DRUG TESTING ADVISORY BOARD

OPEN SESSION

March 7, 2006

Agenda Item: Welcome/Opening Remarks

MR. STEPHENSON (Chair): I would like to open the Drug Testing Advisory Board meeting. We ask that the people who join us sign in at the back and let us know if you want to make a public comment.

The HHS Mandatory Guidelines have been delivered to the Office of Management and Budget (OMB) and they have been distributed to Federal agencies for secondary review and additional opportunities for comments. We know that several of the large Departments have received them, have processed them, and it is our belief have returned them to Office of Management and Budget. I happened to have an opportunity to meet with the OMB examiner about two weeks ago and it was acknowledged that they are there, so we expect to hear something back and we will go the next step with whatever is necessary from that point on.

In the scope of things, this is an extremely good sign and it is one that pushes us towards an end game process, so it is not a done deal yet, we are not all finished, I still cannot tell you exactly what is going to be in the final Guidelines but we are much further along and the process is still working in the way that it was intended to work.

There is a display that you all should take a look at when you get a chance and there is some interesting information that puts a picture to what it is we have been dealing with in the world of adulterants and substitutions and so on, at least in urine, and gives you a hint of what is already being marketed for hair and oral fluid. The display boards list a number of products, these were initially assembled for the Congressional testimony that we provided last May. It has been continued to be updated since then, it has been borrowed by some other Federal agencies to use in some of their presentations, it is being used currently.

MR. MCCUNE (NRC): The HHS personnel at SAMHSA were gracious enough to let me borrow the board for an NRC office display, the Office of Nuclear Security and Incident Response had a show and tell day where they showed the rest of the organization and the public what we did and we displayed the board there.

MR. STEPHENSON: The interesting thing was that sales went up 300 percent on most of these products after that, I do not know if it has any relationship but I hope that doesn't happen today. But the point being that this is a very interesting part of the process and it ties into what we are going to be doing today in talking about some of our PT samples and the processes that we are dealing with alternative specimens, some of the things that you are going to hear about today. They are all related and it seems like we have the attention of the folks that are out there in the regulatory and the law-making part of this business and some of the enforcement arena, so we can only hope that that is a continued interest that will get some results in the not to distant future.

I needed to open the door literally and figuratively and indicate that in the

aftermath of Katrina last year we had lost access to one of our labs, a Kroll Lab, in Gretna, part of New Orleans complex area, and not only were the staff displaced and their homes flooded but the businesses were shut down and roads were denied access to for long periods of time. We were successful in getting an inspection team in the middle of some interesting weather and Kroll has rejoined us as a certified lab open for business again. I would like Pat Pizzo to make a couple of comments if she so chooses about where the status of things are down there.

MS. PIZZO (Board member): First, I thank all of you for helping us get our certification back as quickly as we did, the whole program made a concerted effort to help us get certified and back into testing as quickly as possible. We are back and operational, the city itself is going to be a long time in coming back as I am sure you all realize from seeing the news. It has been an interesting experience and one that we hope not to have to go through in another 40 or 50 years. It was a massive undertaking to go from a gutted building to a certified lab in just three months, so it was an interesting experience and one that I will long be retired before I do again. Thank you.

Agenda Item: HHS Update

DR. VOGL (DWP): We have a flier announcing an NLCP workshop to be presented this summer. It been sent out to the laboratories in our program and other interested parties. We want to make sure that the public is aware of it and are hoping that some of the alternative specimen laboratory people would be interested in attending to get a better understanding as to what is involved in the certification program which will eventually apply to the other types of testing. I hope you can take this back with you, share it with people that you think are interested in attending, and be sure to contact RTI, it is limited to 25 attendees. As it states, if there is a lot of interest there might be an opportunity to present the material more often or at least again in 2007, but we will see how that goes as far as what the interest is.

The next item is our website. Our website is workplace.samhsa.gov and we try to keep it updated, especially all the DTAB material, the transcripts, the agendas, and the meeting schedule. The only information on the schedule besides the date is that the meeting is in this building. You do need to keep view the Federal Register notice when it comes out because that notice tells you when the open session is for the meeting. We also attempt to contact all the people who attend the DTAB meetings on a regular basis by email, usually three or four weeks before the meeting so they are aware when the open session is and what some of the topics are, and can then contact our administrative assistant as far as getting access into the building. It takes time to get people through building security. It is important that we have a prepared list of people who want to attend. It makes it a lot easier to get into the building.

The website is being migrated from one type of software package to another. Half of it has been migrated while the other half has not. When you do go to workplace.samhsa.gov site, it flips to dwp.samhsa.gov, but it is the same website and eventually when everything is migrated then it will stay as workplace.samhsa.gov. If you look at the link, you might think you are no longer on workplace.samhsa.gov, but you are. It is taking quite a bit of time for the IT folks to migrate everything to the new package they are using for the website.

On February 22nd we published a Federal Register notice regarding the

Federal custody and control form. For those who use the form, the use of it expires on July 31, 2006. We are in the process of getting OMB to approve a three year extension of the use of that form for urine testing and this notice is part of the requirement on our part to allow the public an opportunity to submit any comments on the form. We are not changing the form. I have already received calls from a few people asking why we are changing the form. We are not. If you read the notice, it is not changing the form, it is strictly providing the burden hours that it takes to fill out the form and for a couple of other items, like the lab application, and so there is a 60 day public comment period. Once that ends, we will forward the entire package to OMB and hopefully they will clear it in time for us to continue using the form after its current expiration date.

MR. STEPHENSON: I know that this is not part of the agenda, but I would like Ed Jurith from ONDCP to make any comments.

MR. JURITH: Thank you, Bob. It is a pleasure to be here with you all this morning. As you know, the issue of drug testing is important to the President's National Drug Control Strategy. Director Walters and the Administration have placed an emphasis on student drug testing to give school district administrators around the country an additional tool to help students avoid the lure of drugs. We have found looking at the research, looking at the experience of many school districts around the country that schools that have effective student drug testing programs in place give students an additional tool, an additional reason to avoid the peer pressure and the other consequences that may lead them to experiment with drug use. I think the support of the drug testing community in general in terms of providing good technology, good lab certification, best practices, is a help to the schools that choose to use this tool, not in a punitive sense, but really in an identification and an intervention sense to help students avoid drug abuse.

Agenda Item: Nuclear Regulatory Commission Update

MR. MCCUNE (NRC): I would like to start off by reiterating a statement I have made a number of times and, that is, the DTAB and the assistance role of SAMHSA for Federal workplace drug testing programs is critical to just about every other government agency, the NRC included. We have incorporated many of the current testing and processing requirements from HHS into our current policy, 10 CFR Part 26, Fitness For Duty Programs.

I would like to give you an update of where we are with the Part 26 since the last DTAB meeting in December. The public comment period closed on Part 26, we are currently still in the process of incorporating comments and deciding how to address the concerns of the stakeholders that did comment. One of the chief areas that I think is going to be the biggest challenge to us is what kind of drug and alcohol testing requirements we have for our licensee plants during construction. Since the current Part 26 was developed in the 1994 timeframe really up until recently, about a year and a half ago, the NRC had no plans to build new reactors and so licensees really were not considering Fitness For Duty or any other policy that would impact that process. As you are probably aware, through the President as well as the NRC we are onboard for an expedited combined licensee process that really will have designs approved within the next five years and new reactors being built. So the focus on all policy, not the least of which is how you implement Fitness For Duty during construction, is really foremost in

the industry's mind, in the NRC as well.

We have determined without going into too much detail because our decisions are yet made public that to have when the first bulldozer shows up at a green field site a full up and running Part 26 program which is full access authorization and Fitness For Duty testing and monitoring may not be feasible and so what we are trying to do is work with the industry to develop kind of a middle ground for which we can ensure that Fitness For Duty exists on construction sites for nuclear reactors but doesn't present an overly onerous regime for which licensees really cannot comply. I think it is safe to say that we believe at the NRC that standard drug and alcohol testing programs that are evident in the construction industry as a whole are really not appropriate because we are not building office buildings, we are building nuclear reactors, and we want to make sure that we use due diligence to ensure that design flaws or our adversaries do not have the opportunity to build into nuclear reactor designs or construction things that should not be there.

Within the next month and a half we will most likely have a public meeting because the construction requirements for Fitness For Duty regarding Part 26 were not fully understood in the fall when the original rule went out for public comment. We are likely going to have another public meeting so that we can roll out our new concept for Fitness For Duty during construction. And that remains other then some relatively minor aspects of the policy, the major sticky wicket if you will, but I will tell you that it is our responsibility as it is really other government agencies to evaluate current SAMHSA and HHS policy for incorporation into their programs and so we are working very closely with SAMHSA and HHS, we are very interested in alternative specimens, and somewhere down the line we will be doing a revision to Part 26 that will implement alternative specimens and other cutting edge HHS policies as they are applicable to the NRC.

Agenda Item: Department of Defense Update

COL SHIPPEE (DoD): I didn't expect to be sitting at the front table here so I have nothing prepared. But listening to Tim's comments, as you know I've talked with SAMHSA, DoD has looked at alternative specimens and saying it is not for us. As you know, we have a big leg up on everybody else because we do observed urinalysis testing so the impetus there for us to look at other methods has not been that important. However, in the last year or so I have been coming under increasing pressure to get more bang for our buck, there is no more money added to my budget, but I have to do more like everybody else. I have looked at the military accession process, the entrance stations, there are 65 stations around the country that bring new recruits into all the services, and by our directive they have to do a urinalysis before they come into the military. I have looked at that and asked myself why couldn't we use saliva testing or oral fluid, for example, because we do not litigate those and we have never had a Congressional on a urinalysis drug testing in the MEPS situation. In that light, I turned to the command that runs the MEPS, and offered this up. In looking at the literature, I suggested that maybe what we ought to do is just run a pilot study and they agreed.

We have been at this for the last year and a half, looking at the Orasure collection device, mainly because we have had a contract with them for reagents at the Armed Force Institute of Pathology, that is the reason we went that way, and we are going to look at, we are going to collect the oral fluid, along with urinalysis, we would

not hold the applicant liable for the oral sample, it is just for the urinalysis, and run this for probably about a year. We are set up to collect about 30,000 specimens.

It will be a nice study because I have tight control over both specimens. I will be able to link the oral fluid with the urine very positively, and we will monitor as we go along. As we get data, we will share that with SAMHSA.

MR. STEPHENSON: That is wonderful news. That's the kind of contribution that means a lot both now and will continue to contribute later on as we get into the systems development.

Agenda Item: Department of Transportation Update

DR. VOGL: I contacted George Ellis (DOT) and he responded by email that he would not be at the meeting. He did provide, in his email, a couple of items to present this morning. He wanted to thank people for submitting comments to the DOT proposed notice of rulemaking. As you are aware, they put out their notice soliciting public comment to incorporate specimen validity testing into the DOT regulations. He goes on to say that they received over 200 comments from actually 27 different commenters, so obviously many people commented on more then one issue. He believes the comments, wanted to say the comments were helpful, appreciated the public interest, and they are presently working on organizing the comments and working on their development of the final regulation, of course, as we know those things do take some time.

He wanted to mention that they are about to release another proposed notice of rulemaking to allow marriage and family therapists, who are credentialed, to become substance abuse professionals, better known as SAPs, into their program. He expects this to come out in the next few days and again it would be for public comment. I am sure they will receive responses on that request and then move forward with eventually coming out with a final rule.

Those are the two items, that if he were here, he wanted to mention this morning.

MR. STEPHENSON: At this time we are going to ask you all to take a deep breath and get ready to be plunged into a lot of scientific data and graphs and images and the purpose of these two presentations is very well focused, it is to take what it is we have learned, what it is we still do not know and have to learn in the process of addressing alternative specimen proficiency testing and controls development and designs. It is not an issue of just showing problems or the current state, but to give us a benchmark from which to develop an agenda to how to go forward. It is our goal and intention to take action across a number of arenas and you can certainly participate in that process as we go along.

Agenda Item: Pilot Performance Testing (PT) Program for Hair

Note: The PowerPoint slides for the following presentation are attached at the end of the transcript.

DR. MITCHELL (RTI International): We will begin with the Hair Pilot PT Program that we have been running and the most three recent cycles that we have had, that's cycles 9,

10, and 11. Dr. Jeri Ropero-Miller is now the primary person in charge of the Hair Testing PT Program. She has been with RTI for approximately a year, and this is the first three cycles that she has designed and has carried out. We will look at the results, it is no longer my bias as some people might think.

I regret that a lot of this is going to be very technical. We tried to provide sufficient explanation and to look at things different ways to try to increase the understanding of this by everyone, technical and non-technical.

Slide 1 – Title – NLCP Hair Pilot Performance Testing (PT) Program Update Cycles 9 Thru 11

Slide 2 – Objectives

The objective of today's presentation will be to review the design and results of hair cycles 9 thru 11. As kind of an academic but yet informative process, we are going to compare the results of these three cycles to the requirements of the proposed Guidelines from April 2004. We have to remember that these are not the final criteria, but they are what HHS published in April 2004, and also to disseminate future plans for this program.

Slide 3 – Pilot Hair PT Program: Design of Cycles 9 Thru 11

Slide 4 – Pilot PT of Hair: Cycles 9 Thru 11

We will begin with the design of cycles 9 thru 11. In this cycle, we did some things a little bit different, we are always working on the technology of producing the samples themselves and in this one Jeri chose to do something that I did not attempt and that was to put all the amphetamines into a single hair preparation. As you can see that the first sample, or the prototype of the sample contained amphetamine, methamphetamine, and the designer drugs MDA, MDMA, and MDEA. This is the first time we did it and she was very successful in accomplishing the spiking the hair at the levels that we desired.

The second type of sample that we produced was one that contained cocaine, cocaethylene, which is a purported metabolite from people who take cocaine and are also partaking of alcohol, and also another purported metabolite norcocaine. We did not include in this sample benzoylecgonine or BE as you see in the third prototype because one of the problems with cocaine that we found early on in urine is that it can degrade or can be hydrolyzed to benzoylecgonine during extraction procedures. We wanted to look at the ability of the laboratories to extract cocaine from the hair matrix and were they or how good were their procedures such that they did not hydrolyze the cocaine to BE.

The fourth type of sample would contain the opiates including 6-acetylmorphine which is a purported metabolite of heroin, codeine, which we are all familiar with, morphine, and oxycodone, and one of the reasons for oxycodone was to see if this particular compound would interfere with either the determination of morphine, codeine, or 6-acetylmorphine. The fifth sample was PCP, contains PCP, and the last of course, our favorite from urine, the marijuana metabolite, 9 carboxy-THC.

Each of these samples were formulated at three concentrations, we had

one in which the concentrations of analytes would be at 50 percent of the proposed cutoff, that is, the proposed cutoff that was proposed in April 2004, at around the cutoff, and at a concentration above the cutoff, somewhere around 200 percent of the cutoff.

Slide 5 – Pilot PT for Hair: Cycles 9 Thru 11

In these samples, they were not really formulated for initial testing, they were more for confirmatory testing so we did not require or did not ask for initial testing with immunoassay of these particular samples so the only results that we have will be confirmatory results. In doing the confirmatory test we asked the laboratories not to conduct their decontamination procedures that they use to try to remove analyte from the surface of the hair, we had found in previous cycles that using these caused a great deal of variation that we could not account for.

The shipment consisted of 19 spike samples as well as 2 user drug strands. We had one that contained THCA and another one which contained some of the opiates. We sent to the laboratories samples containing 50 milligrams of sample and the reason for this is that even though the Guidelines call for the collection of 100 milligrams of hair the laboratories would not be able to use that if we continue with the split sample criteria, that is, there would be part of that sample that would be reserved for the individual or the donor who was being tested, so 50 milligrams was what was the total amount that we sent to the laboratories to conduct their testing.

We requested that the laboratories submit their results to us within 10 days of receipt and they did a very good job this time of getting the results back to us.

Slide 6 – Pilot PT for Hair: Cycles 9 Thru 11

We shipped the samples in the timeframe from July through December of 2005. There were three shipments sent on alternate months. We had 9 participants and we did not inform the laboratories of their performance until after cycle 11 had been completed.

Slide 7 – Cycles 9 Thru 11 of Pilot Hair PT Program: Confirmation Analysis

When a lab is to be certified or applies for certification, one of the things that is important is that they meet certain criteria. I have laid out some of these criteria just so we could look at them and look at the participants. The first one, by the way, we just have the laboratories, we do not have their names, we just have a letter designation, some of the laboratories were aware among themselves who participates but not everyone is aware of everyone who is participating in this program and there is no requirement for that.

We asked the laboratories to provide us some demographics of their testing. The first one is how much sample do you need in order to conduct drug, confirmatory testing for one drug. You can see that we had two laboratories that required the entire sample amount to do confirmation for one drug class. That is excessive and would probably not be acceptable in a certified program, it is just too much and it means the laboratory couldn't conduct initial testing to begin with and then if they had more then one drug class they wouldn't be able to conduct another confirmatory test.

