 percent for hydrocodone laboratory-positive results.

(Slide 8) Looking at the percent of total verified positives by drug class for the regulated and non-regulated industries in 2006 and 2007, the drug classes include amphetamine; methamphetamine; cocaine; marijuana; the opiates, which have very different definitions in regulated and non-regulated industries; PCP; barbiturates; and benzodiazepines. The overwhelming majority of the marijuana laboratory-positives are MRO-verified positives. Next in order of prevalence is cocaine, followed by methamphetamine, amphetamine, and opiates. PCP is almost nonexistent. Cocaine verified positives decreased over the two-year interval in both regulated and non-regulated industries.

(Slide 9) For Federally-regulated testing, the number of specimens was 223,000 in 2006 and approximately 200,000 in 2007. The total for all drugs for the laboratory-confirmed positive rate was about 1.4 percent. Approximately 85 to 90 percent were verified and approximately 9 to 15 percent were reversed by the MRO. For the five drug classes, the percent MRO-verified rate for amphetamines was about 62 percent in 2006 and dropped to 41 percent in 2007. For cocaine and marijuana, over 99 percent were MRO-verified positive. PCP was 100 percent MRO-verified. Opiates were 30 percent verified positives in 2006, which dropped to 17 percent in 2007. The MRO reversal rates for amphetamines were about 38 percent in 2006 and 59 percent in 70 percent. The MRO reversal rate was 70 percent for opiates in 2006 and 82 percent in 2007, which includes codeine, morphine, and 6-acetyl morphine.

(Slide 10) For non-regulated testing of the common analytes, including amphetamines, cocaine, marijuana and phencyclidine, confirmation panels and cutoffs vary. The total laboratory confirmation rates for all drugs were about 4.1 percent in 2006

and 2007. Overall for 2006 and 2007, 76 and 73 percent, respectively, were verified MRO positives, which gave reversal rates of 24 and 28 percent, respectively. For amphetamines, the laboratory-positives were about 0.3 percent in 2006 and 0.4 percent in 2007 with MRO reversal rates of about 57 and 69 percent, respectively. Cocaine laboratory-positive percentages were 0.58 in 2006 and 0.47 in 2007 with over 99 percent MRO-verified. For marijuana, laboratory-positive rates were 2.1 percent with over 99 percent confirmed by the MRO. PCP also had over 99 percent MRO-verified.

(Slide 11) For the remainder of the non-regulated testing, total opioids include codeine, morphine, 6-AM, hydrocodone, hydromorphone, oxycodone and oxymorphone. Overall, the laboratory-confirmed positive rate was approximately 0.5 percent with about 27 percent in 2006 and 23 percent in 2007 verified by the MRO, producing reversal rates of 73 to 77 percent. For barbiturates as a class, about 0.3 percent was positive in both 2006 and 2007, and approximately 20 percent of those were MRO-verified positives, which gave a reversal rate of about 80 percent. Benzodiazepines were about 0.6 percent in 2006 and 0.7 percent in 2007 confirmed laboratory-positive. Approximately 30 percent in 2006 and 28 percent in 2007 were MRO-verified, which produced MRO reversal rates greater than 70 percent. The denominator for total opioids was 1,062,000 specimens in 2006 and 1,037,000 approximately in 2007.

(Slide 12) For the synthetic opioids, the hydrocodone laboratory-positive rate was 0.31 percent in 2006 and 0.36 percent in 2007 with MRO-verified rates of approximately 20 percent and 15 percent, respectively, which yielded reversal rates greater than 80 percent. Hydromorphone was 0.17 and 0.21 percent laboratory-positive for years 2006

and 2007, respectively, with 21 and 17 percent, respectively, MRO-verified positives and reversal rates of 79 percent and 83 percent, respectively. Oxycodone laboratory-positive rates were 0.27 percent for 2006 and 0.34 percent for 2007 with 35 percent MRO-verified in 2006 and 27 percent in 2007, which produced reversal rates of 65 percent and 73 percent, respectively. Oxymorphone showed laboratory-positive rates of 0.3 in 2006 and 0.46 in 2007 with 34 percent and 32 percent, respectively, MRO-verified positive, producing reversal rates greater than 65 percent. A significant number of the laboratory-reported positives are reversed with MRO verification.

(Slide 13) Looking at the detailed analysis of the synthetic opioids, the number of specimens tested was determined by the following criteria: oxycodone appeared in the testing panel and/or there was a positive oxycodone in the laboratory results. For oxycodone, approximately 215,000 were tested in 2006 of which there were 774 positives. Of these, 29 specimens were positive for oxycodone, 190 were positive for oxymorphone, and 455 were positive for both. In 2007, of the approximately 212,000 specimens, 1043 tested positive. Of these, 63 specimens were positives for oxycodone, 312 were positive for oxymorphone, and 666 were positive for both oxycodone and oxymorphone.

For synthetic opioid testing for hydrocodones, 637,000 specimens were tested in 2006, of which 2138 were positive, with 1051 positive for hydrocodone alone, 129 positive for hydromorphone alone, and 958 positive for both. In 2007, 650,000 specimens were tested for hydrocodone with approximately 2478 testing positive. Of those, 1244 specimens were positive for hydrocodone, 143 were positive for hydromorphone, and 1091 were positive for both hydrocodone and hydromorphone.

(Slide 14) This slide depicts a broken line graph of the percent of D-amphetamine reversed by MROs in calendar years 2003 through 2007. The blue line is the regulated reversal and the red line is the non-regulated. The regulated reversal rate increased from 25 percent in 2003 to 66 percent in 2007. The non-regulated reversal rate increased from 51 percent to 74 percent. For this particular data on methamphetamine, MDMA and MDA positives were excluded.

(Slide 15) In summary, the laboratory-positive rates are consistent from 2006 to 2007 for both the Federally-regulated and non-regulated testing. The MRO reversal rates increased from 2006 to 2007 for both the Federally-regulated and non-regulated testing. A majority of these reversals also appear to be due to prescription use of opiates and amphetamines in the Federally-regulated industry. Increased MRO reversal rates were associated with opioids, amphetamines, barbiturates, and benzodiazepines in the non-regulated industry. MRO reversal rates for amphetamines increased every year since 2003 in both the Federally-regulated and non-regulated testing. Some MROs have hypothesized that this increasing amphetamine rate could be the attention deficit individuals on the amphetamine-like drugs that are entering into the workplace and are workplace drug tested.

(Slide 16) Synthetic opioids, including hydrocodone, hydromorphone, oxycodone, and oxymorphone account for roughly half of the total non-regulated opioid laboratory-positive results as defined by total opioids, which includes codeine, morphine, 6-AM, hydrocodone, hydromorphone, oxycodone, and oxymorphone.

(Slide 17) Lower MRO reversal rates were observed for oxycodone and/or oxymorphone at 65 percent than for hydrocodone and/or hydromorphone at 80 percent.

Barbiturates and benzodiazepines reversal rates remained consistent at approximately 80 percent and 70 percent, respectively, in the two years presented. That concludes my presentation.

MR. STEPHENSON: Any questions from members of the Board? When we look at what we have seen from the MRO experience and map it to the prescription increases over the last few years, we see some concordance in the trend lines. MRO reversal rates and the changes in some of these drugs are pretty significant. In the non-regulated industry, there is the willingness of customers to purchase not only drug testing but also MRO review of results. There is a laboratory-positivity rate and a confirmation rate issue that is embedded in the drug testing and the MRO review costs.

DR. BAYLOR: This was examined from a different perspective and those results were presented at the February American Academy of Forensic Sciences meeting. National, regional, and state trends and demographics for the non-regulated drug testing were given. Copies of the poster that was presented, as well as the abstract from the Academy meeting, are available.

The next presentation will be by Michael Walsh. Dr. Walsh is President of the Walsh Group. The title of his presentation is A Five Year Analysis of Oral Fluid Drug Testing Results from a Medical Review Officer Data Source, 2003 to 2007.

A Five-Year Analysis of Oral Fluid Drug Testing Results from a Medical Review Officer (MRO) Data Source 2003-2007

DR. WALSH: Thank you, Mike. From a historical note, this summer marks the 20 year anniversary of this program being fully implemented. Twenty years ago in

August of 1988, President Ronald Reagan was still in office. The Guidelines were finalized, the laboratory certification program was set up, and most of the Federal agencies plans were certified in accordance with the provisions of law. Ian McDonald, the drug czar at the time, convened all the agency heads in an interesting meeting at the Indian Treaty Room in August of 1988. He directed them that President Reagan wanted all of the agencies to have their programs fully implemented before the election. At the time, George Bush was running against Michael Dukakis, and if you remember in August, Dukakis was ahead in the polls. As I sat there among the agency heads in that room, the philosophy was that they were not going to implement any program at that particular time and take on the unions. They were going to hunker down and stall to see whether the new President would support the Reagan initiative. So here we are 20 years later, and I would like to extend my personal thanks to Bob Stephenson and Donna Bush who persevered all of these years to make this a better program.

(Slide 1) My presentation is on the new area of oral fluid drug testing. We did a five-year analysis of oral fluid workplace drug testing results. These data represent unregulated tests that were developed from a medical review officer data source for the five-year period 2003 through 2007.

(Slide 2) The objectives of this particular project were to compile a cumulative database of laboratory-tested workplace oral fluid specimens to examine the frequency of laboratory positives in the various drug classes and to examine the relationship of the laboratory positives with MRO-verified positive results.