You can see that the others, and this is something that's very nice, is that the levels that are required have come down to somewhere between 10 and 20 milligrams per test, which is getting in the range of acceptability. The thing that we start running into is the sample decreases, there is also the problem of measuring that sample and weighing it and 10 milligrams requires at least some specialized equipment like a five place, at minimum of a five place balance and other things. That is all to be considered in the certification process.

Second, is the sensitivity of the assays and the confirmatory tests that they're using. Are they capable of meeting the cutoff levels? In urine we require the laboratories be able to confirm down to 40 percent of the published cutoff, that has not been established yet in the hair, but I would expect that if a lab had a LOQ exactly at the cutoff that that would not be acceptable. Those are some standards that are yet to be set, but as you can see we had three laboratories that were unable to meet the cutoff level with their confirmatory process.

We also had going to the next column current urine analytes, we thought it wouldn't be fair at this point in time to always just look at all analytes and not consider the fact that the procedures, confirmatory procedures for certain analytes have been worked out with urine and they've been extended into the hair and oral fluids, and so, and they were the first ones that were worked on in the laboratories. We are looking at the current urine analytes that will be analyzed in hair and you can see that most of the laboratories were able to analyze for those even though their cutoffs might not meet the LOQ requirements. We only had one lab and they could not confirm for the 9 carboxy-THC.

Under the proposed analytes this deals mostly with cocaine which is not currently tested for in urine, norcocaine and cocaethylene, as well as the designer amphetamines, MDMA, MDEA, and MDA. You can see that some of the laboratories are still in the process of developing their procedures for these particular analytes and currently do not have them ready to be utilized in a testing program.

Slide 8 – Cycles 9 Thru 11 Highlights

In the past, our focus has been on the variation around a group mean and that is looking pretty much at the accuracy of the program of the participants. We are going to do something a little bit differently, we are going to look at the precision of the individual laboratories today and so we'll go through this, it is a new concept that we have talked about ourselves and tried to come up with a way to explain this. As we go through this, we'll see if we can get this concept over because we are also going to look at the same thing with oral fluids a little bit later. Also, we are going to look at the performance of some selected participants and these are participants who had more then, had analyzed these samples outside of the pilot PT program, and let me explain that before we get into it, it is not necessarily an advantage for a laboratory because laboratories that we use to give us some idea of our spiking process, whether it worked or not, they're given a lot of samples, some of which may end of being used in the program and some which may not, so it is really not an advantage from that standpoint.

The reason we need to do this is that with hair there is no way to tell at this point in time how much drug went into the hair when we spike it. In urine, we can put a known amount, put a known amount into a volume and from that we can determine concentration, but in hair that's not possible at this point in time, we do not have the

technology. We depend upon laboratories to give us a ballpark figure as to where, how much analyte we got into a particular hair preparation, and so some of the labs that we are using that have more tests then were conducted inside the pilot PT program were asked to do this, unknown to them they tested these samples prior to the PT program.

Slide 9 – Distribution of Within Laboratory %CVs for All Laboratories for Amphetamines from Cycles 9 thru 11

First, we are looking at within laboratory percent CVs. The coefficient of variation we use to look at the variance of values around a mean, for example, in this particular part of the program the laboratories received the same sample three times, once with each cycle. We took the three values, we determined a mean, and then we determined the standard deviation. The coefficient of variation is merely an expression of that standard deviation as a percent of the mean, and so it tells us well those values are within plus or minus say 10 percent, or 20 percent of the mean, of the labs own values. We are not looking at the lab, and so this ends up being kind of an indication of precision that the laboratories were able to show during these tests.

In the column here, we have the five different amphetamines, we have amphetamine, methamphetamine, MDA, MDMA, and MDEA. These are the five analytes that we had in the hair. One thing that we can see here is that the variation for individual samples varied. Now we are not showing whether there is no indication of whether this particular sample was one at 50 percent of the cutoff or at the cutoff or 200 times the cutoff, it just says that that is a sample that was analyzed three times and the variation in the analysis of that sample by that lab was looks like about plus or minus 90 percent of the mean of their three values, so that is a pretty high variation.

But the thing that I would like to point out is that down here we have a lot of labs that are analyzing samples well within what we would consider acceptable variation, somewhere around plus or minus 10 to 15 percent. And we have that on each of the samples even though it somewhat decreases as we go across into the newer analytes and that's because probably we do have fewer determinations that have been made.

One of the problems that we have always been worried about with the hair since we do not know what's in there, I mean exactly the amount, the question is are the preparations so variable that laboratories will never be able to get precise results, that is, consistent results from one test on one day to one test the next day or a month later, and it looks like yes, we will be able to obtain with these preparations samples that will give us the uniformity that we need in order to run this program.

Slide 10 – Accuracy and Precision

Maybe I should have started off with this slide, but I thought since we have seen it, let's talk about the difference between accuracy and precision. In the previous slide we were looking at precision, in precision all that tells you is how are the values grouped about a point. You can see here we have precision, but we also have very low accuracy, if we had accuracy it would be like precision and accuracy would be distributed around a known point or a point that we are trying to obtain. Accuracy on the other point talks about how well do the values, the individual values when grouped together predict the value that they are supposed to represent. Over here we have very

low accuracy because you can see if we tried to average these the middle would be somewhere in there, so it is off of the center point.

These we have low precision, you can see we have scatter but they're scattered about the point that we desire in a pretty uniform way and therefore we have accuracy but we have imprecision. When we look at the individual CVs within labs, we are looking at either this point or this point, we can be looking at essentially what is the precision of these labs.

Slide 11 – Precision versus Accuracy – Amphetamine

To go into this a little bit further we took some results from the amphetamines and we determined the accuracy and precision using these CVs. This represents the three values that were reported by a laboratory and we can see here that this is within plus or minus, these values are within plus or minus 10 percent of the mean of those values. However, by accuracy the mean differs from the mean of these values, differ from the actual mean by 26 percent.

In going up, we see that with these three values we have a precision of 8 percent but the accuracy, how much they vary from the true value that we are looking for, is 33, and again we have real precision, we are down to 4 percent, but the accuracy is off at 41 percent. Now these values, this does not reflect a single laboratory, we picked examples which were going to point out what we wanted to point out here this morning as far as accuracy and precision, so do not try to infer any of these values to a specific laboratory.

Slide 12 – Methamphetamine %CV Across Laboratories

We can look at the CVs for each of the samples for methamphetamine for each of the laboratories and these are the within lab CVs again. One of the things that we are looking for is what is the distribution of these samples within the CVs. One of the kind of things that scientists think about is that the higher concentration within certain limits then the better you're able to determine that value, and so we are looking to see if we have some type of bias within the system toward the higher levels, and the higher levels is the green, and you see that we have green at high concentrations as well as, I mean at CVs as well as the lower CVs. We can see the same thing with each of the samples, at the samples at 50 percent of the cutoff you can see that we have labs which are able determine them within 20 percent easily, we have others that are not. We do not really a see an overall system bias due to the concentration, that is lower concentrations are not as easy to determine as are higher concentrations, we do not see that in this particular system.

Now for a point of reference, we have been talking about CVs and in hair we are talking about CVs within laboratories, we want to try to show you what's going on in the urine labs to give you a point of reference and the urine of course is a mature industry, we have been going since '88 with this program and so the laboratories have standardized their procedures pretty much, they've developed all the processes that are needed.

Slide 13 – Distribution of Between Laboratory %CVs for All Urine Laboratories from Occasion 77

Here we are not looking at within lab, we are looking between lab or among lab CVs. And they can vary, if you have labs that are out, if you're looking at the population, you can see much greater variance in these and that's one of the reasons we are looking at the intra or the within lab CVs with hair today. With urine you can see that the CVs of the samples, and we had five different samples for each analyte, this being amphetamine, methamphetamine, THCA, BE, codeine, morphine, 6-acetylmorphine, and PCP, and you can see that the CVs across the urine system are down around 10 to 15 percent overall, which is very good, and that's where we'd like to see hair and oral fluid as they mature.

Slide 14 – Between Laboratory Performance on Urine PT Sample 2009 for Amphetamine

If we take the amphetamines and we look at the distribution of the 50 labs and their values around the mean of this particular sample we'll see that they all lie, well, most of them lie within plus or minus 10 percent, and that's what we'd like to see in hair is that most of the values will lie within plus or minus 10 percent and certainly within plus or minus 20 percent is the goal that we have.

DR. NIPPER (Board member): I just wanted to ask you about the X-axis on that chart, that's just the, from left to right that's just the number of the laboratory that was doing the testing? That's not day to day or time or anything like it is usually on the laboratory chart?

DR. MITCHELL: No, this is kind of a chart that we made up, what we did was we plotted the values for the laboratories, we just numbered them one through 50 at random and then put their values, plotted them on to this. This was just to illustrate the type of distribution that we see in the PT program for the urine with amphetamine at this point in time.

Slide 15 – Distribution of Within Laboratory %CVs for Cocaine and Related Compounds from Cycles 9 Thru 11

Okay, I think we have talked enough about amphetamines, let's look at some of the other analytes within hair. You can see that this is dealing with cocaine and related compounds, we have the cocaine, CE, BE, and norcocaine, and again we are looking at the percent CV and each one of these representing three determinations on a single sample over the three cycles by a single lab. And you can see again that we have a number of laboratories that are able to obtain values that are down around the 10 to 15 percent. In norcocaine you see is actually pretty good, but we only have 9 determinations so there is a limited number of labs that are doing this at this point in time. We do have some acceptable precision with these particular samples.

Slide 16 – Distribution of Within Laboratory %CVs for All Laboratories for Opioids from Cycles 9 thru 11

Looking at the opiates, again a similar situation as far as the distribution,

we have some that are down below 20 percent but we also have variation that goes all the way up to 60 percent, for in this case it is the codeine, and we are dealing with morphine here and 6-acetylmorphine.

Slide 17 – Distribution of Within Laboratory %CVs for All Laboratories for THCA and PCP from Cycles 9 thru 11

THC and PCP, THC as you realize is always in the urine over the years has been shown to be very variable and difficult to spike into samples. I think part of what we are seeing here is that, but also if you'll remember the concentrations that we are looking at in hair are, for the cutoff is 1 picogram/milligram which is, we are moving into areas of trace analysis in essence and so we would expect higher variation if the instrumentation is not capable of analyzing those samples. Also we are looking at other variables such as weight and extraction efficiency from extraction distraction which would affect these.

PCP is the old standby, but we do have considerable variation even with the PCP.

Slide 18 – Comparison of THCA %CV Across Laboratories

Looking at the across lab CVs of the four different samples you can see that we have considerable variation and we have some labs that were unable to do this. Some labs were able to get down to the cutoff but couldn't go any lower, also some labs missed a 200 cutoff, 200 times the cutoff, so this would indicate that the procedures really have matured for this particular analyte at the cutoffs that we are looking. We have some labs that are able to go down to the 50 percent of the cutoff, which would be 0.05 picograms/milligram, and we have others that are not able to reach that.

The human hair, user hair here, is a fairly high concentration, it was up between .8 and 1 picogram/milligram of hair.

Slide 19 – Performance with Amphetamine

Let's look at, change the way we are thinking and let's look at a couple of things. Remember I said we were going to look at the performance of selected laboratories, and these are laboratories that had more then three analysis of each sample. We are looking at the, this blue is the mean of their determinations prior to the PT sample being sent out. The mahogany color is the mean of the total, of all the laboratories over the three cycles. And then the white is the, one of the laboratories, its mean and standard deviation, and I didn't point that out. This little extension on top of these bars is an indication of the standard deviation for those particular, for their determinations. And of course is the second lab.

As you can see that with this amphetamine we had fairly high standard deviations overall, at the higher concentration, and it did not improve as we went down, in fact one lab as we went down in concentration seemed to have some problems in quantitating the sample and their variation was very high. The other lab on the other hand had fairly tight down here standard deviations as we can see for amphetamines. Now amphetamine I believe was about the best, the amphetamines are about the best that we had overall.

Slide 20 – Performance with Methamphetamine

Methamphetamine, now methamphetamine is one that when we started this program many of the laboratories were analyzing for methamphetamine but not for amphetamine. I think that's reflected in that we see at the lower concentration fairly good CVs on methamphetamine indicating that these laboratories overall, including the group mean, have the capability of analyzing the methamphetamine at the concentrations that we are expecting to utilize in the Hair PT Program.

Slide 21 – Performance with MDMA

MDMA, here we see some variability in the means of the laboratories, this lab appeared to have a little bit of a high bias. We can see even though the standard deviation for the determination by these two labs at the beginning was fairly tight. But overall the standard deviation appeared to be fairly constant throughout the three concentrations that we looked at with MDMA.

Slide 22 – Performance with MDA

MDA again, a similar situation in that we saw differences in the standard deviations of the variability among the labs as well as their ability to quantitate this even though they had been involved early on in a separate determination with a very tight CV between these two labs.

Slide 23 – Performance with Cocaine

Cocaine, on the reference mean we did not have sufficient values to determine a standard deviation so that is why this extension is missing off of here. But we can see that the standard deviations, group standard deviations at the higher concentration are higher, slightly higher then that of these two individuals, but overall when we get down here the variations are very small. One of the things that we did see is that there is very little conversion of the cocaine, there is some but very little conversion of cocaine to BE.

Slide 24 – Performance with Benzoylecgonine

And for the samples that were BE only, did not have cocaine, we have no contribution from hydrolysis of cocaine, we see that there is overall when we first analyzed these samples we had a fairly high CV, or standard deviation, the group mean was about the same, and the individual labs seemed to have that same type of problem. And this was exhibited all the way through both concentrations.

Slide 25 – Performance with Cocaethylene

Cocaethylene, you can see at the higher concentrations we did pretty good, but then we had down here, this is the type of variability that we'll see, all at once we'll have outrageous values show up and I believe this was one laboratory if I remember

correctly had, reported a value which was nonsense, it was so high that it was nonsense, but yet it has to be included in the mean to demonstrate the type of variation that we can see on samples in hair.

Slide 26 – Performance with Norcocaine

Norcocaine, we see the same thing here. On two samples we had outrageous values, on another one we have a very tight CV and that's pretty hard to explain when we are looking at a PT program.

Slide 27 – Performance with Morphine

Morphine, we had high CVs in morphine. The question is is there something happening to morphine in the hair. Overall, we had fairly high standard deviations or variations for the morphine, whether it was in the initial testing or whether it was during the PT program and so that is something that is going to take better precision for us to be able to, across the system for us to be able to understand what's going on.

Slide 28 – Performance with 6-AM

6-acetylmorphine, there appeared to be some loss of material but if you look at the group mean versus some labs but other labs it appeared to be on, so here we get a mixed message from the analysis as being conducted as to what the true value of the 6-acetylmorphine is in a particular sample. We see that all the way across the three and that yet has to be resolved.

Slide 29 – Performance with Codeine

Codeine, again we are seeing the typical variation in the group mean meaning that we have individuals in the system which have an extremely high variability. The two labs, their variability as a percent of their mean varies from sample to sample for codeine as it does with other analytes.

Slide 30 – Performance with PCP

PCP, this is always, to urine has always been what people though it was a gimme because it was fairly easy to extract from urine and was not hard to quantitate. But with hair at least at the higher concentrations some labs appear to be having problems, as you can see even the selected labs which provided some of the initial testing have some issues associated with their values. Overall the PCP, especially at the lower levels, appear to be fairly good at least for these two laboratories, so it is attainable.

Slide 31 – Performance with 9-Carboxy-THC

9-carboxy-THC, I have the three spiked samples here with the concentrations down around the cutoff and lower, and you can see that the group mean varied a great deal and I think that's because of the methodologies that are being used in

the laboratory, we haven't, it is a challenge to get down to the 0.1 or lower concentration. I think these variations that we see by these two labs are indicative of the type of performance that we can expect and you can see here even with one of these laboratories that gave us the initial value, which had a mean down here, their mean is high when we look at their performance over three cycles.

With the user hair we see the same type of variation, we would expect that. One of the problems that we have with user hair is the values that you can see in user hair will be somewhat dependent upon the drug use patterns and since it is deposited from the blood into the hair and so we would expect overall to see higher variability in user hair then we would in spiked hair if we can get it in with spiked hair. So that's why we have been working primarily with spiking the hair to try to get uniform concentrations across the hair. Again, with THCA, we are not only dealing with concentration problems, we are dealing with THCA problems, that is the inherent instability of that particular analyte.

Slide 32 – Performance with Opioids in User Hair

Performance of the opiates in the hair. You can see that with morphine we had considerable variation, looking at it again, and this is the user hair, we had the morphine and the 6-AM is much higher in this particular one but you see the variation is still very great. Now there are a lot of user hairs we know from experience and talking with lab, hair drug testing laboratories, is that in a person who is using frequently that very, very high concentrations of these analytes are found especially 6-acetylmorphine. However, we do know that in use by or recreational use of heroin, it may be chipping, I guess it is commonly referred to as chipping, they may use one or two times in a weekend and that's it and so only you would have very spotty deposition into the hair and you could end up with very low concentrations. And for the users we have never had a problem, I mean the people who are addicted we have never had a problem, cocaine or heroine in urine, we haven't a problem detecting them but now with hair we do have possibly the capability of looking at use over a longer period in people who have used smaller amounts or infrequent use.

Slide 33 – Performance Testing and Certification of Hair Testing Laboratories

That is the first part of looking at the actual data, let's look at some summaries. Before I do that I'd like to review the scoring guidelines for a laboratory that is trying to become certified, and this is the initial hurdle that hair testing laboratories will have to go over before they can become certified. Again, I am using those proposed regulations from the April 2004 Guidelines.

Slide 34 – Section 9.6

Section 9.6 says what are the PT requirements for an applicant laboratory to conduct hair testing? It starts off with an applicant laboratory that seeks certification to conduct hair testing must satisfy the following criteria on three consecutive sets of PT samples. One is have no false positives, now these really are essentially a direct conversion or use of the current ones that are applicable to the urine drug testing

laboratories. Second, one is correctly identify and confirm at least 90 percent of the total drug challenges on the three sets of PT samples.

Slide 35 – Section 9.6 continued

Three, would be correctly determine the quantitative values for at least 80 percent of the total drug challenges, that means all challenges, all drugs, to be within plus or minus 20 percent or plus or minus two standard deviations of the calculated reference group mean. So of all the challenges that are given they have to identify and quantitate them within 80 percent of the group mean.

Four, have no quantitative value on a drug concentration that differs by more then 50 percent from the calculated reference mean.

Slide 36 – Section 9.6 continued

Five, for an individual drug, say for amphetamine, they must correctly detect and quantify at least 50 percent of the total drug challenges. By correctly detect and quantify, the quantify means within 20 percent of the mean.

Slide 37 – Laboratory Performance Compared

Okay reviewing all that, applying these standards to what we have seen in cycles nine through 11. Okay, first, we had no false positives reported however remember they were directed by drug class so they knew which drug class to test in the sample and there was no initial testing which could have thrown a sample which contained no drugs into a confirmatory batch. There was some restrictions on that but those things will be looked at a later time.

Two, two labs correctly identified 90 percent of the analyte challenges over three cycles. Now I thought that we ought to break that out a little bit and look at the current urine analytes and see if there was any difference and we did. When we look at only the urine analytes we found that 5 laboratories met this criteria, they were able to identify 90 percent of these challenges. When we were looking at the new analytes, that is cocaine, norcocaine, cocaethylene, MDMA, MDA and MDEA, two laboratories were able to meet the criteria for these analytes. We will have some work to do within the system at these other, with these other analytes.

Slide 38 – Laboratory Performance Compared (continued)

No laboratory quantitated 80 percent of all analyte challenges within 20 percent of the mean. All laboratories had one or more 50 percent quantitation errors. And no laboratory quantitated 50 percent of all individual analytes within 20 percent of the mean. We have some work to do and that's what I am trying to point out to the laboratories by this is that we have this hurdle, we have to determine how we are going to get there.

Slide 39 – Pilot Hair PT Program

I think the first cycle that we sent out was in 2000, the purpose of the Pilot

PT Program was to provide information on the state of the hair testing science, to help guide the development and implementation with expanded mandatory guidelines. And under that we had to develop appropriate PT materials for the certification program and that was part of the purpose. It was also to provide the opportunity for interested labs to develop accurate and precise test procedures before implementation of the expanded guidelines. I think we are still working on this one.

Slide 40 – Variation in Hair Pilot PT Results

And the reason we are working on it, we are seeing large variation existing among labs, and this is not within labs, among labs, and possible reasons are that the labs are using a variety of methods for preparing the hair for analysis, we have labs using powders, we have powdered hair, we have snippets, we have solubilization. We have to come up with the process that is best and we are going to have to standardize that, the process that's best for removing, allows removal of the analyte from the hair matrix.

We also have varying methods for extraction of the drugs from solid hair matrix. Some the extractions are just extractions of the whole hair itself, others are extractions of a solubilized hair, and so the best method has to be recognized and developed within the industry to provide, if we have any hopes of meeting the criteria that were in the 2004 guidelines.

The next thing is that we still, we had labs who were conducting confirmatory testing with a wide array of instruments and some of these do not have the necessary sensitivity to meet the cutoff criteria and the 50 percent or 40 percent of the cutoff criteria that will be in the guidelines, or I presume will be in the Guidelines.

Slide 41 – Variation in Hair Pilot PT Results (continued)

And we have large variations within labs and some of the reasons, and I think one of the big ones right now since we are seeing precision is reference materials are not commercially available and by this I mean reference materials that are at the concentrations that we are looking at in hair. There are some SRMs available from NIST but their concentration is very high compared to the cutoffs that we are looking for in this hair program.

And not all labs have developed procedures that are accurate and precise, we saw that we had precision in some labs but we didn't have the accuracy. This could be from sample measurement, the extraction procedures, variability there, and also of course instrumentation always plays a part in this.

Slide 42 – Variation in Hair Pilot PT Results (continued)

Now the question we have is sample composition may account for some of the variability but with the variability that we are seeing in the tested methodologies it is going to be difficult in those particular instances to determine that. We do see and it is very encouraging is that we do have labs that are able to provide results with CVs less then ten percent, or around ten percent, and that indicates that maybe we do have some consistency within these samples.

Working against that though with BE, benzoylecgonine, here we call it BZE, sometimes we flip back and forth between BE and BZE in this program. This is

benzoylecgonine and 9-carboxy-THC, they appear to change over time and so that is something that I am not sure what we are going to be able to do on that but usually just as with urine it is taken us since '88 to work out a process that provides a stable PT sample that we can, that has stability for long periods of time, I feel sure that we'll be able to do that with hair over time. These are challenges that we are going to have to meet in the PT composition.

Slide 43 – Variation in Hair Pilot PT Results (continued)

And again the lab quality control procedures may largely account for variability, we have the standards used to calibrate do not contain drug analytes at the concentrations required for drug testing, we already talked about that, but these are the standards that the laboratories are trying to use within their labs in the absence of something that's commercially available. And also the controls included in test batches do not ensure accuracy and precision of the testing process, in other words we are seeing variability within the controls that the laboratories are using.

Slide 44 – Road Map for Successful Implementation of Guidelines

What do we do? How are we going to go to the future if we are going to implement these guidelines, or whatever the final guidelines are? We feel that part of the problem may have been the way that we have been running the Pilot PT Program in that we have three cycles in which the laboratories get no feedback, and so it is not until six months later or four months later that they find out how well they performed and by then they have probably changed controls, they probably changed their calibrators, it provides a disconnect to the system. We feel that this, one of the things that we need to do is increase the dialogue between the NLCP Pilot PT Program and the participant laboratories to produce an exchange of ideas and solutions.

We plan to do this by having meetings or teleconferencing, webcast meetings where we can have immediate feedback from the laboratories and feed information directly to the laboratories about the most recent cycle. And review these test results with the labs and encourage the group to work together as a group to develop the solutions to the analytical problems.

The thing you have to realize is that urine started out with procedures that had already gone through this process, through the military program. The military at the time had been developing their analytical procedures since 1982 and they had standard procedures by 1988, there were standard procedures almost in all the military labs even though at that time it was the Army had their procedures, the Navy had theirs and the Air Force had theirs, but still, they were standardized within. We do not have that pre-testing or that pre-implementation process from a government agency and so it is going to be up to the industry to get together and to work on their procedures and to improve the message and come up with solutions to analytical problems.

Slide 45 – Road Map (continued)

We want to obtain a commitment from the labs to use these future PT cycles as a resource to develop and improve their accuracy and precision. We also want to use these cycles to resolve issues concerning sample stability and lab variation. And

we are going to facilitate the development of appropriate calibrator and control materials so that they will be available for the laboratories. And that commitment has been made by the NLCP, HHS has given their approval for that facilitation.

MR. STEPHENSON: I told you this was going to be pretty intense and we are at a point in time for a break. Let's have a group process, think about how we want to do this, do you want to hear the oral fluid presentation and see how much sticks from the process that we framed for hair and apply it to oral fluids, do you have burning questions that you just cannot wait to ask that you want to deal with hair first, either way we can accommodate that, but let's do it after the break.

MR. STEPHENSON: There is always a risk of reconvening a meeting when you're having such amazingly animated and interesting networking that's going on as you stand up and talk to each other, that's also a part of the process going on even when you have a break and I am glad you all were able to take advantage of it.

A couple of things I want to point out in the hair PT data analysis, there are two things I want to advise or caution any of those who take one of these sets of presentations handouts away from here. Do not try to correlate this to a specific lab, we have been extremely devious and efficient in masking and randomizing the results, that's why in some areas you have alpha numerals for the alpha designators for the various labs, and another set of data looking across labs or among labs we used numbers, and we changed the relationship so you cannot go back and do A, B, C equals 1, 2, 3, it would not work. And so with that caution it was not our intention to mask the ability of a lab to understand their own values but we wanted to be careful not to do anything at this point that would unintentionally destroy the credibility or efforts or intent or desire to work together in the future.

What will happen in the future will be that we will work at getting the information out quickly after each cycle, we will increase the number of individual samples that are submitted, or the specimen types that are submitted to the labs, there will be at least five tests within the cycle. We are going to look for consistency in analytic ability within the individual lab and we are going to look at consistency of information collected across the labs for a given specimen in a single cycle and working together as a group we think that they'll be some ways that we can do this. We also intend to approach others in the Federal government who have responsibility for developing standards and request that there is some work that's done in that arena also.

There are several things that we are willing to put on the table and help broker and help facilitate in a way, but it calls for the participation of the labs themselves and a real commitment to doing the analyses consistently and doing as many of the target analytes as possible to try to drive some improvement in this system or to learn where the issues are to help us remove the variables that we can control as the program. That's what this is about, we have to get to a place that's better then where we are, we think we can, and it is going to be a joint process and we are willing to help make that happen.

Agenda Item: Pilot Performance Testing (PT) Program for Oral Fluid

Note: The PowerPoint slides for the following presentation are attached at the end of the transcript.

DR. MITCHELL: We completed the hair and then we cloned that as near as possible for oral fluid so that some of the explanation that I've been through before I hope will not be necessary, will not be as lengthy, and even though Bob gave me the same amount of time it probably will not take the same amount of time to go through this because we are now familiar with the formats that we have used.

Slide 1 – NLCP Oral Fluid Pilot Performance Testing (PT) Program Update Cycles 4 Thru 6

The Oral Fluid PT Program has been run by Frank Esposito at RTI. He has done a tremendous job running both the urine and the oral fluid, and in the future we plan to spread out and Dr. Peter Stout will be running the oral fluid program in the future. He will be able to give his full attention to it and I think that getting new ideas and new approaches is going to help also in the oral fluid, just as it has in the hair over the past year.

Slide 2 - Objectives

Again we are going to review the design and results of the Oral Fluid Pilot PT Cycles 4 through 6. If you remember, we have gone through 4 through 6 before but we are looking at them differently this time, we are not looking at the between lab or among lab values, we are now looking at the precision that we see in the laboratories that are doing oral fluid testing. We are also going to compare these test results to requirements of the proposed guidelines of April 2004, and just as we did with hair we are going to disseminate our future plans for this program.

Slide 3 – Pilot Oral Fluid PT Program: Design of Cycles 4 Thru 6
Slide 4 – Pilot PT of Oral Fluid: Cycle 4 Thru 6

Design of cycles 4 through 6. In this we had a series of samples, again we are talking sample composition, amp and methamp, in these we were using human oral fluid. We had the designer amphetamines together, we had cocaine and BE split for the same reason that we had it in hair, we had 6-AM, codeine and morphine, all the opiates together, we did not put oxycodone in this one. PCP and THC, now remember we looked for THC, 9-carboxy-THC in hair and in urine but in oral fluid we'll be looking for the parent compound, tetrahydrocannabinol, as an indicator of marijuana use.

Each of the samples was formulated again at below the cutoff, the cutoff, and 200 percent of the cutoff except for the THC, coke, and BE, which was at 300 percent of the cutoff.

Slide 5 – Pilot PT of Oral Fluid: Cycles 4 Thru 6

Again, we asked for confirmatory testing only. Each shipment consisted of 21 spiked oral fluid samples and so the samples were sent each cycle to each of the laboratories. We sent the challenge as 2 milliliters of oral fluid so we are only addressing neat oral fluid at this point in time, none of the issues associated with collection devices and things of that nature. We asked that the results be submitted by labs within 10 working days, unfortunately oral fluid was not quite as responsive as the hair was at that

point in time, but I can look forward to better results on that in the future.

Slide 6 – Pilot PT of Oral Fluids: cycles 4 Thru 6

Now you see that these samples were back from 2003/2004 and it will become apparent why I had to go back then in order to get these results as we go through this particular one. We had three shipments that were sent during that period, we had 12 participant labs, and again as we did with the hair the results were provided to the laboratories after we completed the third cycle which in this case was cycle 6.

Slide 7 – Cycles 4 Thru 6 of Pilot Oral Fluid PT Program: Confirmation Analysis

Looking at the lab procedures and meeting the requirements to be a certified laboratory we see that in the amount of specimen that's required, usually it is somewhere about 0.25 to 0.1 milliliters of oral fluid, and we see though that still we had some laboratories which were requiring fairly large amounts, up to one milliliter in order to be able to conduct confirmatory testing which is if you've ever tried to collect oral fluid you'll know that trying to collect 5 or 6 mLs of oral fluid would be a problem and so I do not think that we would be able to utilize laboratories that had those high, where the volume requirements were that high.

LOQ, everyone was meeting the LOQ requirements except for one lab which did not have the sensitivity for the 6-AM. We had one lab that was not analyzing for opiates from the current analytes that we are testing in urine. Of the new analytes you can see that many of the laboratories did not have the procedures in place at the time of these particular cycles.

Slide 8 – Cycles 4 Thru 6 Highlights

Again, this is the same, we are going to look at the quantitative variation, the within lab variation, talk about accuracy and precision, and then look at the performance of some selected participants. In this case, because of stability problems with oral fluid we were making the oral fluid samples right before we sent them out for the first cycle and did not have time to obtain reference values like we did with the hair. But in oral fluid like urine you have a good idea of how much analytes you put into that solution and so the concentrations we will talking about will be theoretical concentrations which are going to show some things. And the selected labs again, we'll show you an example of one of the better labs on that particular sample and also one of the not so good labs results.

Slide 9 – Distribution of Within Laboratory %CVs for All Laboratories for Amphetamines from Cycles 4 thru 6

Okay, looking at within laboratory CVs for the amphetamines, three cycles, and again we are dealing with the same analytes that we did with hair, we have amphetamine, methamphetamine, MDA, and MDEA. And again we can see that variability here in the oral fluid we have below 20 percent for amphetamine, we have most of the analysis that were conducted which were 36 were at 20 percent or low. We

can see the same thing for methamphetamine, most of them had a variable CV of 20 percent or low. MDA, we had many that were below 20 percent but we also had some aberrant values reported by some of the laboratories.

Remember, these are the means of three separate determinations on a single sample by laboratory. MDA, we have some that are down at 10 percent or less, some within quite more, 20 percent or less, but we also have some values which are very high and again these were the analytes that some of the laboratories had not developed procedures for at, confirmatory procedures for at the time of these three cycles. And with MDEA we do have some precision in here, some nice, but we are still, we are only dealing with 9 determinations.

Slide 10 – Accuracy and Precision
Slide 11 – Comparison of Methamphetamine %CV Across Labs

I am not going to go through accuracy and precision again. Let us look at comparisons of the three samples over all the participants, and again as Bob said, these things have been pulled out of the hat and homogenized such that I cannot tell you which lab is which. But we can see that we have within this population for methamphetamine we have very good precision because all except for two aberrant values on a cutoff, that is at 50 percent of the cutoff, are down below 20 percent. This looks very good for precision for almost all of the laboratories.

Slide 12 – Distribution of Within Laboratory %CVs for All Laboratories for Cocaine and Related Compounds from Cycles 4 thru 6

With cocaine we see a little bit of change, when we get to cocaine we find that we do have laboratories that are below 20 percent but also we have variation here and the exact cause of these, we cannot tell whether it is lab procedures or whether it is something in the way they processed the sample and the same thing with BE. We have not been able, we have not as yet teased out the information that we need. However, we can see that we are able, on the same samples we are able to get a good precision among the laboratories. Now we couldn't, when we looked at these we could not, there was no one sample that stood out as having a high variation.

Slide 13 – Distribution of Within Laboratory %CVs for All Laboratories for Opioids from Cycles 4 thru 6

When we look at the opiates, the opiates as you will see presented some problems, some challenges for the NLCP and we'll talk about that but we have high variation, you can see that this is not the same type of precision, number of labs that we saw for the amphetamines. 6-AM you see we have very wide variation. But with codeine we see some pretty good precision in many of the laboratories but still it goes up to better then 30 percent in the precision.