(Slide 3) We obtained approximately 650,000 oral fluid specimen records, which were obtained from a single MRO data source. The specimens were collected during

the five year period from January 1, 2003 through December 31, 2007. (Slide 4) The majority of specimens were analyzed by two large laboratory systems. All blind QC samples were excluded from the data analysis.

(Slide 5) Each record contains 254 data elements, including donor demographics, employer information, collection site information, laboratory results, and the MRO determinations. All HHS human subject protection criteria were followed.

(Slide 6) From 2003 to 2005, the number of oral fluid specimens being submitted through the system was constant. In 2006, submissions began to rise exponentially. Out of the 650,000 specimens, more than half were collected in 2007.

(Slide 7) Overall, there were 648,372 specimens tested. The laboratory-positive rate overall was 4.3 percent. The MRO-verified positive rate was almost 96 percent with a reversal rate of 4 percent. Most of the reversals were due to legitimate prescription use of opiates and amphetamines.

(Slide 8) Looking only at the illegal MRO-verified positive drugs identified in the oral fluid matrix, the overwhelmingly majority is marijuana at 60.4 percent followed by cocaine at 24.1 percent. Thus, 85 percent of the total positives were due to marijuana and cocaine. The methamphetamine-verified positive rate was 6.4 percent while the amphetamine rate was 4.3 percent. The MRO-verified positive rate for opiates was 3.9 percent and for PCP was 0.5 percent.

(Slide 9) Looking at the MRO-verified positive reversal rate by drug, overall, 4.3 percent were positive with a 96 percent MRO-verification rate. The percent MRO-verified positives range from 99 to 100 percent for methamphetamine, MDMA, cocaine, marijuana, and PCP. Most of the MRO reversals occurred were in the amphetamine, at

47 percent, and opiates, at 57 percent, categories. In the last five years, the amphetamine reversal rate increased. The reversal rate in 2007 was close to 70 percent. Thus, the reversal rates for amphetamines in oral fluids parallel that seen in the urine data.

(Slide 10) Of the 650,000 specimens analyzed, a little over 8000 were rejected for testing. This table shows the reasons why in the category of fatal flaws. Over 4000 specimens were rejected for volume not sufficient for testing. Roughly another 2700 specimens were rejected because the seal was broken or showed signs of tampering. Another 448 specimens had ID numbers on the bottle and the chain of custody that did not match. There were 164 specimens for which there was no printed collector name or signature.

(Slide 11) For the uncorrected flaws, the majority was because the CCF (Custody and Control Form) was incomplete or never received by the laboratory. The second most frequent category is that the specimen was not received or was destroyed in transit or at the laboratory.

(Slide 12) Some oral fluid specimens were categorized as invalid. Of the 614 specimens reported as invalid, 483 had no detectable immunoglobulin G (IgG). When these specimens were analyzed, 28 were drug positive. Seventy-two specimens exhibited interference with the GC-MS analysis. QNS refers to an insufficient volume of sample to complete all of the confirmation assays required. A small number of other non-specified reasons are listed in which we could not find in the record why the specimen was identified as an invalid.

(Slide 13) In summary, the use of oral fluid testing in the non-regulated workplace is increasing. Laboratory-confirmed positive rates and the percentage of the positives by drug class in oral fluid appear to be comparable to urine drug test result rates typically observed in the non-regulated workforce. The overall positive rate for oral fluid of 4.3 percent matched up closely with the Quest data that Dr. Sample showed earlier this morning for the urine data.

(Slide 14) Overall, the MRO-verified positive rate for oral fluid results of about 96 percent is higher than typically observed with urine test results. The majority of the MRO reversals are due to prescription use of opiates and amphetamines. I thank you for listening.

MR. STEPHENSON: Any questions from the members of the Board?

DR. COLLINS: For the last year or two, the numbers for reversal rates for amphetamines were more similar to those in urine. Is the same true for the opiates?

DR. WALSH: I did not look, but we have those data. I can look and tell you.

DR. COLLINS: They look significantly different as they are presented here. If the window was narrowed, would they look similar to the urine results?

DR. BAYLOR: I have the data here in my briefcase, which I can look at quickly.

DR. COLLINS: Thank you.

MR. STEPHENSON: Any other questions? This was an interesting peek into an area that was an unanticipated benefit of setting up this database. Thank you.

DR. BAYLOR: Dr. Jim Ferguson is our next presenter. He is the Chief Medical Review Officer for Verifications, Inc. The title of Jim's presentation is MRO Interpretation of Expanded Panel Laboratory Results.

MRO Interpretation of Expanded Panel Laboratory Results

DR. FERGUSON: (Slide 1) Thank you, Mike. Thanks for inviting us. My presentation is focused on workplace urine testing.

(Slide 2) Regardless of the panel, specimen type, or reason for testing, the MRO asks the same questions. Is it the right specimen? Are we reviewing hair, urine, et cetera? Is the chain of custody intact? Is the laboratory report accurate and complete? And more importantly, is there some reason from the donor for the laboratory-confirmed positive results?

(Slide 3) For the review reconfirmation process, MROs need to remember what they learned in their coursework as well as what we learned historically. For certain analytes, D- and L-isomer analysis may be required. As drug panels increase in size, MRO reporting turnaround time also significantly increases with expanded panel reviews. With more laboratory positives comes a higher MRO review rate. There will be prescription issues, whether they are real or imaginary. We cannot simply hang up the phone, verify a positive, and transmit the report. There are protocols for verifying prescriptions, including response time, which increase turnaround time. This is a bigger issue for employers because many of these will be MRO-verified negatives. Since the majority of non-regulated testing is pre-employment, these are applicants that employers want to hire. Employers will pressure MROs for reports. Many of these applicant donors have already told their recruiters that they have a prescription. The recruiters, in turn, are calling us saying, “The donor has a prescription, so why do not we have a negative report?” The answer is we have not yet seen the prescription.

(Slide 4) For most of these, there is no Federal oversight for expanded panel testing. Expanded panel cutoffs may vary. DOT regulations do not apply, but in every case where we can, we use them as a model because the principals are time-tested and valid. Since DOT regulations are not in place, there are many state regulations that have to be taken into consideration both by employers and MROs.

(Slide 5) Expanded panels include mostly prescription drugs. (Slide 6) To be reported positive, there must be verifiable illegal use or we must be unable to verify that the medications were legally obtained. The most common form of verifiable illegal use is the use of somebody else's medication. Or, the donor may tell us that they have a prescription, but they cannot show us the documentation.

(Slide 7) As a single entity MRO, by ourselves we cannot verify abusive use of legal prescriptions. With six digit nanograms per milliliter levels, we can presume abusive use of legal prescriptions. In the vast majority of the cases, we cannot. Urine specimens do not allow us to do that. Can we verify impairment? No. We are not able to determine whether someone is fit for duty simply on the basis of a urine drug test result.

(Slide 8) Why do this testing if we cannot verify it? An MRO should talk with his/her client to understand what the employer is trying to do with an expanded panel. Listed on this slide are some potential reasons for employers to perform expanded panels.

(Slide 9) The old mantra of more drugs is better is still believed. MROs would like to do as much as we can to dissuade this perception, but the mantra still exists. As service agents for these employers, MROs need to know what their goals. What are

they trying to obtain by doing this testing? The goals must be consistent with the realities of the MRO's review of the results.

The MRO review is not a fit for duty evaluation. If an employer is performing an expanded panel to determine if somebody is impaired or fit for duty, they are barking up the wrong tree.

(Slide 10) Workplace drug testing works best for illegal street drugs; if the drug is present, it is bad. Workplace drug testing programs serve as deterrents. For expanded panel testing to work, a team approach is needed. The fit for duty decision ultimately is does not belong to the MRO; it ultimately belongs to the employer. Does that mean that every time a prescription is verified as negative that the employer thinks that he/she must have a full and complete fit for duty evaluation? The answer is no, but sometimes maybe it is. It depends again on what the employer is striving for. Why are they doing expanded panels? Try to know the answers to the questions before you ask.

(Slide 11) Before interviewing donors, MROs need to know what the employer is after. An employer without a fit for duty program should not be performing expanded panel testing. Possible fit for duty program components include requirements for employees to divulge medications, fit for duty medical evaluations, light duty assignments, SAP (substance abuse professional)/EAP availability, et cetera.

(Slide 12) For expanded panel review, MROs focus on drugs not panels since one ten-drug panel is not the same another ten-drug panel and different cutoffs are used.

As MROs verify prescriptions for expanded drug panels, they must be concerned about Health Insurance Portability and Accountability Act (HIPAA), something that is not

an issue in workplace testing. We asking questions whose answers would normally be confidential. This has not been tested in court, thus the specter of HIPAA looms in these programs. How old a prescription will you accept? How many prescriptions are there? What is the potential for abuse? Two medications, carisoprodol and tramadol, were touted at their release as having no potential for abuse. I am seeing evidence from my patients to the contrary. Presence indicates potential impairment. Part 40 language - likely in the MRO's reasonable medical judgment - makes that decision easier. Who are you going to report these judgments to and how are you going to report it to the employer? What if the employer designates a secretary to be the only one who is authorized to receive the results, and they expect either positive or negative? All of this needs to be taken into consideration early on.