Slide 14 – Distribution of Within Laboratory %CVs for All Laboratories for PCP and THC from Cycles 4 thru 6

PCP and THC. This is PCP, you see most of the values are down here

below 20 percent but we do have some aberrant values from laboratories. And THC is, what's going on here, we do not have any precision, so the question is what's going on here. We will look at this as we go through this presentation.

Slide 15 – THC %CV Across Labs

You can see that it doesn't appear to be affecting one sample more then others, they're all having a problem, or the labs are having a problem with that laboratory because we have very imprecise determinations being reported by the laboratories.

Slide 16 – Performance with Amphetamine

Now talking about with the selected labs first we have a theoretical mean, which is the amount that was placed into the oral fluid, we have the value that the group determined, and then we have the values of two of the laboratories, one having a very low or very good precision as designated by the standard deviation here, and another one which had a fairly high. But still relatively small for the population, not like some that we have seen earlier. You can see that this pattern goes all the way across but this laboratory, the bad laboratory, or not bad but the lab with the most variation is shown here and you can see that there is a significant variation within that laboratory for amphetamine itself.

Slide 17 – Performance with Methamphetamine

The same thing we see the precision, we have again the theoretical, the group mean, looks like accuracy is pretty good overall, and we see that even with the laboratory which had the higher variation their accuracy was pretty good. We see the same thing except a little bit on the accuracy going out here, we see more variation on the higher concentration, and that increases as we go up and we see the variation appears to increase as we go up in concentration. Overall accuracy is pretty good when we look at the mean, the group as a whole.

Slide 18 – Performance with MDMA

MDMA, very reminiscent at the lower concentrations of what we see with the other amphetamines but as we go up we start seeing some aberrant values coming in where the poorest performers, remember, this is a new assay, is fairly large compared to what the mean of the values was, it would be at least, it looks almost like about two-thirds is the variation that they have.

Slide 19 – Performance with MDA

MDA, a very similar situation to what we see with the MDMA, we do have variability within the group, do not know if this is real or what it may be due to the variations but it would appear that the spiking, the amount that we are able to, we may be losing some of MDMA, we do not know yet but hopefully we will be able to look at that in the future because this value represents how much was put in, this is the group mean. And the group means are very good with amphetamines but we do have an increased

variability in some of the labs.

Slide 20 – Performance with MDEA

MDEA, this looks pretty good. The theoretical, the group mean, the best performer, the poorest performer, not much difference at these lower concentrations. So MDEA appeared fairly good performance, we did have some variation is still there though with some of the laboratories.

Slide 21 – Performance with cocaine

Cocaine, in cocaine we can see that the means, the mean agrees well with the theoretical in all three. Some labs have very small variability, others have larger variability which is what we expected in this population, and so overall it is not too bad but these laboratories that give this type may have problems in some of the PT samples.

Slide 22 – Performance with Benzoylecgonine

Benzoylecgonine, this kind of parallels what we see with the cocaine; however, it appears that for some reason, and this may just be by numbers, mathematical, that we ended up with the group mean being slightly less then what was spiked in to the oral fluid. Again, we see the difference between the best performer and the not the best. Their means are fairly close, but there is still a good bit of variability within the whole population.

Slide 23 – Performance with Morphine

Morphine, we are seeing variability here, you can see that at this concentration there is a decrease, it is even more pronounced as we go up in concentration, so that would indicate that we are having a problem with stability of the analyte, but also we are seeing large variation so the question is this due to variability in the laboratories or is it due to the sample itself. We will try to answer that question as we go on through here.

Slide 24 – Morphine Degradation During Cycles 4 Thru 6

And in answer to that looking at the same samples but looking at the means over the three cycles and what we see is from theoretical over the three cycles we see a decrease in concentration so this, a large part of this variability is due to instability of morphine in human oral fluid, this is a sample problem, we cannot say that it is, we cannot measure the problem with a laboratory, this is a sample.

Slide 25 – Performance with 6-AM

6-AM, as you can see when we look at theoretical and group mean there does appear that there may be some decrease and we have high variability, we go to the next slide, and here's what we see is that we do have a decrease overall, it appears though after that initial, after some type of initial decrease then the amount that we lose is not as

great so we do have some problem at least in, at least one of the cycles and that is the first cycle we had some problems with stability of the 6-AM.

Slide 26 – 6-AM Degradation During Cycles 4 Thru 6

So that caused, that type of sample problem will increase the variability that is observed from the values of the laboratories so 6-AM was not a good sample to judge performance of the labs.

Slide 27 – Distribution of Within Laboratory %CV for All Laboratories for Opioids from Cycles 8 and 9

Looking at the opioids, looking at morphine and codeine, looking at the CVs of all the labs after we have hopefully solved the problem, this is in cycles 8 and 9, these are later cycles, we went back and did some things to try to stabilize the morphine, and you can see now we have a major number of the determinations which are down here in the below the 20 percent and so that's the type of performance we'd like to see. We still, we do not know if this is due to sample or not with the 6-AM, that will, we will continue to look at that and check that out over time on the stability of the 6-AM.

Slide 28 – Performance with Codeine

Codeine, we really didn't see a significant decrease in the concentration over time, as we can see here we are looking at the theoretical, the group mean, and the best lab and the not best lab, and you can see that the group mean and the theoretical are fairly close for the codeine. The standard deviation for the best of the performers is very small and these are similar variations that we saw in other members of the participants. Codeine seemed to be okay, it doesn't seem to have the same problem with stability that we have with codeine and 6-AM.

Slide 29 – Performance with PCP

PCP, I do not see a lot except that the variability, well, among the labs it varies greatly, you can see that this lab is very tight and very close, this one is off by maybe 30 to 40 percent with a large variation, that is the mean is, and the theoretical and the mean tend to be fairly close, we may have had a small loss but you cannot really tell whether that is driven by the variation of the laboratories and their accuracy. PCP is usually thought to be a fairly easy analyte to work with, but we do some variability among the labs.

Slide 30 – Performance with THC

THC, like I said, we had a problem with THC. RTI has been working with THC for years and they find that the parent compound is even less stable then the 9-carboxy, the metabolite, and so you have to do some things to stabilize it in solution. As you can see in these, in neat oral fluid we had a great disparity between the concentration that we put in and what was found by the laboratories. When you have that then you do not know the rate at which it is degrading, whether all the samples are degrading at the

same rate and how they are handled in the lab, if they are unstable, they can increase the instability for example. We sent these frozen to the laboratories, if they thawed them and didn't start testing immediately then you could expect more degradation in a lab then in a lab that immediately started testing. We would expect the high variability that we saw.

Slide 31 – THC Degradation During Cycles 4 Thru 6

And just to point it out to you, looking at by mean, this is theoretical, this is mean of the first cycle, second cycle, third cycle, you can see that there is a large loss and then it slows down a little bit, but there is a loss of material over the three cycles as was indicated by the previous slides.

Slide 32 – THC Performance from Cycle 7 in Artificial Oral Fluids

To try to solve this problem we went to an artificial oral fluid, there is a lot of those in the literature and we came up with our own, I mean took one of those as a basis and then modified it to stabilize the THC performance. We get very good agreement between the theoretical and the group mean so it appears that we have solved that issue of using artificial oral fluid. I am not sure that we will be able to use actual human oral fluid in these particular samples for this reason, the inability to sterilize the oral fluid to remove all the bacteria, and also the issues associated with the safe handling of oral fluid. We are actually investigating and plan in the future to investigate the use of artificial oral fluids containing the same components that you find in human oral fluid but using this in this particular program.

Remember when we started, I said these 4, 5, and 6 cycles were from 2003, 2004, and 2005. As you can see we spent a large portion of our time trying to solve issues that were identified in 3, 4, and 5 and that is, we are ready now to start back with sending a full array of analytes to the laboratories, we concentrated on the opiates and on the THC in 2005 and now we are ready to start looking again at all the analytes now that it appears that we have solved the problems with analyte stability.

Slide 33 – Performance Testing and Certification of Oral Fluid Testing Laboratories

We are going to go through the same analysis with the oral fluid results and we will take some of these issues with the samples into consideration as we go through this. Again, we are looking at the proposed guidelines as released for public comment in the Federal Register, Volume 69, on April 2004.

Slide 34 – Section 9.6

Again, it reads the same, the oral fluid, except that, the actual standards are the same, the only difference is it says oral fluid instead of hair. They have to meet the criteria on three consecutive sets of PT samples, have no false positives, identify and confirm 90 percent of the total drug challenges on three sets, over those three sets, correctly determine the quantitative values of at least 80 percent of the total drug challenges, that's over the three sets, within plus or minus 20 percent, or two standard deviations of the calculated reference group mean.

Slide 35 – Section 9.6 (continued)

Also have no quantitative values in which they have what we call a 50 percent error in the urine vernacular, in other words, did you quantitate a single sample outside of 50 percent of what the group mean or reference mean is.

Slide 36 – Section 9.6 (continued)

The other one is for an individual drug, must correctly detect and quantify at least 50 percent of the total drug challenges for that drug, and that means and for all of them.

Slide 37 – Laboratory Performance Compared to Section 9.6

Again, no false positives, of course the same caveat, we directed the confirmation, we did not do initial testing.

In spite of all the problems we did have one lab that identified 90 percent of the analyte challenges over the three cycles. If we look at the urine analytes, we see that 10 labs met this criteria and if we removed morphine and 6-AM which we had the problems with in stability all 12 of the participants met the criteria. When we look at cocaine, the new analytes, cocaine, MDMA, MDA, MDEA, and THC, one lab met the criteria and if we removed the THC, two labs would have met the criteria. This reflects that we will have some development to do on these particular analytes in the analysis at that point in time.

Slide 38 – Laboratory Performance Compared to Section 9.6 (continued)

One laboratory quantitated 80 percent of all the analyte challenge within 20 percent of the group mean. If we remove morphine, 6-AM and THC we had two labs. Now what does that tell you? That tells you that we still have some issues if only two out of that 12 were able to meet it.

For the urine analytes we can see that 7 labs met this criteria, if we remove the morphine and 6-AM results 10 labs met the criteria. For cocaine, for the other analytes, one lab met the criteria without any correction because of analyte stability, if we remove the THC, 2 labs met the criteria. Again it appears that most of our issues are dealing with the new generation of analytes.

And I do want to, as a reference, many of these same analytes, especially MDMA, MDEA, MDA, are going to be required in urine and I am not sure our urine labs have all their procedures developed yet. We have not put them under the spotlight and that will probably start sometime in the not too distant future and I will be up here talking about them and where they are progressing. I just wanted to put it in the proper perspective at this point in time with all of the matrices that we are working with.

Slide 39 – Laboratory Performance Compared to Section 9.6 (continued)

We had 2 labs that had no quantitation errors greater than or equal to 50 percent of the group mean. For the urine analytes, we have 5 laboratories and if we took

out the morphine and 6-AM, we would have had 8 laboratories. For the new analytes, new generation, we had 3 laboratories that met this criterion and without THC we had 5 labs that also met the criteria for those analytes. It looks like in the oral fluids we are making some progress towards the new analytes.

Slide 40 - Laboratory Performance Compared to Section 9.6 (continued)

No lab quantitated 50 percent of all individual analyte challenges within 20 percent of the mean. Urine analytes, 2 labs met this criterion, without morphine and 6-AM, 9 labs would have met this criterion. And one laboratory met this criterion with all of the analytes and without THC we had 3 labs that met that criterion.

Slide 41 – Pilot Oral Fluid PT Program

The purpose, we have already gone through this, was to provide information so that this program could be developed for the Federal government, the use of this analyte, and so that the expanded Guidelines could be developed as well as PT materials to support that. Ss you can see, we have had quite a few labs that have taken the opportunity to work in the PT program and develop procedures for the analytes that will be included in the new guidelines.

Slide 42 – Variation in Oral Fluid Pilot PT Results

There are some issues, we have some excessive variation among the labs and again, probably the wide array of instruments, not having necessarily sensitivity, appears to be an issue in some places. Another issue that we found was relating the information, doing the math and relating the confirmatory results to the neat oral fluid and there is some reasons for that because of the way they are operating now and what we are asking them, the way we are asking them to do things, so there is some reasons for that, that may produce some of the variation, may even account for some of the very high values that we have that did not make sense.

Slide 43 - Variation in Oral Fluid Pilot PT Results (continued)

Also failure to use standards from sources outside the laboratory, this is something that is extremely critical to the urine drug testing is having standards from an external source so that you can determine if you are making the standards within your laboratory you know if you are having a problem with what you have made or if you purchase all, some of the labs even purchase all their standards and controls from a commercial source. I am not sure that this is available or being used at this point in time in the oral fluid, well, uniformly throughout the oral fluid industry. And of course the instability of the morphine, 6-AM and THC, we cannot forget that that is part of the excessive variation and it is some of it that we observed.

Slide 44 - Variation in Oral Fluid Pilot PT Results (continued)

Within labs, instability was definitely a problem, the reference materials that are not always available commercially may be a problem with the oral fluids. The

laboratories need to work on their accuracy and precision in the sample measurement. Oral fluids, because they are kind of viscous, can be an issue, and also use the best extraction procedures and the best instrumentation procedures, make sure they have the required sensitivity and repeatability.

I guess I am beating a horse, but I have to since it is my responsibility, stability of the analytes, we definitely had problems but it appears that we have solved those problems in the PT cycles that we conducted in 2005.

Slide 45 - Variation in Oral Fluid Pilot PT Results (continued)

I have already talked about this, lab quality control procedures may account for some of the variability in some labs, and using standards and controls from an external source.

Slide 46 – Road Map for Successful Implementation of Guidelines

Just as we have proposed for hair, we want to do the same thing, we want to increase the dialogue between the NLCP and the laboratories that are participating. We are going to do this through the same mechanisms that we proposed for the hair, we are going to hold meetings as webcast meetings, thank goodness for the web, it makes it very easy now to have participation from multiple participants from multiple locations, so we are going to make use of those resources in this program. We are going to review the results of the test that they have conducted and go over those with the laboratories and encourage them to, just as we are with the hair encourage them to improve their methods and come up with solutions to problems, especially analytical problems.

Slide 47 – Road Map (continued)

We want to obtain the commitment from the participants to use these PTs to prepare themselves for certification whenever the guidelines will permit that. To use these cycles that we will be sending out to resolve issues of sample and lab variation as well as start looking at the immunoassays, remember it has been a long time since we have looked at the performance of immunoassays in the system and that is coming up in the near future. We have not surveyed the industry at this point in time as far as the availability of the standards and controls like we have in the urine drug testing system, but we are going to look at facilitating the development of those materials for the use in the oral fluid at the levels that we need them to be to support this program.

MR. STEPHENSON: Thanks, John and the RTI team, you all did a great job of going through the process and assembling this and we really beat them up pretty significantly over the last week trying to get some internal consistency and be very clear of what was being said. At the risk of now muddying some of the clear understanding, the very last slide that we had put up on the oral fluid and pretty much this reflects the same thing with hair, that we want a commitment from the labs that are participating in these PT programs and the industries to use the materials and resources that we are committing to help drive the industry and the performance of individual labs to a level that they will be able to successfully apply for and become certified to perform testing using that specimen.

This is not a program that is designed nor can we tolerate the use of our

PT specimens and materials simply for fun and games, these are very expensive to develop, they come at a cost that is distributed to the taxpayer funds, they are not reimbursed by the individual contributions from the labs because there are no applicant labs at this time and we have great variability that's occurring amongst the participants so far. We ask the labs and the industry itself to look in your own hearts, look in your own pocketbooks, look at your own commitment, are you really interested in getting into this and if so join in the process individually and collectively to work with us and with each other to develop the standards across the industry such that they will generate good performance over time. There are a lot of us that are invested in this process to make it work and we are willing to commit the resources that are necessary to do that but we have to engage everybody equally in this process over the reasonably short future in order to get us to a point where we are able to do more then what we are able to do right now.

Accept that for what it is, we have to demonstrate that we can do some things, I am not asking for a pint of blood from anybody, I am not asking for any kind of commitment other then maybe they'll be some agreement that we'll put together, that will come out, restate this, it is not a contract but it will be an understanding between the participants in the laboratory environments and the program. Then participate in the meetings and share the information, share the data and share your own insights because it is collectively we have to perform better. What we will give back is more timely updates, changes in the challenges to meet the needs as we evolve them, as soon as we get clearance for final parameters of the mandatory guidelines in these specimens we'll refine and redefine the standards as they're necessary, make sure that they get out in a timely manner, and begin to do that level of work until we are able to demonstrate proficiency across the group.

Is that acceptable to the board as a challenge? Because you have to be our partners in this part of the process and with what we are talking about with oral fluid I think this is something that if it can help you as a benchmark, as a beginning point, and then sharing back information over time this will greatly help do this systems improvement for both sets of parties.

COL SHIPPEE: Are you using a racemic mixture in your amphetamines?