(Slide 13) For prescription verification, we want to see something that we can read. We may receive copies of bottle labels, which sometimes are legible. Asking for doctor's notes is the least favorable thing because doctors do not like writing notes, and they take forever to produce them, leading to turnaround time issues. Many pharmacists will not release information because of HIPAA or confidentiality issues. Sometimes we can do conference calls with donors and pharmacists. If we have all of the information on the label, including patient name, prescription number, pharmacy name, pharmacy phone number, prescribing physician name, and date the prescription was filled, we can sometimes convince the pharmacist to provide us with a simple yes or no answer to a non-directed question. Is this a valid prescription? Sometimes we cannot. Be aware that the donor name on the prescription may be different than the name that appears on the

custody control form. Verify that the time frame of the prescription is consistent with the specimen collection time. Two days after collection does not work.

(Slide 14) A urine drug test should be remotely, distantly tied to reasonable suspicion issues. Reasonable suspicion issues should be based on observable behaviors that are actually observed. MROs cannot be observing these behaviors because we are on the other end of a phone. We can hear about it, but we are still obtaining information via a secondary source. We cannot make a decision about an employee being impaired by a telephone consult.

It is not known whether non-observable complaints, such as missing formulary, word of mouth about the DUI (Driving Under the Influence) the employee got last night, word of mouth about paraphernalia seen in the car in the parking lot, et cetera, qualify for reasonable suspicion. This may require a case-by-case investigation.

(Slide 15) MROs should query employer decisions, such as what panels, what drugs, and why. Are all familiar prescriptions being defined as belonging to somebody's sister or parents? For instance, I accidentally picked up the Adderall in the medicine cabinet because it was next to the Tylenol. You will not pass a drug test with that excuse. Many employers will not get these nuances early on. All criteria need defining. MROs must know the answers before asking the questions. Is the employer going to disallow a child's cough medicine when the whole family is sick, just like they are going to disallow the Adderall sitting next to the Tylenol? Ask the questions.

Regarding outdated prescriptions, if there is a prescription sitting on somebody's shelf for five years, they are not abusing it. They are not even taking it because it is still there. Another problem associated with keeping drugs is diversion, which is a

completely separate issue. I am much more concerned about somebody that had ten prescriptions in the past thirty days than somebody that shows me an outdated prescription. Foreign prescriptions and Internet prescriptions are current issues. Both the MRO and the employer need to agree upon how to deal with these.

(Slide 16) The last slide is another set of concerns that should be decided before the inception of the program. These will necessarily increase turnaround time and expense. The MRO and employer must decide on either single or split specimens. Will reconfirmations be performed? What about medical marijuana? Thanks for listening. Does anybody have any questions?

DR. COLLINS: Do you find that there is a great deal of difference from employer to employer with regard to how they view use of somebody else's prescription or outdated prescriptions?

DR. FERGUSON: Yes, and it is a constant challenge to the IT (information technology) group to manage our client databases so that all of the different employer requests are integrated into a useable system. When we are doing our MRO reviews, we need to know that this employer wants to accept this type of familial prescription but the other one does not. There is a huge variance.

DR. NIPPER: I understand that HIPAA is a big concern, but if the drug testing is not done for medical purposes, does HIPAA apply? I know that this will require a legal opinion, but can you get around the HIPAA issue by having a properly worded release in the custody and control form?

DR. FERGUSON: Most of the focus is on the result of the drug test as not being a medical test. The question in that non-medical result is where is the line drawn

because we are obtaining medical information to verify the result. There will not be much dispute that the end result is not HIPAA covered.

DR. NIPPER: This has not been fully explored yet. That is why I raise the issue because I see it coming up and then jumping back down because many of people we deal with are very concerned about violating HIPAA themselves and getting into trouble.

DR. FERGUSON: We give talks to many of our clients about this very issue. How the client uses the result is part of the story. We cannot do impairment. The line separating drug test results from medical results becomes really hard to see.

MR. STEPHENSON: As the issue continues to evolve, there will be two aspects to it. One is evolving into fitness for duty programs in areas that currently do not have them or programs that are being morphed into them by a number of private sector employers. It is potentially a medical test because it is a determination of fitness for duty. The courts will weigh in on this as other administrative review and appeal processes evolve. As a caution, think about what you are doing.

You buried one very important golden nugget in the middle of your presentation which is, if you are not involved in a fitness for duty program, then do not do expanded panel testing.

DR. FERGUSON: Because of the fit for duty issue and because I give a hydrocodone-verified negative result to an employer, the employer thinks it is the same as any other negative result. We go to great lengths to make all results look alike. All of the negative results look alike, even the ones that we verified, unless we give a safety warning or safety concern. For non-regulated workplaces, which are unlike Federal workplaces where by definition they are safety-sensitive, we do not know the donor

duties in the 85 percent of our volume. We inquire during program setup whether they are doing safety-sensitive testing, and if so, do they want 24/7 coverage and all the other issues that accompany safety-sensitive testing. In many cases, with donors from different segments of a company, there is no way that we can be sure whether this person is doing safety-sensitive duties or not. We always default to thinking they are safety-sensitive if we have a concern. What if we do notify the employer of a six-figure nanograms per milliliter level of morphine that we are concerned about, but the test result is negative? The employer has no idea what to do with the safety warning that we are giving them.

MR. STEPHENSON: Let me probe a little bit further here. In some of your dialogue that you have not just with an employer or the specimen donor but with the physician who wrote a script, you are looking for an alternative medical explanation. If you have a safety warning based on the positive drug test results that you are reviewing, how often do the physicians who write these scripts know what their patients are doing on their jobs that might have safety-sensitive implications?

DR. FERGUSON: Two things happen that the vast majority of physicians who are not occupational physicians know about. Long-standing physician - patient relationships are disappearing with healthcare the way it is now. Any physician in a long-standing patient relationship almost certainly knows what the person does for a living.

As much as we try to humanize what we ask in the interview, it is not a friendly one because it is a legal, forensic interview. We have to be very careful when interviewing the prescribing physicians because many doctors are defensive when they

perceive us as being more aggressive than we really are. We are trying to find out if the doctor is aware of what he is prescribing and if he is aware that this might adversely affect his patient's job performance. It is hard to get doctors to talk; interviewing is a very long process. I have seldom talked with a doctor who says he is going to change the prescription based on our results.

MR. STEPHENSON: Any other questions?

MS. GORDON: If somebody is clearly showing signs of impairment, the prescribing physician will swear, even in court, that this patient is getting the right prescription and that there should be no problems. I had one case where a guy was literally falling asleep at the defense table because he was taking too much methadone while the physician was swearing that he was fine to drive.

DR. FERGUSON: I had a similar case with a DOT driver in Canada who was on multi pharmacy. The driver aggressively said that he took them while driving because he needed medication because truck driving hurt his back. The driver was pressuring me to remove a safety warning that I added. I did not remove it.

MS. GORDON: Do you think sometimes employers are abdicating their role in fitness testing because the drug test was negative and so they are fine? Even though the donor may show signs of impairment, they do not want to be crossing that line because they do not want to be sued by the employee.

DR. FERGUSON: Yes. I discussed fit for duty versus MRO and reasonable suspicion versus MRO because they go hand-in-hand with expanded panels. It is an ongoing discussion about the difference between MRO results and a fit for duty result.

MR. STEPHENSON: Thank you very much.

MRO'ing Prescription Drugs

DR. SWOTINSKY: (Slide 1) I am honored to be here and thank you all for inviting me. (Slide 2) I will present to you a perspective from an occupational medicine doctor. Like me, only a few MROs do full-time drug testing review work. Ninety-five percent of what I do is lacerations, physicals, staff and employer interactions, and independent medical evaluations (IME), while five percent of my job is MRO work. My MRO assistant also does many other things besides MRO work.

Our clinic has five different locations where we perform many non-DOT drug test panels, ranging in size from 5 to 10 drugs, and conduct on-site testing. In specific situations, clients request oxycodone analysis.

Most of my clients are employers of small companies, typically less than 15 employees. They are not savvy about drug testing. They know how to cut metal, how to supervise certified nursing assistants, or how to pick up packages.

I am here to give you the perspective into what I encounter as an MRO, particularly related to prescription drugs.

(Slide 3) My presentation is divided it into four parts. First, I will discuss what MROs believe, what employers believe, and what regulators believe about workplace drug testing and prescription drugs. Next, I will cover the reasons why we test for prescription drugs and which drugs should we test for. Lastly, the complexities and ambiguities of interpreting prescription drug positives will be discussed followed by the consequences to someone testing positive for a prescription drug.

(Slide 4) MROs are a rule driven group. In addition to my day job, I am an MRO nerd who spends weekends and evenings teaching courses, writing MRO manuscripts,

working with other MROs, and answering their questions. The bottom line is they all want rules. By contrast, there is an anecdote from Thomas Edison I would like to share. In Edison's Menlo Park studio were several employees working on inventions, including the light bulb. Visiting reporters noticed these employees coming in night and day, yet nobody was clocking in. They asked Edison about his studio policies and how he kept this place organized. Mr. Edison replied that there were no rules here because he was trying to accomplish something. Well, Mr. Edison might not have made a very good MRO because MROs need rules. Without rules, MROs become upset and nervous. They call you at SAMHSA, and they call me. They want to be told what to do. They do not want a decision to be made based on their own opinions because MROs all have different opinions. I will share some cases later that are similar to cases that I present in my MRO courses. When I ask MROs about these ambiguous cases for which there are no rules, a third of the MROs call it positive, a third call it negative, and the rest throw up their hands in despair and say cancel the test.

(Slide 5) Employers believe that drug testing will yield better employees. Employers want drug testing policies that are flexible. They do not want policies that specifically address what constitutes alternative medical explanations, familial prescription drug use, and foreign medicines. That is why they hire Dr. Swotinsky as the MRO. Ideally, these issues should be resolved with your employers, but in truth, the employers do not know nor do they care. They leave it up to us and our affiliated companies. Again, I am working with smaller-sized companies where the owners are not far removed from the production workers, and they are trying to get their jobs done.

The acceptability of the explanation generally left up to the MRO. It is a rare employer who will voice an opinion.

Employers, for the most part, believe that more is better. If marketing offers a five drug panel for $50 or a ten drug panel for $50, the employer will select the ten drug panel. The testing laboratory charges us about the same for both, so it is all the same to us. If they ask for my counsel, I explain that five drug panels are easy while ten drug panels are tough. Similarly, I explain that pre-employment testing is easy while random testing is tough. I recommend that employers initially start with a five drug panel and pre-employment testing. Only after those programs are established should exploring prescription drug testing be considered.

Employers treat all positive drug results the same, whether it is codeine positive or cocaine positive. To them, a positive is a positive. They may treat different employees differently, but the positives to them are all the same.

(Slide 6) In the 1970s, military programs were established to identify soldiers who had drug problems and to get them into treatment. In the 1980s, the Federal five-drug panel with the intent of deterring illegal use was created. In the 1990s, DOT recognized that MROs were obtaining safety-related information on donors. For instance, the MRO learns about the driver's diabetes or heart condition. Because DOT needed to address this, language was inserted into Part 40 for that purpose. In the 1990s, there was growth in pain clinic and impaired professional testing for monitoring compliance and abstinence.

(Slide 7) Where are we going in the future? Will the program accept alternative specimens? Will it test for prescription drugs? If prescription drug testing is performed in

the workplace, then testing is conducted without suspicion. We are drug testing employees who have not done anything wrong or who have no reason for suspicion. If we are doing this, why are we doing it? Do we think it will improve safety? Is this social engineering to encourage deterrence, using decreasing rates of illicit drug abuse in the workplace as an example? Are we doing this to identify people with prescription drug problems and get them into treatment? That last one would be a novelty for my client base.

(Slide 8) This warning, from the label of a prescription medicine, states that when using this product, do not use more than as directed. Marked drowsiness may occur. Avoid alcohol. Alcohol, sedatives, and tranquilizers may increase drowsiness. Be careful when driving a motor vehicle or operating machinery when using this drug. Based on this warning, this medication should be tested for. It is Robitussin cough and cold medicine. An over-the-counter medication is probably not the first thing that comes to mind for targeted prescriptions.

(Slide 9) In the Physician Desk Reference, more than 700 prescription drugs have similar warnings. Alka-Seltzer, another over-the-counter product, has a similar warning on it. The warnings themselves do not tell you what to do.

Which drugs do you focus on? Though I do not have the answers, I did participate in a Federal Motor Carrier Safety panel which addressed the issue of drivers and their use of oxycodone and hydrocodone. We examined international data on the safety and use of controlled schedule II drugs. There was no scientific evidence that long term use of these drugs causes a safety risk for truck driving. There is, however, a limited amount of very soft data regarding short term use and some impairment initially.

If challenged, the Federal government would be hard pressed to present data demonstrating a safety issue associated with oxycodone use.

In the trucking regulations, it is acceptable for truck drivers to use prescription drugs with the prescribing doctor's permission. The one exception is methadone, not because methadone is impairing, but because heroin users are considered safety risks in general lifestyle issues.

In this meeting, much of the discussion involves hydrocodone and oxycodone, which are receiving media attention and maybe under consideration here for testing. The bigger safety issue is alcohol, but similar to prescription drugs, it is legal.

(Slide 10) As an MRO, I must interpret the positive drug results that come across my desk. MRO work for the most part is not brain science. For example, most MROs obtain the right answer when reviewing marijuana positive results because it is straight forward testing for illegal drugs. I am surprised, though, that 0.4 percent of marijuana positive results is overturned because I had one in my life. With prescription drugs, the reversal rates by MROs are 70 to 80 percent. The interpretations with prescription drugs are much more complex and produce more work for MROs, especially with ambiguous issues.

MROs need to understand drug metabolism. Marijuana is catabolized to THC-COOH, which is not that complicated. (Slide 11) With benzodiazepines, the metabolic pathways are extremely complicated. Thus, it is very easy to make a mistake interpreting Xanax usage when the laboratory report lists four or five different benzodiazepines. Where does the MRO start? (Slide 12) The same thing applies for opiates because opiate and opioid metabolism is very complicated.

(Slide 13) The knowledge base for prescription drugs is scant. After 20 years of experience, we understand that poppy seeds cause certain types of morphine levels and that use of Vick's Inhaler produces positive amphetamine results. Unfortunately, we do not know what we do not know. There will be surprises along the way. Only two years ago we discovered that morphine is metabolized to hydromorphone. Testing for prescription drugs will not be as tight a program as we have now for testing for illegal drugs because the database of experience is not there.

(Slide 14) This slide contains one of those cases I mentioned earlier. Jill tests positive for hydrocodone. She informs the MRO that, after her root canal, her roommate gave her a Vicodin. What do I do with this? Is this a positive or a negative? Now assume that Jill is a 61 year old nun who teaches at the Catholic school. She volunteered for a urine drug test to show her support for the school's new student drug testing program. She is still positive.

(Slide 15) A donor states his positive drug result is because he used someone else's medicine. Is that valid? DOT says no because borrowing another person’s medicine is not legally permitted. This is a very common explanation. People do not admit to borrowing their spouses’ marijuana. They do admit to borrowing their spouses’ Vicodin, oxycodone, or Xanax. Most MROs, but not all, will call those positives. But is that what we looking for? Is that the kind of abuse that we are trying to target?

(Slide 16) Jack tests positive for codeine. He tells the MRO that a clinic in Cancun gave him codeine when he burst an eardrum a few days prior to the test. It was a Hospital de la Torres or something like that; he does not remember the clinic's name. The MRO requests prescription information. Amazingly, Jack faxes to me a note in

Spanish from Hospital de la Torres. My teenage daughter in spite of her A's in Spanish cannot read it for me. What do I do?

(Slide 17) Some prescription drugs, such as codeine, are sold over-the-counter in Canada and Mexico. I would have called it a negative, but there are issues concerning medicines obtained abroad and brought back to the US. The guidance from DOT is it is okay to bring back up to a 30 day supply of medicine. Some people buy large quantities of medicine from Canada because they are cheaper there. If you live in Detroit on the Canadian border, you might buy several months worth of medication in Canada to save money. It is difficult to corroborate drugs obtained abroad. How does the MRO find the phone number for Hospital de la Torres and communicate with them? Is this really what we are trying to do?

(Slide 18) Joe tests positive for marijuana. He has a Dronabinol prescription which he takes it for chronic pain. Most MROs faced with a prescription would call it a negative. Does that one Dronabinol prescription give Joe a lifetime pass to use marijuana? Probably.

(Slide 19) What about the scenario in which a person has a prescription that is used, often in excess, for reasons other than those that are FDA-approved? Suppose Joe is prescribed two or three OxyContin a day, but he is taking five or six. Because the laboratory drug level is very high, the MRO finds out. The MRO will invariably report this as a negative result. If the MRO believes there is an associated safety issue, he will report it as such. But the safety issues are very tough to discern unless they slap you in the face. It is difficult to determine a safety issue over the phone. Most of the people

who we deal with are not driving trucks or flying airplanes. They are delivery people for FedEx, for example, and thus their jobs pose a much lower safety risk.

(Slide 20) Jess takes Adderall that his doctor prescribed for him four years ago. When he moved away to college, he started buying it over the internet. For his post-graduation pre-employment test, he is amphetamine positive. He presents documentation from www.canadadrugs.dot com for the Adderall; he has not seen a doctor in four years. (Slide 21) DOT states that without a prescribing physician, this is not a valid medical explanation. Nevertheless, it is common. Are we hindering Jess from obtaining his first job out of college? Is that the goal? Is this the kind of use that we are going after? It is a different use than PCP and crystal methamphetamine.

(Slide 22) Dr. John tests positive for oxazepam for his pre-employment drug test for Massachusetts (Mass) General Hospital where he applied for his surgical residency. He wrote an oxazepam prescription for his wife, and he took some of her pills before his red-eye flight from California just prior to his drug test. Are we going to call it a positive result and deny him his residency at Mass General?

(Slide 23) Some states have laws that prohibit doctors from writing prescriptions for themselves. Some doctors have licenses in multiple states. How does an MRO sort through that? I do not have the answers.

(Slide 24) Jane tests positive for oxycodone. She faxes to the MRO her three year old Percocet prescription. What is your cutoff for how old is too old?

(Slide 25) Medicine bottles list an expiration date that is a shelf life expiration, which reflects the quality of the medicine. The shelf life date is not a legal issue because you can use outdated medicine and not violate the law. Paraphrasing the Capital One

credit card slogan, what is in your medicine cabinet? If a person is using an old prescription, they are not abusing. A drug abuser would use it all up instead of storing it for three or four years. Does one old prescription give you a license to start abusing it for the rest of your life? These are more questions for which we do not have answers.