DR. MITCHELL: No, it is all D isomer.

COL SHIPPEE: It is all D. The second question is when do you expect or how do you expect to bring in the decontamination process in the hair as a variable in the labs?

DR. MITCHELL: I do not think we truly understand all of the decontamination and its impact, and at this point in time I cannot address that.

MR. STEPHENSON: I think one of the things that we'll do is we'll have that as one the elements we'll engage the industry on and the labs that are participating because it is clear that you might get one or two labs that can perform to a level of satisfaction but you cannot drive a cost effective or an efficient system with just one resource out there, just to participation in the certification if distributed amongst the participants, was that the cost for an individual applicant lab could be horrendously high and by definition that's the way our cost sharing has been developed over time. We are absorbing all of these costs now, but at a performance level later on for application and for maintenance and for PTs

they will be distributive costs. It serves everybody to have a larger group of participants and we think there will be, but as an objective outsider, maybe you want to participate in some of those discussions too even though you do not have, you know, well, as long as you bring your body armor it will be all right.

DR. COLLINS: This is with regards to the hair, I wondered how close was your reference lab mean to what your targeted concentration was? Was there reasonable agreement or not?

DR. MITCHELL: If I understand your question you're saying how close was the mean to the theoretical, or what we considered theoretical?

DR. COLLINS: Right, with your reference labs.

DR. MITCHELL: Most of them were within 20 percent, this process that we have we have been working on for years and Jeri has refined it beyond what we had done previously and she's getting most of the concentrations within about, within 20 percent of what she would predict them to be, and again, it is not really a theoretical, it is a guess based upon experience and based upon the performance of hair and it is uptake. After you characterize a hair you can predict within a 20 percent or so what, and under conditions, set conditions, what concentration you will find.

MR. STEPHENSON: We have answered all your questions but it is a little bit mind numbing as the process, the amount of information and the process that its been presented tends to overwhelm you just a little bit. As you go away from this presentation and if there are some questions that you have, think about them, and then we can readdress them either this afternoon or tomorrow morning as follow-up in the next part of our meeting.

I think we have pretty well clarified everything that we had to present for this part of the session. I am very pleased with what they were able to do. We will have an opportunity after we break here for a little bit of that stand-up internal networking before we reconvene in closed session. There will be an opportunity for having some dialogue yet amongst interested parties, not necessarily sure about the amount and detail of feedback we can provide at this time, but at least it will be an opportunity to have some dialogue.

At this time, we have two individuals who indicated they would like to make a public comment. About 10 minutes apiece. Again, this is an opportunity to make comments, there will not be a response and we will not engage in a dialogue on the issues. You are welcome to make the comments and they will become a part of our transcript.

Agenda Item: Public Comments

DR. SOIFER: I am Professor Steven Soifer from the University of Maryland, Baltimore, and also the staff director of the International Paruresis Association. Thank you for the time to present to the committee.

On April 13, 2004, SAMHSA published a notice in the Federal Register for revisions to the Mandatory Guidelines for Federal Workplace Drug Testing Programs,

69 FR 19673, FR Doc#04-7984. Public comments were submitted, or were to be submitted by July 12, 2004. There were 285 public comments submitted, the members of our organization, the International Paruresis Association, submitted roughly one-third of them.

Both in those comments and at these hearings you have heard members of our 1,000 person strong organization explain why accommodations must be made for people suffering from paruresis, or shy bladder syndrome.

Today, I am here to say that it is simply unconscionable that the new Federal regulations have yet to come out, almost two years after they were first promulgated. What could possibly be the reason for such a long delay? Thank God we are not dealing with a Federal emergency like Hurricane Katrina.

Because of the length of the delay, members of the IPA have had to enlist U.S. Senators and Representatives in their home states to look into why there has been such procrastination in releasing these regulations. Moreover, we are particularly asking our Senators on the Health, Education, Labor and Pensions Committee, HELP, and Representatives on the House Energy and Commerce Committee, which oversee SAMHSA, to find out why there is a problem.

Hopefully, when we return here in three months the newly proposed rules will be out and this will no longer be a problem. All we need are more Congressional hearings on why our government isn't working efficiently these days.

Thank you.

MR. STEPHENSON: Thank you for your comment.

MR. SPEIDEL: My name is Paul Speidel. I work at Psychemedics Corporation. I just had a question, but you addressed it essentially which was the status of the proposed guidelines. The comment that I did have though is if there is any guidance that you might be able to provide, either in these meetings or some other way where we could find out where the guidelines are, in other words not just the status but where they actually might be in the process, perhaps maybe these meetings are the best way.

MR. STEPHENSON: This is always one of the more delicate things about government and process of review and timing and again for both commenters, a generic response that there are multiple levels of review that a document and a process like this go through. The first groups are internal construct validity and scientific accuracy within the Department, those have been done and completed. The legal reviews that are done for consistency with government regulations from process are undertaken by attorneys and those have been done. The third level of process is external to the department in looking at the larger role of government and process across multiple government agencies with multiple needs and agendas that have to be satisfied in aggregate over time and to make sure that all thoughts have been considered and so that process has been undertaken and inputs collected although we haven't seen them yet.

There has not been a time to my best recollection where it has taken us more then about a week to address issues that have come back through edits and comments. The point is that they are not being held at our level and they are not being held internally. The concerns that always come up and that always throw a monkey wrench into the precision of a stopwatch is what happens if someone presents something new that you haven't thought of that is scientifically valid and it is challenging to the

point that you do not have answer for it, and that's always the risk. To this point that has not happened, we have been able to accommodate to the public comment process and through the reviews the ability to address those kinds of variables to the point that there is satisfaction, one, that we have been responsive to the public comments and second, that we have been responsive to the science and the precision that we need to address in developing these.

But these are a big deal and when you look at them over time getting them right is going to be an important benchmark starting point. We have learned in earlier iterations of mandatory guidelines for urine that often an industry or those who produce materials, assays, instrumentation, for testing that's performed in this arena will not take action until there is a final published guideline, until there is an actual define aiming point that the government has committed to and an implementation date that establishes a window of opportunity. What will happen is that you can see some of the things that will start to evolve under their own impetus once there is published guidelines. There is nothing that we want more then to get the guidelines out the door with an implementation timeline and an opportunity to begin to work on refining and defining those remaining variables that we need to fix and to get the system up and running.

I cannot say any more because I do not know any more, but I have shared with you very openly and honestly the philosophy that's there, it is not derogatory or condemning of any party in the process, but this is a huge issue that cuts across this whole society, and quite honestly there is nobody else on this planet who is doing this kind of work at this level compared to what we are. We are gathering interest from other parts of the globe and the issues that we are addressing will be informative to them and the things that others are doing across the other parts of this planet will certainly continue to help influence the things that we develop too.

That is the end of the public comment process.

The open session was adjourned.

Attachments:

First Presentation: NLCP Hair Pilot Performance Testing (PT) Program Update Cycles 9 Thru 11

Second Presentation: NLCP Oral Fluid Pilot Performance Testing (PT) Program Update Cycles 4 Thru 6

NLCP Hair Pilot Performance Testing (PT) Program Update Cycles 9 Thru 11

Drug Testing Advisory Board
March 7, 2006

John M. Mitchell and Jeri D. Ropero-Miller

ROCKVILLE, MARYLAND AND RESEARCH TRIANGLE PARK, NORTH CAROLINA

Objectives

- Review the Design and Results of Hair Pilot PT Cycles 9 Thru 11
- Compare Test Results to Requirements of Proposed Guidelines of April 2004
- To Disseminate Future Plans

2

Pilot Hair PT Program:

Design of Cycles 9 Thru 11

3

Pilot PT of Hair: Cycles 9 Thru 11

- New Production of All Analytes
  - AMP, MAMP, MDA, MDMA, MDEA (1st time all together)
  - COC, CE, NCOC
  - BE
  - 6-AM, COD, MOR, OXYCOD
  - PCP
  - THCA
- 3 Concentrations for Each
  - 50% Cutoff
  - Cutoff
  - 200% Cutoff

4

Pilot PT for Hair: Cycles 9 Thru 11

- Confirmatory Testing Only
- No Sample Decontamination by Labs
- Included in Shipment:
  - 19 NLCP spiked hair strands
  - 2 drug user hair strands
- Each Sample: 50 mg of Hair Strands
- Results Submitted by Labs within 10 Working Days

5

Pilot PT for Hair: Cycles 9 thru 11

- Samples Shipped July - Dec 2005
- 3 Shipments- Alternate Months
- 9 Labs Participated
- Analyses of Results Were Provided to Labs at End of Study (after cycle 11)

6

Cycles 9 thru 11 of Pilot Hair PT Program: Confirmation Analysis

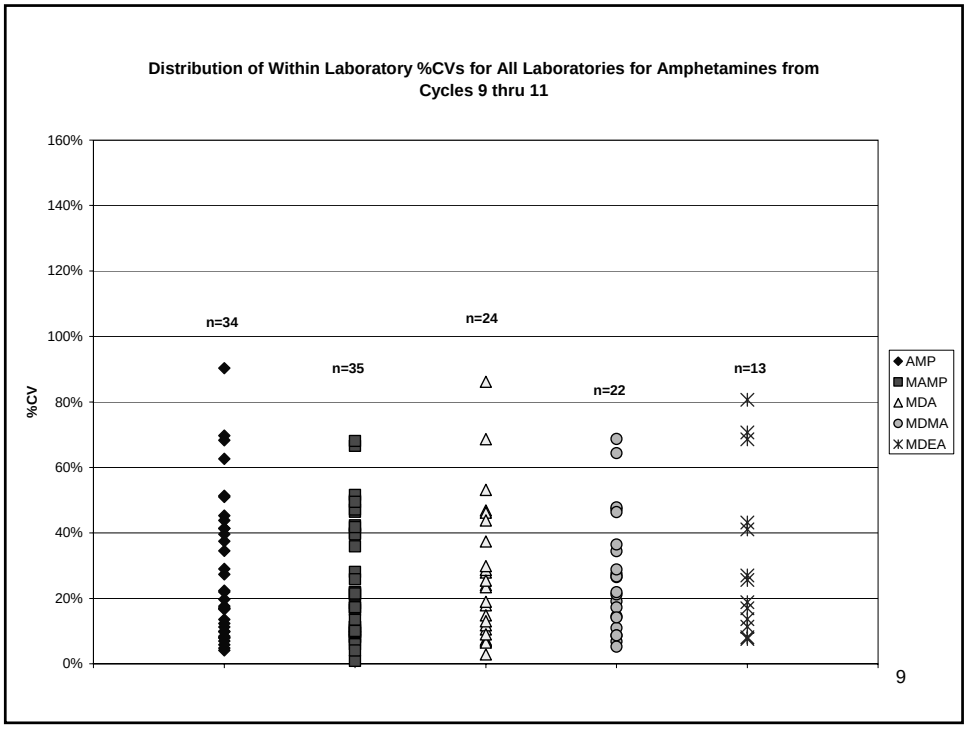
Laboratory	Specimen Required per Drug Class Tested (mg)	LOQ ≤ HHS Proposed Cutoff	Current Urine Analytes Analyzed	Proposed New Analytes Analyzed
E	50	THCA: 1.0 pg/mg	Y	No: MDEA No: NCOC
G	10	Y	Y	Y
H	20	Y	Y	No: MDEA
I	50	BE: 1000 pg/mg MDEA: 400 pg/mg	No: THCA	No: NCOC
L	20	THCA: 0.3 pg/mg	Y	No: CE No: NCOC
M	THCA: 20 Others: 10	Y	Y	Y
O	20	Y	Y	Y
P	20	Y	Y	No: NCOC
Q	20	Y	Y	No: MDEA No: NCOC

7

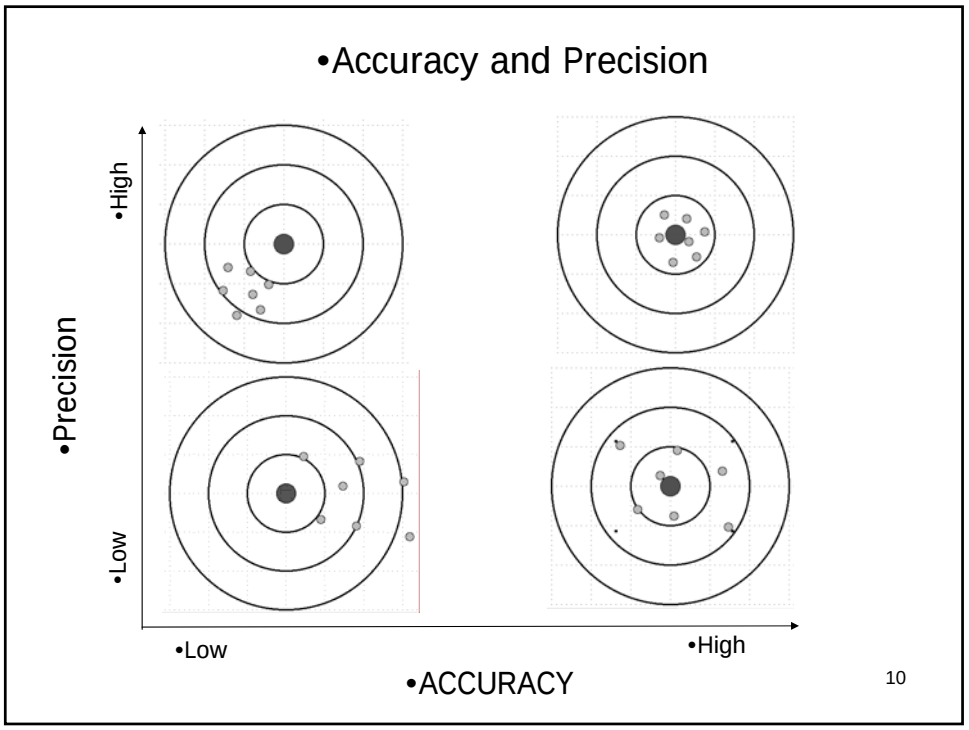
Cycles 9 thru 11 Highlights

- Quantitative Variation
  - Within Lab Variation
  - Accuracy and Precision
- Performance of Selected Participants

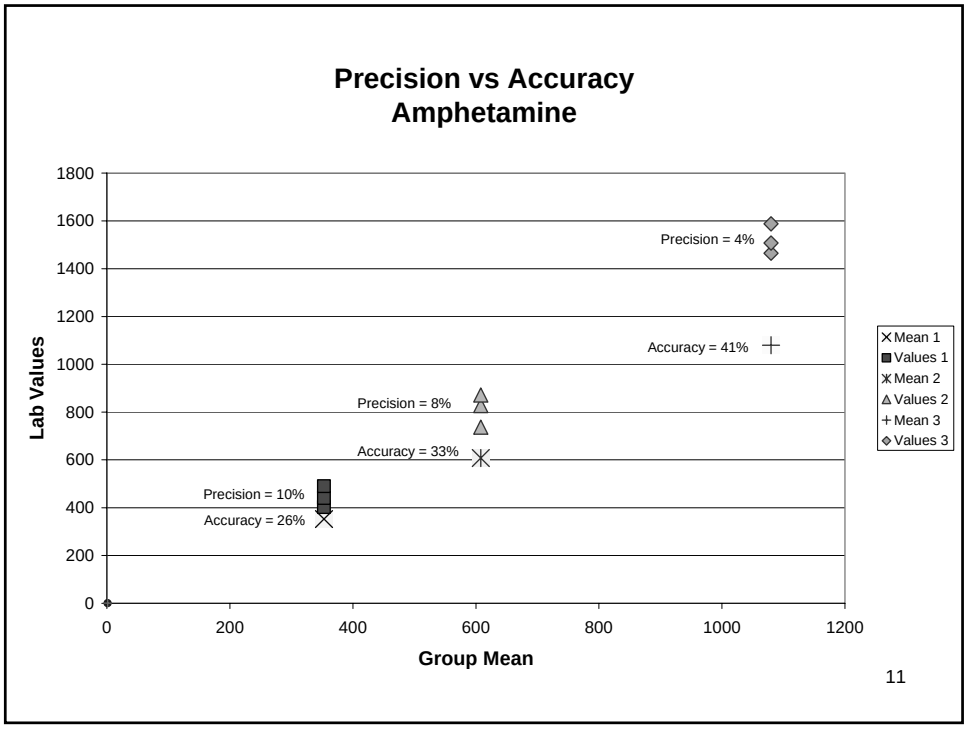
8

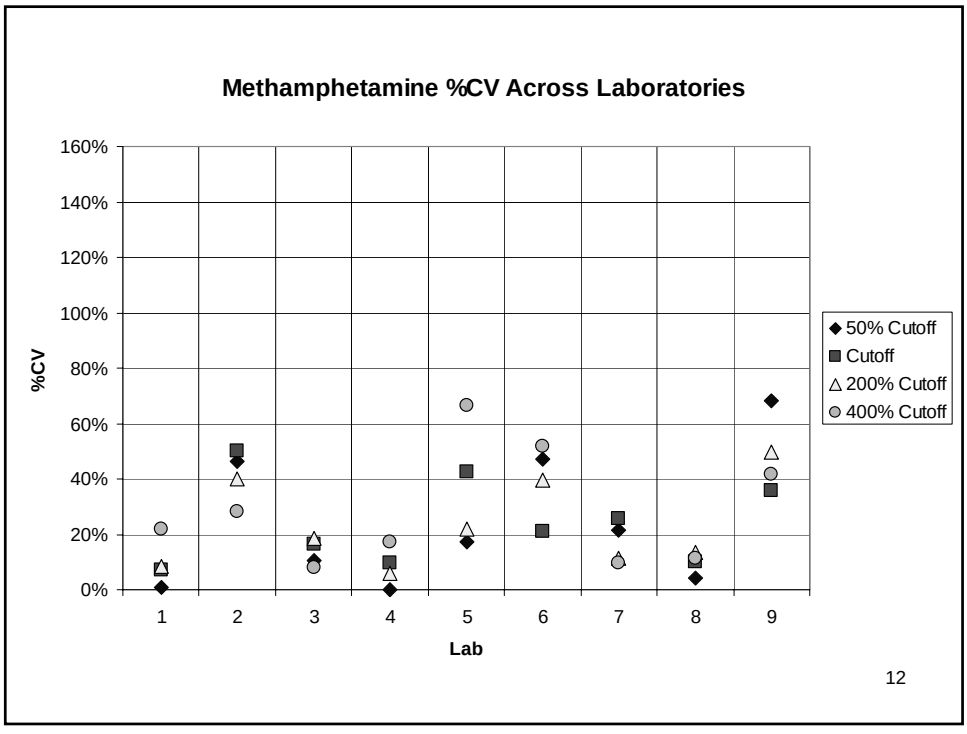

Distribution of Within Laboratory %CVs for All Laboratories for Amphetamines from Cycles 9 thru 11
160%
140%
120%
100%
80%
60%
40%
20%
0%
%CV
n=34
n=35
n=24
n=22
n=13
AMP
MAMP
MDA
MDMA
MDEA

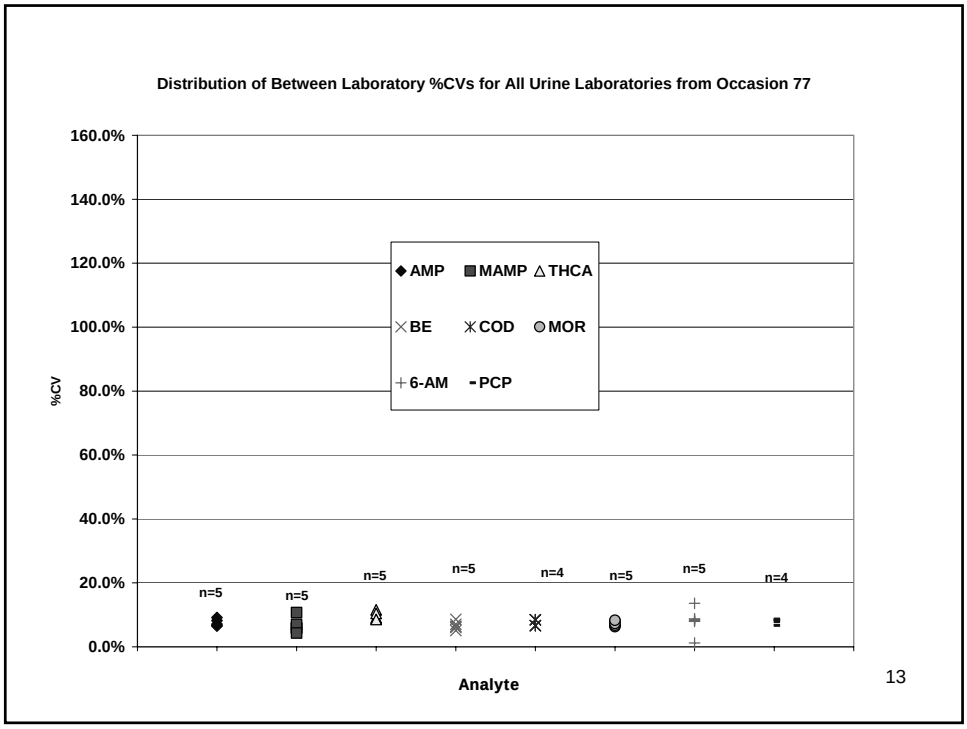
9


•Accuracy and Precision
•Precision
•High
•Low
•Low
•High
•ACCURACY

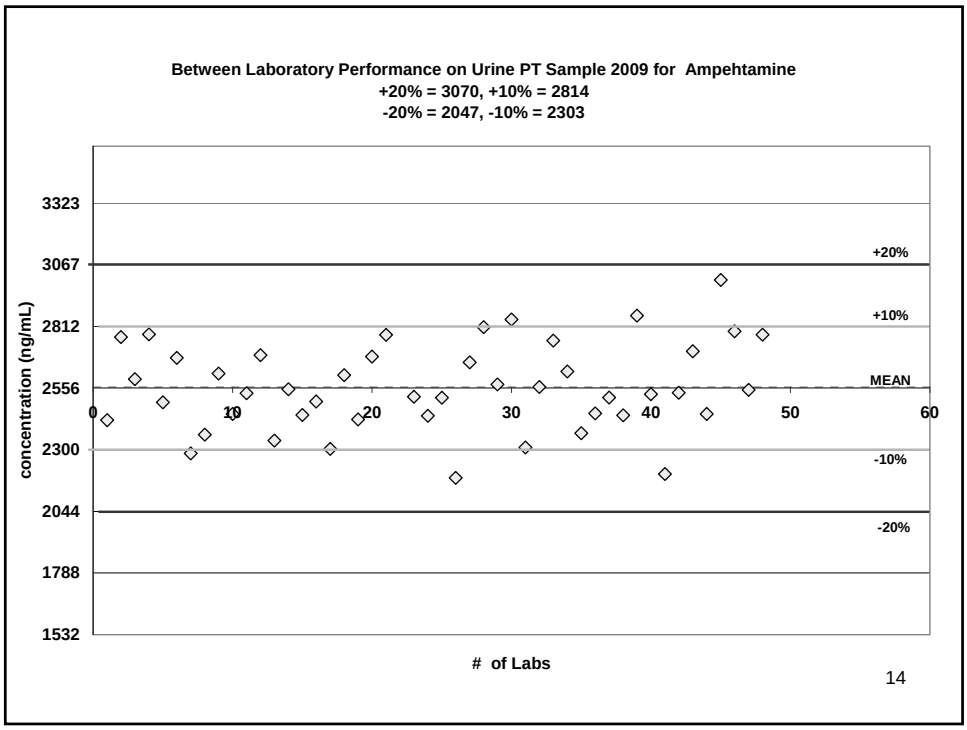
10


Precision vs Accuracy
Amphetamine
Lab Values
Group Mean
Precision = 4%
Accuracy = 41%
Precision = 8%
Accuracy = 33%
Precision = 10%
Accuracy = 26%
Mean 1
Values 1
Mean 2
Values 2
Mean 3
Values 3
11


Methamphetamine %CV Across Laboratories
%CV
Lab
50% Cutoff
Cutoff
200% Cutoff
400% Cutoff
12

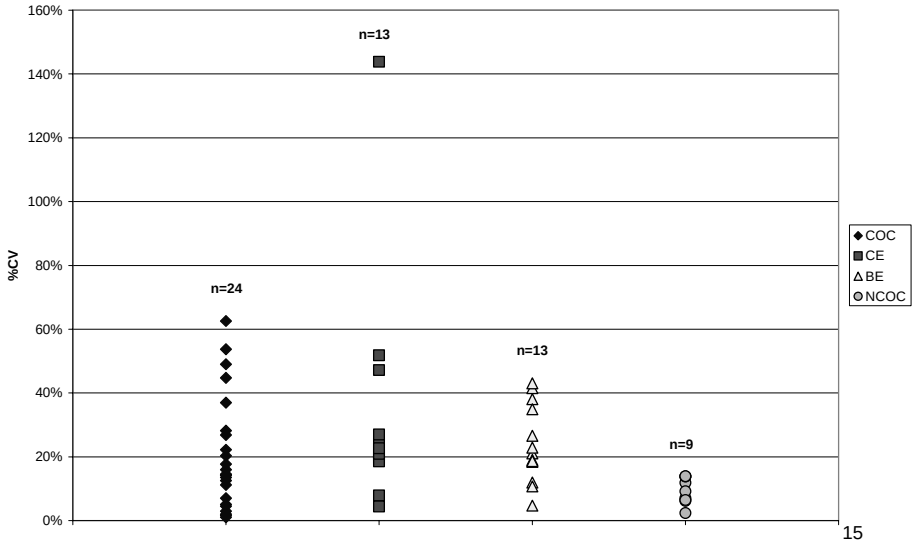

Distribution of Between Laboratory %CVs for All Urine Laboratories from Occasion 77
160.0%
140.0%
120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
%CV
AMP
MAMP
THCA
BE
COD
MOR
6-AM
PCP
n=5
n=5
n=5
n=5
n=4
n=5
n=5
n=4
Analyte

13


Between Laboratory Performance on Urine PT Sample 2009 for Ampehtamine
+20% = 3070, +10% = 2814
-20% = 2047, -10% = 2303
3323
3067
2812
2556
2300
2044
1788
1532
concentration (ng/mL)
+20%
+10%
MEAN
-10%
-20%
0
10
20
30
40
50
60
# of Labs

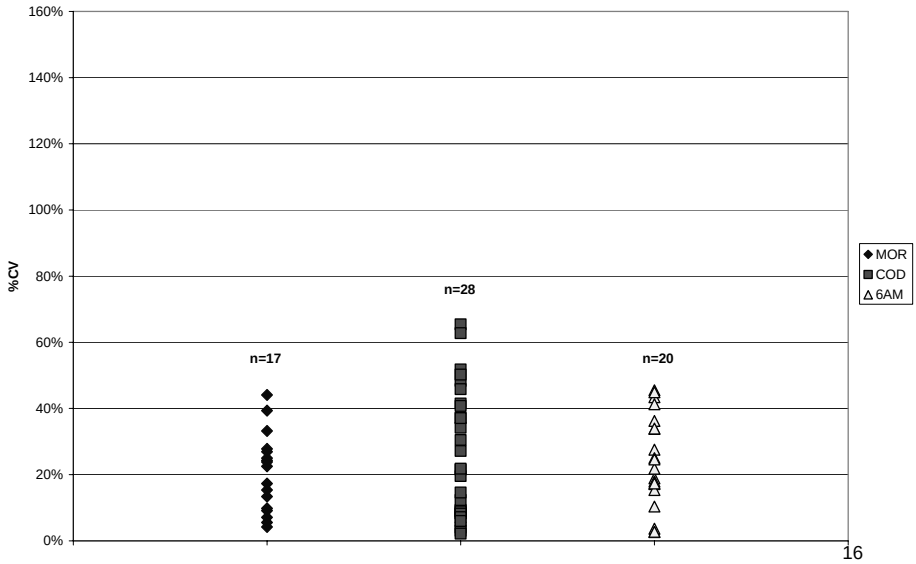
14

Distribution of Within Laboratory %CVs for All Laboratories for Cocaine and Related Compounds from Cycles 9 thru 11

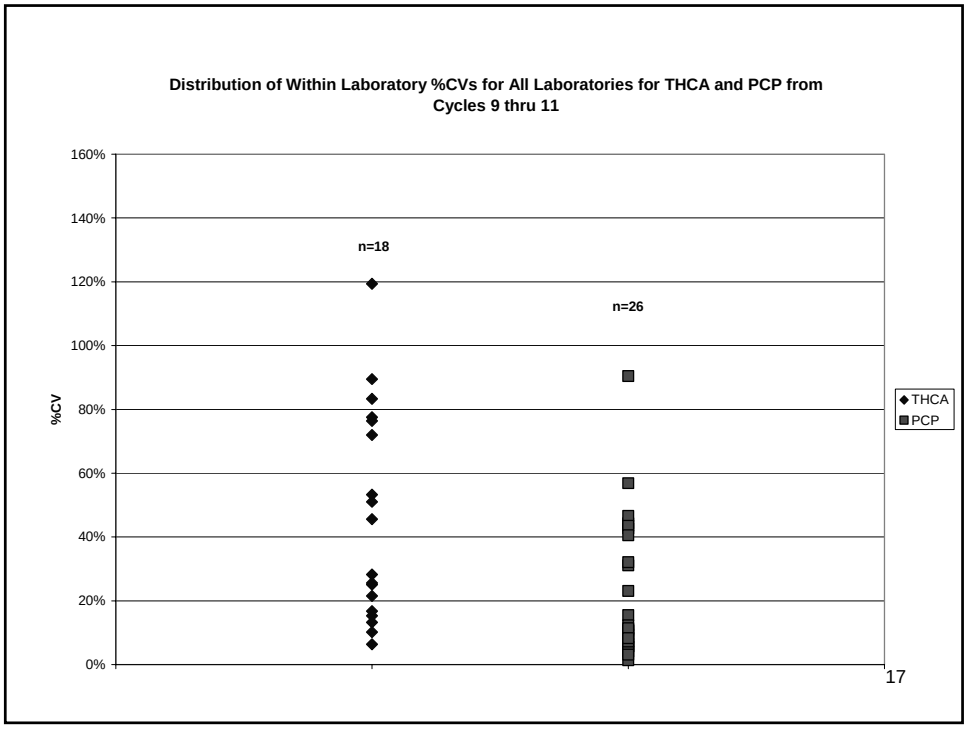


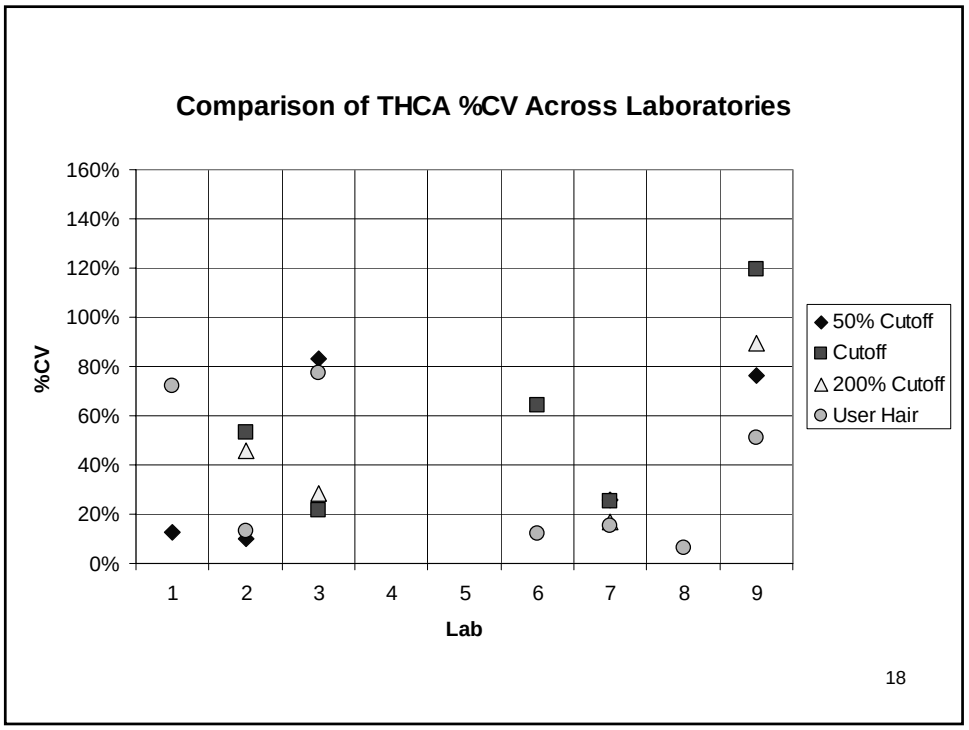
15

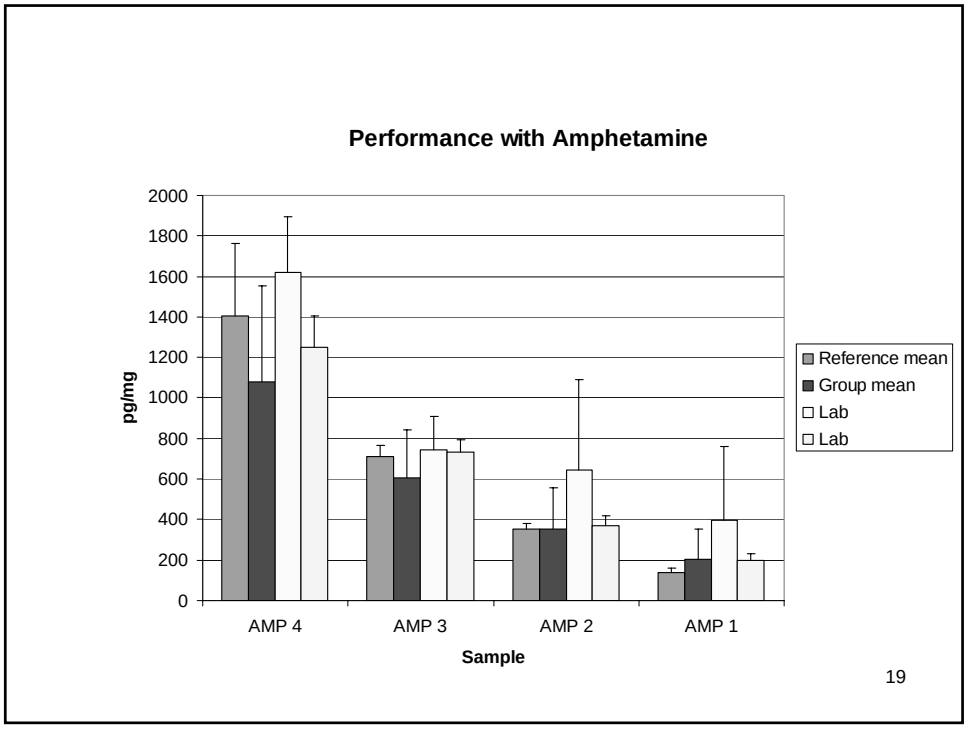
Distribution of Within Laboratory %CVs for All Laboratories for Opioids from Cycles 9 thru 11