(Slide 26) Jeff, who has a morphine prescription for lower back pain, has very high levels of urine morphine. Is this result positive or negative? Where do you set the cutoff?

(Slide 27) There is no written guidance for prescriptions taken in excess. Typical people who abuse prescriptions will take them at high doses. At least 20 percent of people who abuse prescription drugs are abusing prescriptions that their doctors' wrote for them. It is difficult for an MRO to call a result positive due to a valid prescription. The MRO may alert the employer to safety concerns. This situation is a judgment call; put 100 MROs in the room and you get 100 different judgments.

(Slide 29) To employers, all positives are the same, whether due to codeine, Xanax, or crystal methamphetamine. With a positive result, they will take whatever action they see fit. In the DOT world, action options include removal of the person from work and referral of the person to a substance abuse professional for treatment.

I also do substance abuse professional work. With cocaine and marijuana abusers, I know what types of treatments are appropriate. For the person who borrowed another’s medication, I refer him/her to treatment and tell him/her do not do that again. I am not sure what the right treatment is for these people. It is difficult to treat those who do not believe they have done anything wrong.

Then there is the legal issue. Would courts say that testing for prescription drugs in these situations where you have no individualized suspicion is a reasonable thing to do? Is that a societal goal? It may not be a safety goal.

(Slide 24) There are many different ways that society could address prescription drugs. As a doctor who prescribes oxycodone and hydrocodone and covers for 240 other doctors who also prescribe those medications, the prescription drug issue will not necessarily be fixed by drug testing. The issue needs to be fixed by doctors and the way medicine is practiced. In our country, medicine is a consumer product. The consumers go to doctors, and the doctors try to satisfy their patients and meet whatever need the patient is expressing. This is why doctors write prescriptions for 180 Vicodin or oxycodone with three refills. It is a prescribing issue. Maybe there should be a law that you cannot prescribe more than 20 at a time, or if you do, you have to jump over a number of hurdles. This is a prescribing issue and not necessarily a drug testing issue.

If the Federal government adds prescription drug testing, please provide MROs with clear answers on what to do in these situations. MROs do not share the same opinions about what should be done. We spent time making sure that our chains of custody are bullet proof and that our laboratory tests are better than Ivory Soap. When a positive laboratory result scenario is presented to a room full of MROs and one-third says yes, one-third says no, and the other third says cancel, is that variability acceptable? What kind of program are we running here? We need clear answers. With that I close for any questions.

MR. STEPHENSON: Questions from members of the Board? Your insights are a reiteration of things that we have heard. Your information about dealing with small

employers is an important issue because they do not have the outside counselors and they do not have standards. In your experience dealing with small employers that you serve and educate, how much time do you spend with employers to adjust their sense of expectation from fantasy to reality of what the drug test can tell them and how you are able to differentiate licit from illicit use in prescription drugs?

DR. SWOTINSKY: We do not talk to employers for the most part. Our job is to process patients. I am not complaining; that is what we get paid to do. Most of my clients I have never spoken with. Sometimes I will speak to them if there is a positive drug result and they have questions about it. The programs and panels are set up by marketing people. Some of my very large clients delve into these questions, but for these smaller employers, I do not even know their names. I would not know them if I met them on the street.

DR. NIPPER: My laboratory does all non-regulated testing, and we have a number of smaller clients. One of the opportunities that I have is to guide them to use an MRO, even when an MRO is not required by any law under which we operate. Even with the imperfect MRO system, with its pitfalls and trap doors, it is better to have the MRO than not. I cannot tell you how many times a person who contracted with us to do testing called and said, “You gave me a positive test. What am I supposed to do now?” I ask our marketing people not to sell drug testing to people who do not know what they are going to do with it. But, we need the business.

MR. STEPHENSON: This is not problem-solving; this is problem-shifting, right?

DR. COLLINS: In the data that Charlene Lewis presented when she talked about past month nonmedical use of prescription drugs, it is not differentiated whether the use

involved taking your own two year old medication for a new ailment versus somebody taking it to get high. The SAMHSA data are combining those two and perhaps SAMHSA should separate those reasons.

MR. STEPHENSON: The Office of Applied Studies (OAS) did this special report at our bequest last year entitled: Worker Substance Use and Workplace Policies and Programs. It was a secondary analysis of the National Survey on Drug Use and Health Data Sets for three years. They plan to redesign the survey, and we are engaged with them to expand the definitions and understand the issues of prescription drugs and these policy issues in the workplace. Perhaps as a collective group, we can provide some input. Redesign of the NSDUH will take another year and a half. Once administered, 50,000 respondents a year are expected. There will be 150,000 respondents data file elements that can be aggregated into secondary analysis that will apply for workplaces. When the report was published last year, it was phenomenally well-received. Only 2000 copies were printed, but the report is available on the OAS website within http://www.samhsa.gov/. It is a valid resource.

If there are no other questions, it is time for our scheduled break.

DR. BUSH: Let us adjourn for a ten minute break. The meeting is long, but we have only two more presentations. There are some things to tie together yet.

(Break)

DR. BAYLOR: The next speaker is Colonel Timothy Lyons. Dr. Lyons is a Deputy Director, Forensic Toxicology Division of the Armed Forces Institute of Pathology, Department of Defense. His topic will be DOD Experience with Prescription Medications. Tim.

DoD's Experience with Prescription Medications

DR. LYONS: (Slide 1) Thank you for the invitation to speak today. I will mostly be discussing our random urine analysis program within the Department of Defense. I will also make some comments about some of the special testing that we do at the Office of the Armed Forces Medical Examiner. This Office is part of the drug testing program and oversees the drug testing laboratories, quality assurance, and inspections. We also do special testing for those laboratories. The drug testing laboratories do not analyze for prescription drugs. Those specimens are referred to our division where we perform the special testing. We are involved with many more missions besides the drug testing program, including data and information related to investigative cases, postmortem cases, fitness for duty, et cetera.

(Slide 2) As a historical perspective, within the Department of Defense, we do not have much experience with prescription medications. We have routinely pulse tested for codeine and morphine since we began our current program in the mid to late 1980s. Oxycodone pulse testing was implemented in October 2005.

We do have years' worth of experience with prevalence testing for some of the prescription medications, including methadone and benzodiazepines. Later I will present prevalence test data for benzodiazepines that were collected in 2005 and again in 2007.

We do have data and/or experience from the special testing that we do with the medical examiner as well as from postmortem and investigative cases.

(Slide 3) The pulse testing goal for codeine and morphine within the Department of Defense is 15 to 20 percent of the total specimens received at the laboratories will be screened. The screening cutoff for codeine and morphine is 2000 nanograms per

milliliter with morphine used as the calibrator. Per DoD policy, for example, 20 percent of specimens be screened for oxycodone. Some drugs require mandatory, 100 percent testing, and many of those are either required by regulation or by policy.

One of the differences in the DoD system versus the civilian world is our approach to our screening. We have a two-tiered screening approach. Any initial positive screening result is subject to a rescreen. For the codeine and morphine, for example, the initial screen and the rescreen are done by the same methodology. The specimen with a positive second screen is subject to confirmation with GC-MS. The cutoffs are 4000 nanograms per milliliter for the morphine and 2000 nanograms per milliliter for codeine.

(Slide 4) In the first eight months of fiscal year 2008, we achieved our goal to test between 15 and 20 percent of the total specimens received with our 19 percent screening test rate for codeine and morphine. The confirmed positive rates were 0.04 percent for the morphine and 0.11 percent for codeine. The overall confirmation rate of positive screens confirmed by GC-MS is about 65 percent. What that means is that of those specimens that screened positive on the initial and the rescreen tests, 65 percent of them confirm positive for codeine or morphine by GC-MS at or above the cutoff. This confirmation rate does vary somewhat between the laboratories.

(Slide 5) Oxycodone and oxymorphone testing has been in place for not quite three years yet. The testing for the oxycodone and oxymorphone is by DoD policy, which dictates that 15 to 20 percent of the specimens would be screened. The screening cutoff is set at 100 nanograms per milliliter with oxycodone as the calibrator. Once again, we use a two-tiered screening process in which all initial screened positive

specimens are rescreened using the same screening immunoassay kit. If the second screen result is positive, the specimen proceeds to confirmation with GC-MS. The cutoffs for GC-MS are listed.

(Slide 6) For the first eight months of this fiscal year, oxycodone and oxymorphone were screened at about the same rate, 19%, as the opiates. The GC-MS confirmed positive results are slightly higher than what we saw for the codeine and morphine, with oxymorphone almost five times higher. The overall confirmation rate for what screens positive is confirmed positive is relatively good at 85 to 90 percent. This is a reflection of a strong screening kit with minimal cross reactivity with other substances.

The majority, 90%, of these oxycodone and oxymorphone confirmed positive results are determined to be due to legitimate prescription use after medical review. Thus, we are not litigating many of these cases in court.

With the opiates, codeine and morphine, the majority of the confirmed positive laboratory results are reversed by the MRO. Once again, we rarely litigate codeine or morphine positives. In 13 years of expert witnessing for the Department of Defense, I have done two cases total for codeine or morphine. I have yet to do one for oxycodone or oxymorphone.

(Slide 7) For hydrocodone and hydromorphone, we have not done any prevalence testing because of the unavailability of a commercial screening kit. There has been some discussion that we need to aggressively lobby for a FDA-approved kit. From anecdotal data derived from postmortem and investigative cases, hydromorphone is definitely out there. It is not known whether its presence is abuse versus legitimate use since our postmortem data are not typically reviewed by an MRO. When we do look

at the prescription records of individuals for fitness for duty and postmortem cases, we have found that there is quite a bit of the hydromorphone out there.

(Slide 8) We have been testing for the 6-AM since 2004 using a commercially available kit that was marketed in 2003. In 2004, we established a policy to perform 100 percent screening of all of the specimens that come into the laboratories for 6-AM using this kit. In addition, we do pulse testing for the opiates at a 20 percent screening rate. The confirmation rate for the 6-AM is significantly lower at 50 percent than any other assay we have. Over the last year, we addressed that concern. What is the interference? What are the antibodies cross reacting with? What could be the cause of that failure to confirm some of these 6-AM screening positives? To answer these questions, we conducted a study designed by Dr. Jemionek to determine whether the 6-AM immunoassay is detecting some of the other opiates and whether we can use that cross reactivity to our advantage.

(Slide 9) The slide depicts heroin positive results for all the Department of Defense services analyzed at all of the laboratories. Heroin positive results have been increasing since 1999. In 2004 until 2005 we began 100 per cent testing for heroin. For the first eight months of this fiscal year, there have been 89 6-AM positives. These positive results are equally distributed among the services and among the laboratories.

(Slide 10) In this slide are our criteria, including ratios, concentrations, and metabolites, for interpreting codeine and morphine positive results to determine the drug source.

(Slide 11) In a prevalence study that we did this past year, we reviewed the results from specimens that screened positive with the 6-AM kit. Those specimens that

did not confirm positive were isolated to determine the cross-reactive substances present. The table presents the breakdown of that study. The majority of those specimens that screened positive with the 6-AM kit but did not confirm were morphine positive, with morphine concentrations above 10,000 nanograms per milliliter. The hypothesis is that the 6-AM kit was cross reacting with morphine present at concentrations greater than the 10,000 cutoff. Initially, we thought this cross-reactivity was a disadvantage, but we have a strategy to use this morphine cross-reactivity to our advantage. We have developed some proposals on how we want to handle that in the future. (Slide 12) Opiates, primarily morphine, account for these presumptive positive specimens that do not confirm.

(Slide 13) Our proposal, though we have not committed ourselves to yet, is to take that 6-AM positive specimen from the initial screen and rescreen it on both the 6-AM kit and the opiate kit. This strategy is designed to detect some of those high morphine specimens that would otherwise be missed since we only pulse test at 20 percent for opiates.

(Slide 14) The procedure would be as follows. If an initially screened specimen tested positive for 6-AM and was positive upon rescreen for only 6-AM, the specimen would only receive a 6-AM confirmation. However, if the specimen was positive for both the 6-AM and opiate upon rescreen, then confirmation would include not only 6-AM but also codeine and morphine. If the specimen was only opiate positive on the rescreen, then only opiate confirmation for the codeine and morphine is performed. Our current confirmation cutoffs of 10 for 6-AM, 2000 for codeine, and 4000 nanograms per milliliter

for morphine would be used. This would also allow us to meet our requirement of having two immunoassays for a positive result.

(Slide 15) To conduct prevalence studies, negative specimens from the laboratories that are ready for discard are obtained. Those specimens are analyzed to determine the prevalence of positive results for specific drugs. A methadone prevalence study was conducted several years ago by the Armed Forces Medical Examiner Division of Forensic Toxicology using the Microgenics DRI kit. The prevalence of methadone was quite low at 0.01 percent, which equates to only four positive specimens out of the nearly 28,000 specimens analyzed. Of those four positives, two were due to legitimate prescriptions. The methadone confirmation rate was 75 percent for this screening kit, compared to our typical confirmation rates for our illicit drugs of 90 to 95 percent, exclusive of 6-AM.

(Slide 16) For the benzodiazepine prevalence study, almost 12,000 specimens, originating from the war zones of Iraq or Afghanistan, were analyzed. Seventy-seven specimens were positive, and 66 of those specimens confirmed at a detection limit of 25 nanograms per milliliter. The confirmation rate for the benzodiazepine screening assay was 86 percent for that kit in this study.

(Slide 17) The overall benzodiazepine positive rate was 0.55 percent, which is higher than the methadone, codeine, and morphine positivity rates. (Slide 18) This slide presents the benzodiazepines detected and their frequency of detection. These benzodiazepines reflect the use of those drugs prescribed in the field by DoD and are also mirrored in our postmortem and investigative cases.

(Slide 19) In another prevalence study done for benzodiazepines with about 10,000 specimens, the positive rate was similar to that found in the first prevalence study. Of the 71 specimens that screened positive, 61 of those confirmed. For this study, several different immunoassay kits were utilized. The screening kits varied in their confirmation rates, with some kits performing better than others. (Slide 20) The CEDIA reagent exhibited the best confirmation rate because of its ability to cleave conjugated metabolites.

(Slide 21) For mandatory testing, the overall drug positivity rate must exceed 0.25 per cent in a prevalence study. We regularly perform prevalence studies for different drugs, such as the study we recently completed for ketamine. Benzodiazepines did meet the mandatory testing criteria, making it a drug class that we will consider monitoring.

When these prevalence studies were conducted, we did not have the capability of matching positive drug results with prescription data to determine legitimate usage. With the merged DoD database described yesterday by Colonel Shippee, the pharmacy database is readily accessible. For example, for our special investigative testing, prevalence studies, and court preparation, an individual's prescription history is available. With a claim of Adderall usage, for instance, I can now verify the prescription record back over a period of years.

(Slide 22) If DoD decided to initiate benzodiazepine screening because of the drug class' high prevalence rate, screening for only 5 of the 13 benzodiazepines would detect the majority of the positive specimens.

(Slide 23) Because of the current war situation, many soldiers are prescribed pain management drugs and benzodiazepines. Many of the pain management drugs, including morphine, oxycodone, and tramadol, are being prescribed for chronic pain conditions expected to last for days, weeks, months, and years. Often, multiple drugs are prescribed for these conditions. In some of our postmortem and investigative cases, special testing is performed to detect these prescription medications. It is amazing to see what these individuals have on board and the volume and the frequency of what is being prescribed. Unfortunately, this is part of the reality of what we are dealing with right now in the Department of Defense. This is not short term care. There are individuals, who are on extremely high doses of morphine, oxycodone, et cetera, that are going to work every day and expected to function at their jobs. This has been an issue as well.

The analytical problem with many of these pain management drugs is that there are no commercially available screening kits. Since most testing for these pain management drugs is performed by GC-MS, prevalence studies would be extremely difficult to perform from a production standpoint. Even more impossible would be routine testing or random analysis of these analytes.

(Slide 24) Future initiatives include the tandem approach to 6-AM opiate screening. Another prevalence study is overdue for methadone since it has been about four or five years since the last study. Routine methadone screening is unlikely unless the frequency or the prevalence rate has increased. The prevalence rate for benzodiazepine is relatively high and meets our criteria for mandatory screening. Thus, this drug class is under consideration for screening. Since the high prevalence rate is

linked to high legitimate prescription use, mandatory screening may not be warranted, especially considering the complexities of benzodiazepine testing factored into our production-type laboratories. Thus, benzodiazepines require an in depth analysis to determine whether the required effort and resources make it worth pursuing.

(Slide 25) For hydrocodone and hydromorphone, we would be interested in pursuing routine testing based on what we see with our oxycodone kit. Without an FDA-approved screening kit, it is not feasible to incorporate testing for hydrocodone and hydromorphone from a production standpoint in our urinalysis program. Testing for these drugs is currently performed on a regular basis at the laboratory for those small number of specimens associated with postmortem or specialty cases. The cross reactivity associated with the opiate kit is used as a pseudo screen for the hydrocodone. All screening positive specimens are analyzed by GC-MS.

We have talked with several in vitro diagnostic vendors about our interest in an oxycodone screening immunoassay.

COL. SHIPPEE: There is much political sensitivity around taking care of the soldiers. The Wounded Warrior Program is well funded so money is available for prescription medications. DoD does not want a soldier reporting to the Washington Post that he/she could not obtain pain medication. This availability of medications has produced a secondary effect. Anecdotally, a while ago I hurt my back and was given Ibuprofen for pain. I did not receive Tylenol number 3 until I was diagnosed with a herniated disk. Recently, Aaron Jacobs had a hip replacement, and physicians were forcing pain medication on him. Our soldiers today are victims of the pervasive atmosphere of prescribing pain medication.

DR. LYONS: I agree with Colonel Shippee. For those of us who have been in the military while, historically, whenever you went in the clinic for any injury, the classic treatment was to administer 800 milligram tablets of Ibuprofen. This is not the case anymore; now oxycodone, Vicodin, Tramadol, or Tylenol 3 with codeine at the very least is dispensed. This represents a change in the philosophy of prescribing.

DR. NIPPER: Colonel Lyons, I appreciated your presentation. I have a question about DoD's double screen. What happens in the scenario where the initial screen result is exceedingly positive but the rescreen result is negative? Do you investigate, accept the best two out of three, or do you just kill it?

DR. LYONS: Our program is a two-tiered screen. From my experience as the Commander of two different laboratories, if a specimen produces a very high initial screen result and rescreens as negative, the result is reported as negative. Before reporting, I would investigate why that happened to ensure there was not a specimen mix-up or an assay failure. However, if troubleshooting points to specimen mix-up or an assay failure, then you would rescreen the specimens. Everything would be documented. This does occur on occasion.