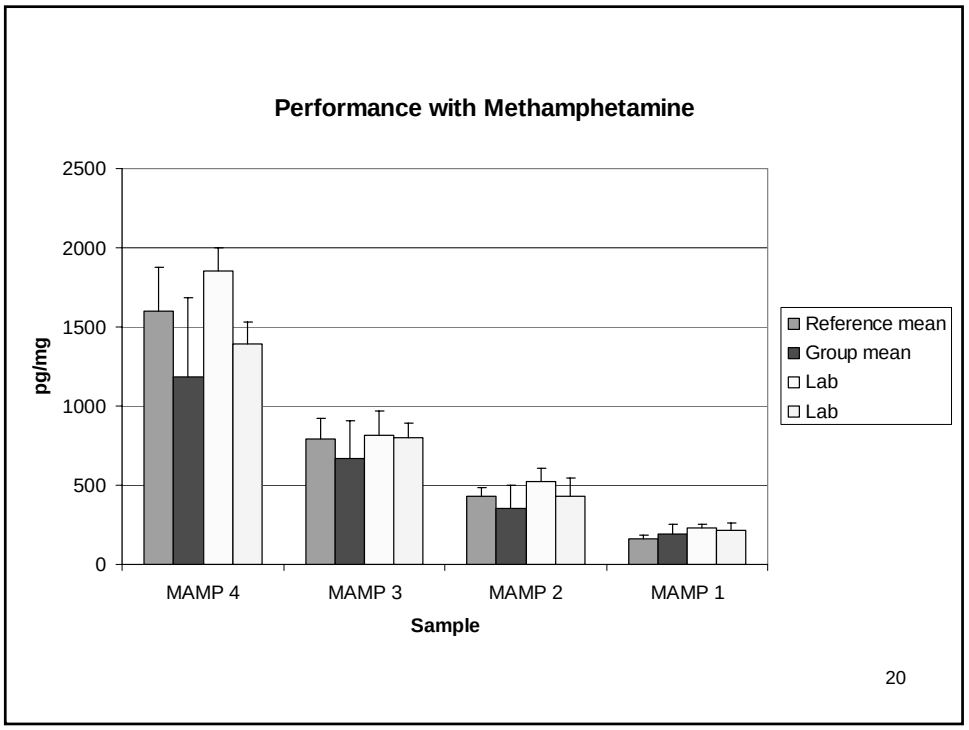


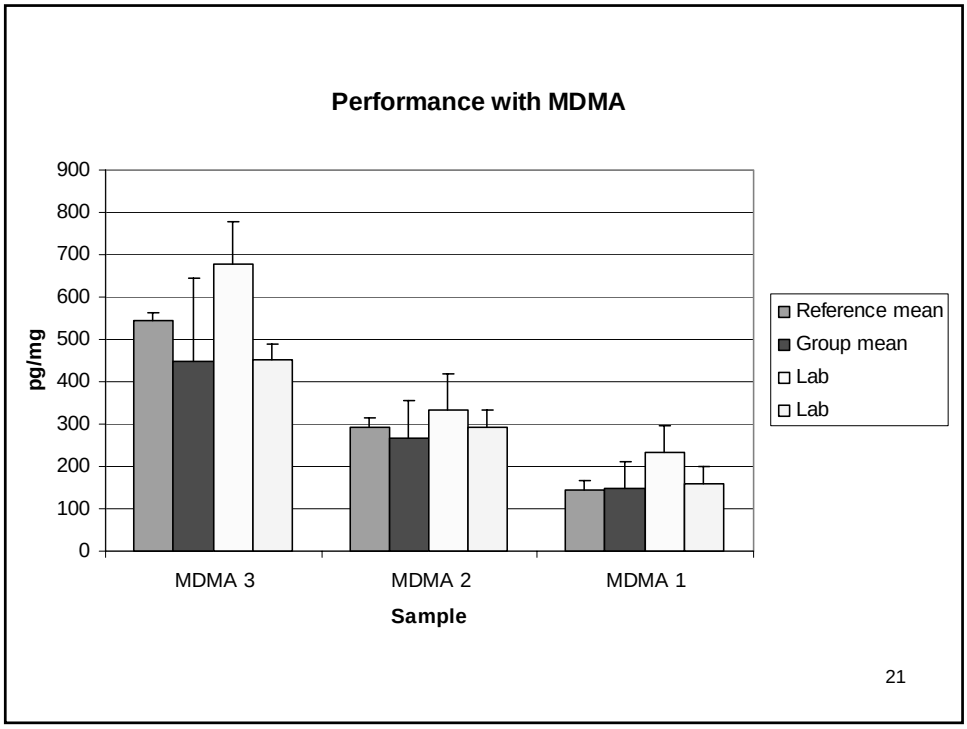
16

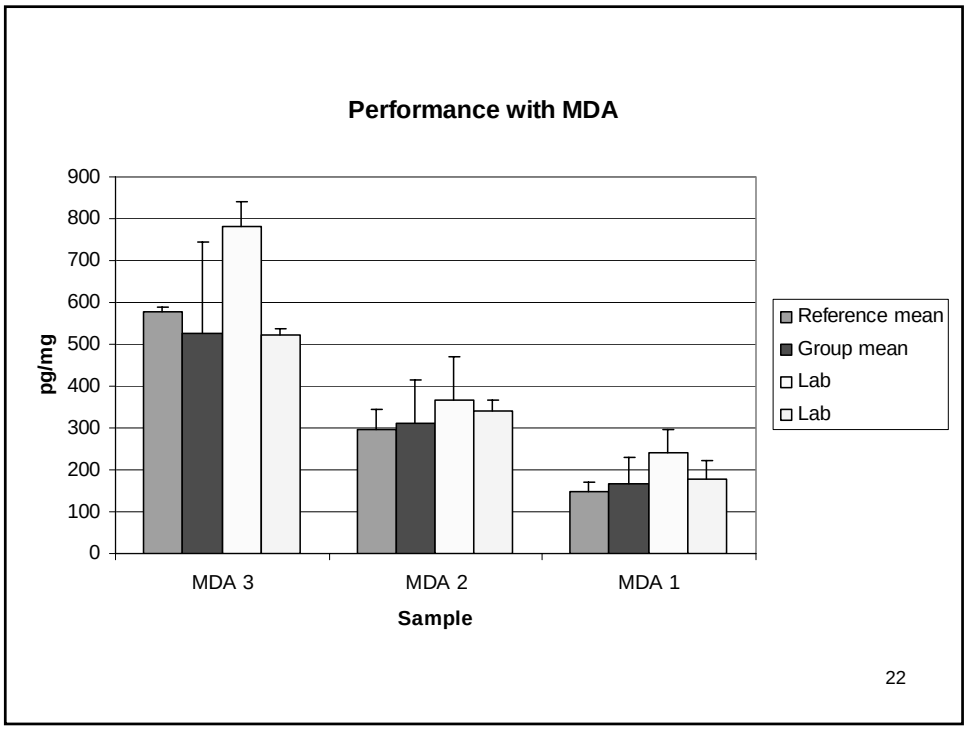

Distribution of Within Laboratory %CVs for All Laboratories for THCA and PCP from Cycles 9 thru 11
160%
140%
120%
100%
80%
60%
40%
20%
0%
%CV
n=18
n=26
THCA
PCP
17

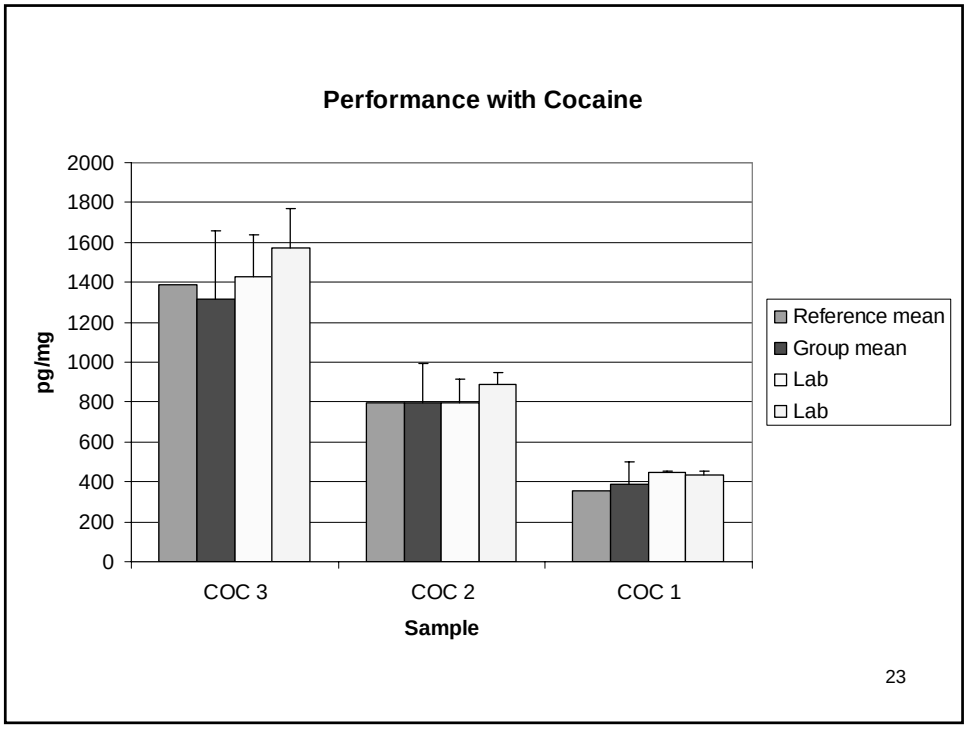

Comparison of THCA %CV Across Laboratories
160%
140%
120%
100%
80%
60%
40%
20%
0%
%CV
1
2
3
4
5
6
7
8
9
Lab
50% Cutoff
Cutoff
200% Cutoff
User Hair
18

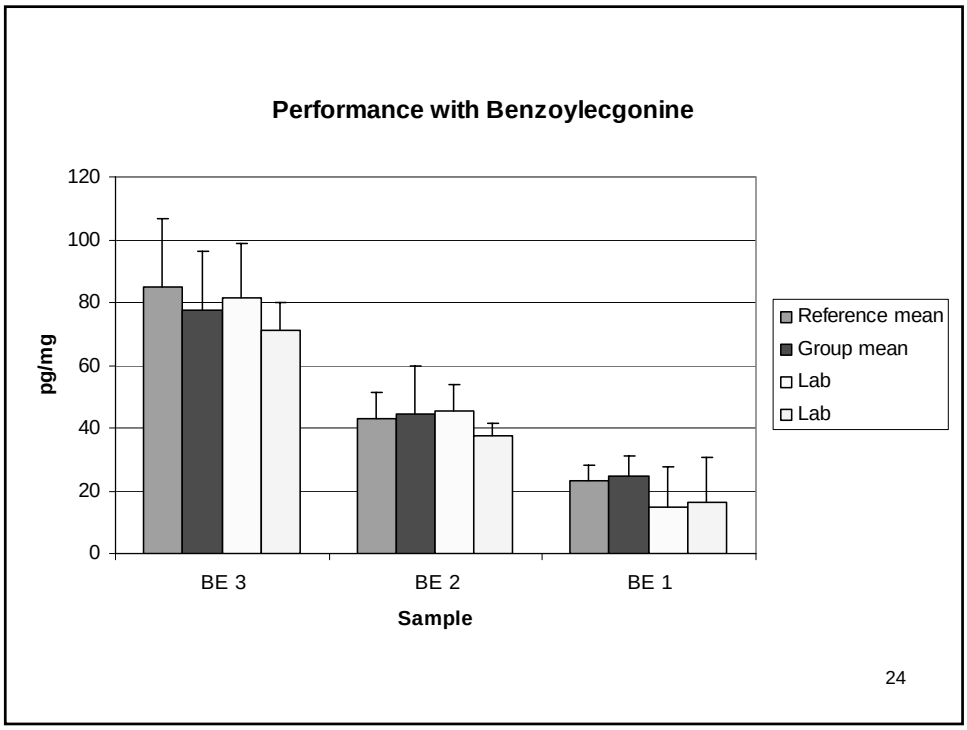

Performance with Amphetamine
2000
1800
1600
1400
1200
1000
800
600
400
200
0
pg/mg
AMP 4
AMP 3
AMP 2
AMP 1
Sample
Reference mean
Group mean
Lab
Lab
19

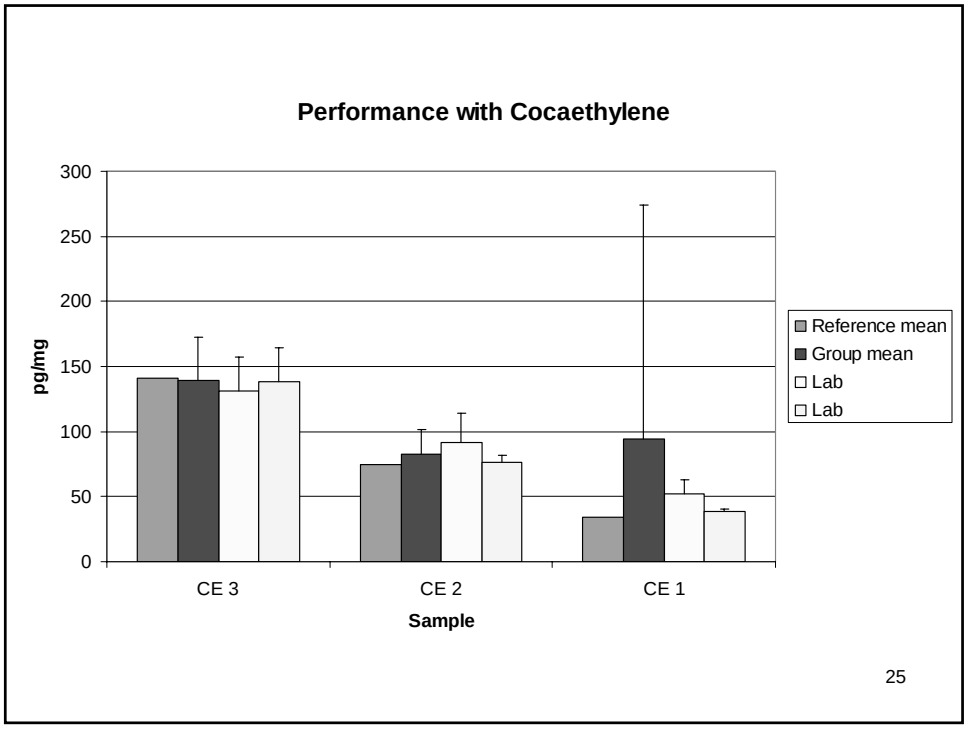

Performance with Methamphetamine
2500
2000
1500
1000
500
0
pg/mg
MAMP 4
MAMP 3
MAMP 2
MAMP 1
Sample
Reference mean
Group mean
Lab
Lab
20