DR. NIPPER: If you do find a suspected laboratory error, you repeat the runs?

DR. LYONS: Yes, depending on the circumstances and documentation that indeed that there was something wrong, such as a control failure. Over the 12 to 13 years that I was at the two laboratories, it did happen on occasion.

For the majority of the drugs, about 99 percent of initial positive screens will screen positive on the rescreen. Discrepancies usually occur when the results are close to the cutoff. For instance, an initial screen result of 101 with a 100 cutoff is reported as

positive but the rescreen result of 99 is reported as negative. This is typically what is seen when there is a miss-match between the screen and the rescreen.

COL. SHIPPEE: Our two-tier screen protocol is a luxury that DoD can afford but commercial laboratories cannot. Reasons for keeping this two-tier screen are our Judge Advocate General (JAG) officers are familiar with it, we ultimately answer to them, we must defend ourselves in court, and it is inexpensive.

With amphetamines, we use adjunct testing to our advantage. A different kit is used for the rescreen.

DR. LYONS: I performed a cost analysis for the two-tiered screen, and it does not cost us much more in manpower or in money. The system gives us flexibility, for example, with the amphetamine adjunct test, resulting in confirmation rates for amphetamines of about 85 to 90 percent compared to the historical rate of 30 to 40 percent.

MR. STEPHENSON: Regarding the earlier presentation of Lt. Commander Belouin on the FDA data, you are in a unique position with your access to your pharmacy database, which allows you evaluate changes over time of the prescribing practices and the numbers of dispensed units for some of these drugs that you are ultimately going to test. Comparing your data with what is happening in the surrounding civilian community gives you a much more powerful handle than anyone else has in our country. This may be a collaborative project that is population- or geographically-based which could ultimately be related to physician education to prevent more medications than you really want in home medical cabinets.

COL. SHIPPEE: Absolutely. I am developing a working relationship with the pharmacists. I have discussed linking our laboratory LIMS to the prescription data to promote these types of studies.

DR. TURK: Is your second screen performed on a separate aliquot?

DR. LYONS: Yes. It is a separate pour except for the adjunct test. For the rescreen, a second aliquot is removed from the original bottle. It is a different set of controls, different chain of custody, everything.

Review of E.O. 12564 and Reasonableness

DR. BUSH: (Slide 1) This presentation is a Review of the Executive Order 12564 and the concept of reasonableness. This will just set the stage for further discussion at a future time. If what we have heard here over the last two days gels, the science sets in, and the concerns diminish, then we can assess where we are in the Federal program. Remember, our Executive Order is what drives us in the Health and Human Services, SAMHSA, and the National Lab Certification Program. It dictates Federal agency employee drug testing programs and drug-free workplace plans.

Other entities, such as DOT and NRC, have separate statutory authority, separate marching orders, and different implementations but are required to use our SAMHSA HHS-certified laboratories to conduct their drug testing analyses. This Executive Order pertains to just to a small number of Federal employees. Because we do such a good job at providing accurate and reliable drug testing, others have decided to utilize our program too.

No matter what, we always must reset our own clock to our Executive Order and obtain our marching orders through public law.

(Slide 2) I have excerpted passages from the Executive Order 12564 issued September 5, 1986 by President Regan. Section one defines drug free workplace.

A. Federal employees are required to refrain from the use of illegal drugs.

B. The use of illegal drugs by Federal employees, whether on or off duty, is contrary to the efficacy of the service.

C. Persons who use little illegal drugs are not suitable for Federal employment.

This was the backbone and cornerstone of a deterrent-based program which focused on demand reduction for the flood of illegal, illicit substances that were entering the country at that time. This program was easy to establish because illicit drugs are just that - they are illegal and against the law. The complications of medical review were not a factor. For example, phencyclidine is a schedule I drug with no legitimate use as a prescription medication in the country or will it ever have.

The program focused on heroin, methamphetamine, THC, PCP, and cocaine, which are illicit, illegal drugs of abuse. At program inception, very few medications, such as Dronabinol today, conflicted with the mission and thus very few prescriptions had to be reviewed. The only issue was codeine and morphine which were alkaloids harvested from the opium poppy plant.

(Slide 3) The Drug-Free Workplace Program is a demand reduction program for Illicit, illegal drugs. In Section 7 in that Executive Order, the term illegal drug means a controlled substance, included in Schedule I or II as defined by that section and title of

the United States Code, whose possession is unlawful under Chapter 13 of that title. The term “illegal drug” does not mean the use of a controlled substance pursuant to a valid prescription or other uses authorized by law.

The Drug-Free Workplace Program tests for schedule I and II drugs. Heroin is listed as a schedule I drug while amphetamine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, methamphetamine, and morphine are schedule II drugs. A few of the prescription drugs discussed here do fall into Schedule II. Barbiturates fall into schedules III and IV while benzodiazepines are classified as schedule IV.

We are digressing away from our marching orders when we consider these other prescription drugs in the context of testing for schedule I and II drugs. This is the cornerstone for where we are now. I do not see any nexus of us moving ahead to test schedule III and IV drugs under the Executive Order that exists now under which we work.

MR. STEPHENSON: This meeting is for informational purposes. No one should interpret the purpose of this meeting to change what we are doing. We must be informed about what is out there and what the threats are to our everyday activities. This is a timely, appropriately-focused meeting. We have brought resources together that have never convened before so that we will be better informed about what is out there. This informational meeting is not a prelude to changes that will occur in the next few months. That does not mean discussion of prescription drugs is off the table, but it means it is not a clandestine march towards a specific goal right now.

DR. BUSH: (Slide 4) When the Mandatory Guidelines for Federal Workplace Drug Testing programs was issued as a final notice April 11, 1988, HHS adopted the

same 300 nanograms per milliliter cutoffs for opiates used by the Department of Defense for testing service members at that time. These levels were selected in an attempt to provide the greatest opportunity to identify anyone who may have used heroin. However, with experience, we learned from medical review officers that these laboratory-positive opiate results may not represent heroin use but instead the use of prescription codeine or morphine medication or the ingestion of dietary amounts of poppy seeds.

(Slide 5) How do we proceed with the prescription drug issue when our marching orders are for illicit, illegal drugs? The purpose of the drug testing program is to deter and detect individuals using illicit drugs. In the language of the preamble from the Notice of Proposed Revisions issued November 16, 1995, adjusting the cutoff for opiates to the proposed 2000 nanograms per milliliter and adding the requirements to detect 6-acetyl morphine at 10 nanograms per milliliter eliminated the identification of most persons using legitimate opiate-containing pharmaceuticals available by prescription, over-the-counter preparations, or poppy seeds.

(Slide 6) These changes to the Guidelines were done in a very systematic way and with laboratory derived data. The number of specimens tested in our laboratories at that time was about 1,100,000, of which 11,528 specimens initially tested positive for opiates. These positive opiate specimens were confirmed by GC-MS, and the number of specimens reported positive for morphine and or codeine totaled 7294.

(Slide 7) Remember, for these data, we were screening and confirming at the 300 nanograms per milliliter cutoff. The data was binned by concentration to determine a defensible break point. Based on scientific data, a logical, reasonable break point was

determined to be at 2000 per nanograms per milliliter for GC-MS. These data were never included in that November 1995 Federal Register Notice because, for the purposes of a proposal for public comment, the Secretary did not need it.

(Slide 8) To obtain the medical review officer's viewpoint, we harvested data from three medical review officer data sources. These data included approximately 317,500 non-federal and Federally-regulated specimens tested for opiates. The number of laboratory screened and confirmed positive results for morphine and/or codeine were 1294 while the number of MRO-reversed results was 1128 or 87 percent. The number of MRO-verified results was 146 or 11 percent. Nineteen results or two per cent were reported as unable to contact and one specimen was reported as rejected.

(Slide 9) Of those 1128 laboratory-positive results for either morphine or codeine, results that were MRO-reversed, 955 specimens or 85 percent, were due to the valid use of a prescription issued to self or others in the family. MRO-reversed results consistent with poppy seed ingestion totaled 134 or 12 percent. Reversals due to no clinical evidence of unauthorized use were 2 percent. Only one percent of the reversals were related to foreign pharmaceuticals from Canada where these medications were available by non-prescription from behind the pharmacist's counter.

(Slide 10) Remember from previous data that the number of MRO-verified results for morphine and/or codeine was 146. (Slide 11) The reasons for these MRO-verified results included non-valid prescription use of a family member or friend's medication. Ninety-six results or 66 percent were in this category. Clinical evidence of unauthorized or illegal use accounted for 15 results or 10 percent of those. The presence of the heroin marker, 6-acetyl morphine, occurred in five results or three percent. The use of

foreign pharmaceuticals, which represented 30 results or 21 percent, was dismissed as a valid reason at the time.

(Slide 12) With any future proposal to change or add to the Guidelines, this is the type of data evaluation that we must prepare. Why? Because the concept of reasonableness is right around the corner. Reasonableness comes to us in the form of the Fourth Amendment, which I have presented here in excerpted partial statements: "…whether a particular search meets the reasonableness standards is judged by balancing its intrusion on the individual's Fourth Amendment interests against its promotion of legitimate government interests…". I am very familiar with constitutional law because of the Fourth Amendment challenges to this program since its inception in 1987 and 1988. It has been well established that collecting urine for a Federal employee workplace drug test is considered a search under the Fourth Amendment to the Constitution.

(Slide 13) Another aspect of evaluating reasonableness is a special needs doctrine. This was developed by the U.S. Supreme Court through a series of cases permitting suspicionless drug testing in certain situations. (Slide 14) Under the special needs doctrine, the court identifies a special need, which makes impractical adherence to the warrant and probably cause requirements, then balances the government's interest in conducting the particular search against the individual's privacy interests upon which the search intrudes. Scientists in this program balance legal and technical testing issues with searching a Federal employee's urine specimen for legitimate medications, whether they are schedule II or certainly if they are schedule III or IV. This

balancing act will be problematic under our current Executive Order. Reasonableness will quickly come into play as a concept.

In the framework of our purpose, do illegal drugs mean misuse of a prescription? What about purchasing legal drugs, such as oxycodone or Vicodin, without a prescription on the Internet? How do we parse that away from this marching order? Is it covered under some umbrella? I do not know because I have not talked to our attorneys about it yet. These are the questions that I want to pose to you, keeping in mind the history of how we approached adding morphine, codeine, and 6-acetyl morphine and changing cutoffs while balancing our mission focused on illicit drugs.

Public Comment

Concerning a previously submitted question, “Does it matter whether a substance is legal or illegal, therapeutic or not? Rather, isn't it the concern of whether or not it has impairing affects and hence creates an unacceptable safety risk?”

This program was established as a demand reduction for illegal drugs. It had absolutely nothing to do with impairment or safety risk at work in the context of therapeutic drugs.

“Although urine drug test results do not indicate or correlate with a level of impairment, is it scientifically feasible to associate results of chemical urine drug tests with levels of impairment in the same way that a blood or a breath alcohol level is associated with intoxication?”

No. Urine, conveniently for us humans, is a fluid that is stored in the bladder inside our body until a convenient time for elimination. Urine is not in equilibrium with

the central nervous system (CNS) as is blood or breath for the purposes of ethyl alcohol testing interpretation. Though urine is still contained in the body, it reflects what happened in the past. In no way is that fluid in equilibrium with the CNS, hence impairment cannot be assessed.

DTAB Panel Discussion

MR. STEPHENSON: We are at the end of the day and at the end of a very powerful meeting. I hope that you are not all so numb that you do not have a sense of how you could take this to a next point. Where are there some natural nexus for the consideration or exploration? As members of our Board, interested members of the public, and Federal partners, looking at the history and a spirit of reasonableness, we have set ourselves upon that path with the discussions that we had over the last two days. We have generated a better understanding of what is out there. We have identified some opportunities for better understanding the elements of that relationship that could inform us if we were to put out a Federal Register Notice. But more powerful than that is a general understanding of where we are and what it is we need to do. I invite the members of the Board to inspect the things that are there and explore issues in your own mind of where are the holes in what we have presented. What are some of the unanswered questions that we should continue to explore in our future sessions? Are there thoughts that you would like to share even here today? Please search your soul and the spirit that you brought into this meeting and give us feedback if you can.

DR. ESTAPE: After listening to Donna's presentation, hearing what the MROs are doing, and listening to the other presentations, I realized that SAMHSA has done

much with drug testing and specimen collection. What will be the role of SAMHSA in regulating and providing guidelines to the MROs? I am very concerned when you see data on the variability in MRO reporting. We are so controlled and regulated at the laboratory level with inspections and collections, but what are we doing about the MROs?

MR. STEPHENSON: In 2004, we submitted a Proposed Notice for Public Comment and a subsequent Final Notice for Revisions to the Mandatory Guidelines. Some of those elements addressed both of the collection site and the MRO issues, including certification and documentation of competency to do the work that we are discussing here. Those are not going away. We will have further discussions with you on a conference call within the next month, but for purposes of this meeting, there is nothing else that we can say beyond the fact that the current Proposed Final Notice for the Mandatory Guidelines has been posted with the Office of Management and Budget and that it is undergoing review at this time.

Other questions?

DR. ESTAPE: I want to congratulate you for the meeting. I have learned much, and it was a great idea to have an informative meeting. We have heard so many things and truly we have to go back and think.

DR. BUSH: This meeting was Bob's conceptual idea about a month ago. The drug testing team and I asked ourselves how and what were we going to do this. It was a team effort that pulled all of this together. Graciously, every one of our presenters accepted the challenge to present another facet of this issue because it is so vast. In 2001, the National Transportation Safety Board (NTSB) and FDA held a joint meeting to

examine the effects of medication on vehicle operators. Their appendix, if you go on the website, has a safety recommendation from the Coast Guard that was issued March 2, 1979 looking at drug testing for prescription drugs. This issue has been around, so do not feel like we are alone or it is all brand new; it is not.

MR. STEPHENSON: Other comments from members of the Board?

DR. COLLINS: Again, I would agree that this introduces a whole new level of complexity into the program. It would force everyone to reexamine the purpose and the charter. It is a different program, and it is not just deterrence. Perhaps it is more of a fitness for duty program. How it is possible to manage that? Dr. Swotinsky talked about the challenge of changing physician behavior. There are many different pieces of culture that surround this that are going to be challenges. It is not just prescribing behavior but also public perception. You need a pharmaceutical; how you use your medication and how long you keep it are population cultural changes that will be challenges. Another challenge in introducing new compounds into the program is how you do that because there are so many pieces involved. Are the screening tests appropriate for the compounds that you want to test for? If not, how much time do manufacturers need to create a test that you can utilize? We are looking at trends, such as hydrocodone prescriptions. If you get to where everything is in place, have the trends changed? All those things are big challenges, and it is difficult to grasp how to possibly approach this and make it something that is manageable.

MS. GORDON: These are challenges that are not unique to this group. All states are struggling with this as they look at mandating legal limits for cases involving driving under the influence. There is a different complexity there, but they are the same issues

that the general public is becoming aware of, which is impairment with prescription medication. We are moving there, but it can be a pretty slow process.

MS. PIZZO: Bob, I brought two slides to show how adding the extended opiate panel would impact a single client that is doing testing nationwide.

MR. STEPHENSON: Are they available, Mike?

MS. PIZZO: First, a little background history on this client. This is a union client who was testing for codeine and morphine at the 2000 nanograms per milliliter cutoff. Their membership expressed a concern about a safety issue concerning the abuse of hydrocodone and oxycodone on the job site. They wanted an extended opiate panel, which included hydrocodone, hydromorphone, oxycodone, and oxymorphone at a 300 nanograms per milliliter cutoff.

(Slide 1) The first slide shows you the calendar year 2006, January through September. They had a total number of 707 positive drug results that year. Of those, only 5 percent were positive for opiates, which included codeine and morphine at a cutoff level of 2000 nanograms per milliliter. Using an average reversal rate of about 80 percent from MROs, their positive rate for opiates would decrease to about 1.4 percent.

With the 300 nanograms per milliliter cutoff expanded opiate panel, the positive ratio increased to 45 percent. If you use an 80 percent average reversal rate for opiates, the reversal rate decreases to about 9.4 percent, which is still an 8 percent increase. The companies' and the unions' concern was the money spent on MRO reviews when 80 percent is reversed. Was it really worth doing this? They realized they had 200 members of that union who were illegally using opiates in the form of either

hydrocodone or oxycodone. They then decided it was worth it from a safety risk and have continued to promote the use of extended opiate panels among unions.

MR. STEPHENSON: That is an interesting point. What it does point out is the need for us to explore, under a concept of reasonableness, what we are about. What is to be gained? Who is paying the bill? What is the burden, and it is appropriate? There are tremendous roles for deterrents, public education, and access to appropriate treatment. Both coerced treatment and an open door policy are needed to deal with issues around access to treatment, recovery, and ongoing support. Deterrence plays a powerful role if it acts as an encouragement to people to seek treatment.

This is a partnership that cuts across several different layers. In the prescription drug dilemma is the importance of professional education for the prescribing physician. We have those who receive those prescriptions, place them in medicine cabinets, perhaps do not properly secure them, and attend to other family members' and visitors', including younger kids, interest in them.

That is an area in which we need to pay increased attention. This is not a simple linear relationship to increase the number of drugs in a testing panel. It is a complex issue for society to deal with in the future. We have started on that path, but we did not initiate this because it has been around for a long time as an awareness. We found the best and brightest to share their data and provide us with their insights. We thank every single one of the presenters and the people around the table.

I want to say a special thanks to the RTI team, who along with the other contractors and logistic support, have made this meeting possible. Everyone has done wonderfully as a group. You have been tolerant, helpful, and provided insight to us that

we have captured. I particularly appreciate the insights from Larry Bowers and the issues around the concept of reasonableness and the way the testing process is approached. That was a powerful insight of how to get beyond the simple approach when it really counts. Collectively, we all have an opportunity to do more in this arena, and we will be working on this in the future given your help.

Are there any other comments? Donna, did anyone register for public comments?

Public Comment

DR. BUSH: No one has registered for public comments, but we should ask for a last call.

MR. STEPHENSON: Donna, do you want to call a close to the meeting?

DR. BUSH: If the Board has no other comments, at this time, 4:30 p.m. on August 20, 2008, we will close this session of the Drug Testing Advisory Board. Thank you much.

(Whereupon, the meeting was adjourned at 4:30 p.m.)