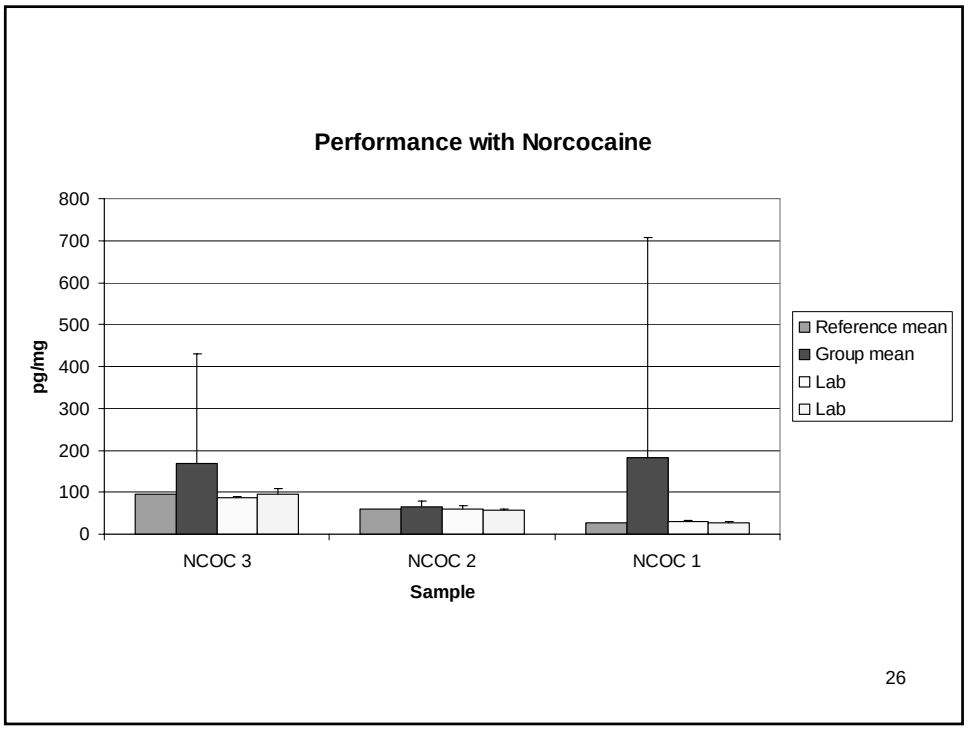

Performance with MDMA
900
800
700
600
500
400
300
200
100
0
pg/mg
MDMA 3
MDMA 2
MDMA 1
Sample
Reference mean
Group mean
Lab
Lab
21

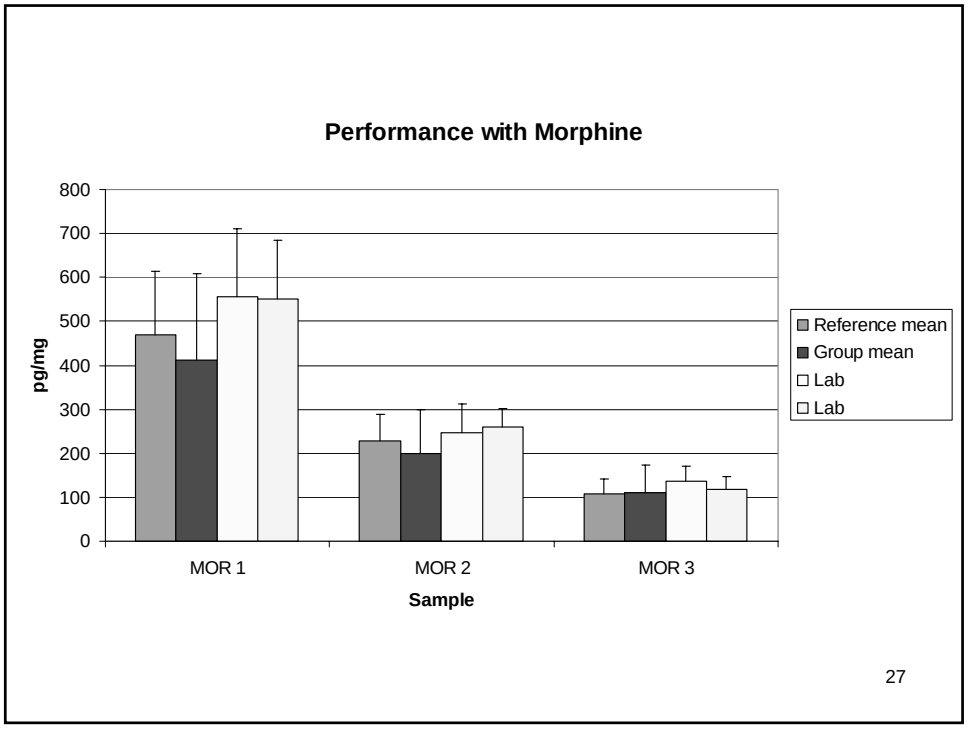

Performance with MDA
900
800
700
600
500
400
300
200
100
0
pg/mg
MDA 3
MDA 2
MDA 1
Sample
Reference mean
Group mean
Lab
Lab
22

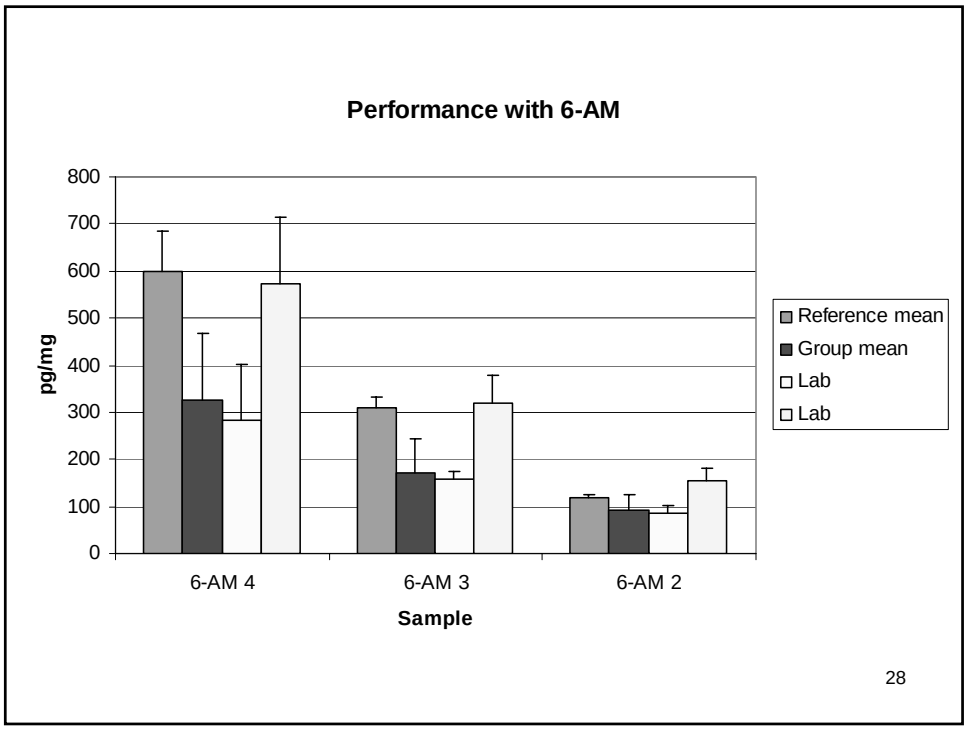

Performance with Cocaine
2000
1800
1600
1400
1200
1000
800
600
400
200
0
pg/mg
COC 3
COC 2
COC 1
Sample
Reference mean
Group mean
Lab
Lab
23

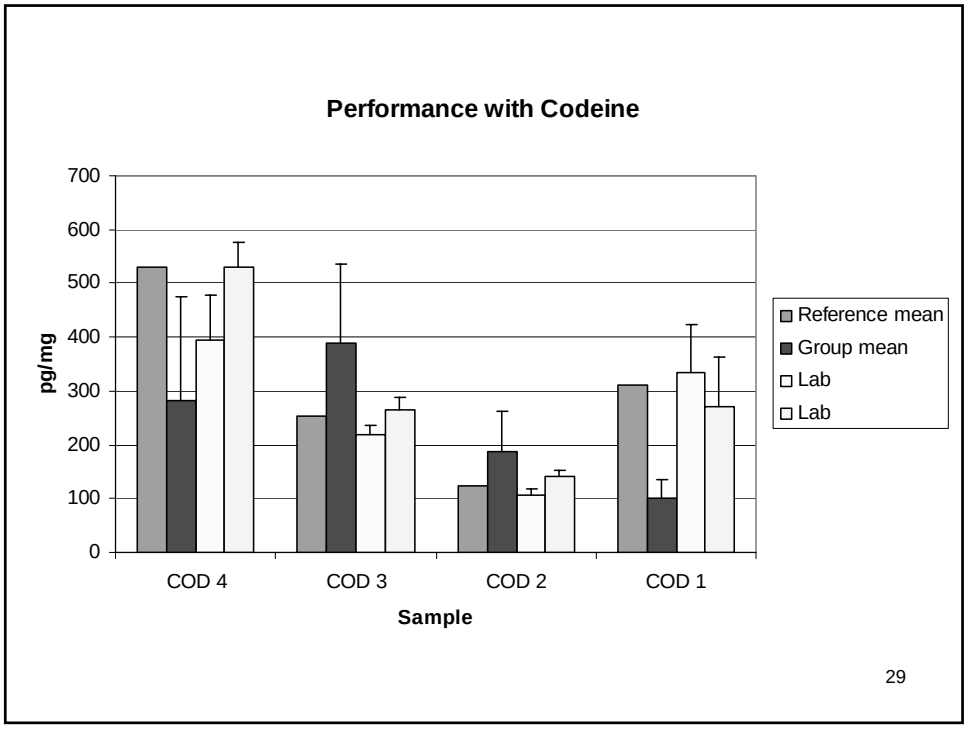

Performance with Benzoylecgonine
120
100
80
60
40
20
0
pg/mg
BE 3
BE 2
BE 1
Sample
Reference mean
Group mean
Lab
Lab
24

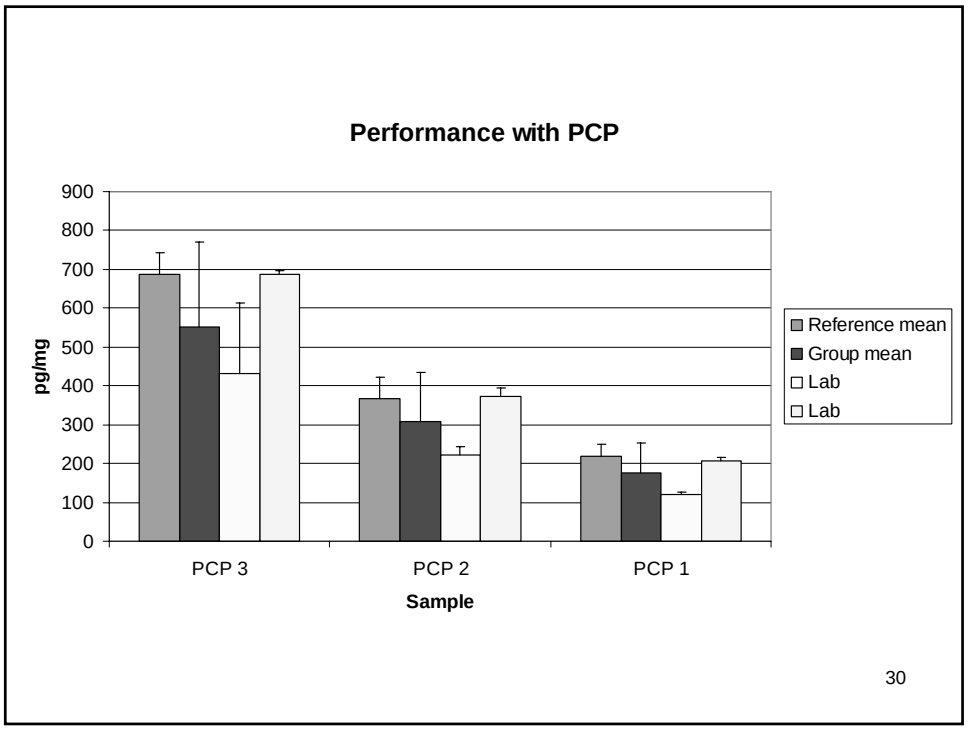

Performance with Cocaethylene
300
250
200
150
100
50
0
pg/mg
CE 3
CE 2
CE 1
Sample
Reference mean
Group mean
Lab
Lab
25

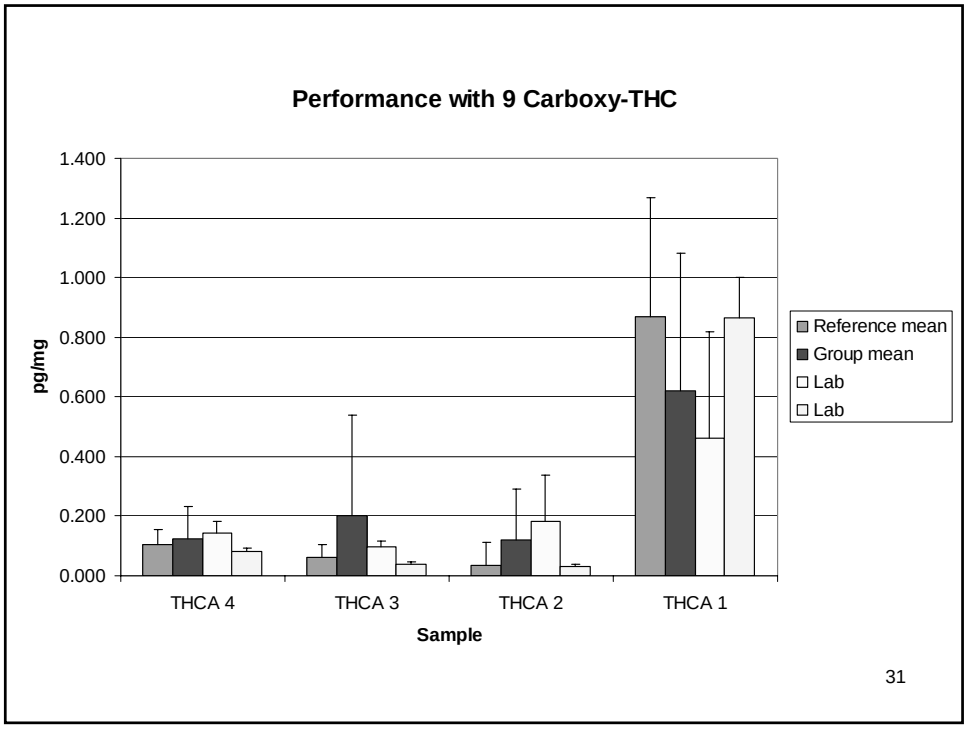

Performance with Norcocaine
800
700
600
500
400
300
200
100
0
pg/mg
NCOC 3
NCOC 2
NCOC 1
Sample
Reference mean
Group mean
Lab
Lab
26

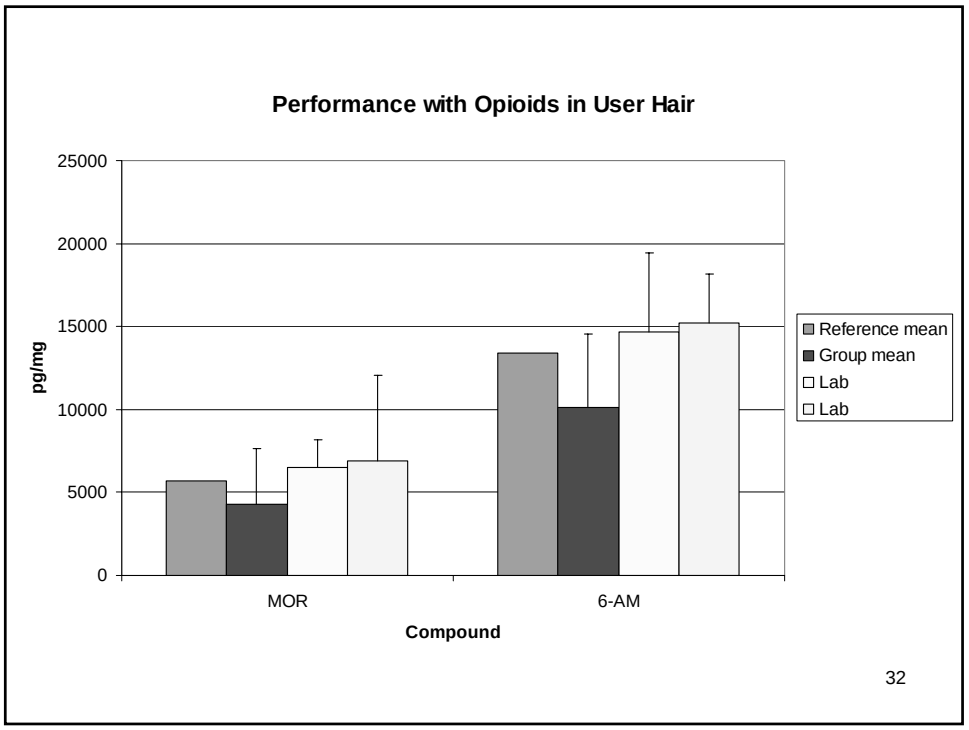

Performance with Morphine
800
700
600
500
400
300
200
100
0
pg/mg
MOR 1
MOR 2
MOR 3
Sample
Reference mean
Group mean
Lab
Lab
27


Performance with 6-AM
800
700
600
500
400
300
200
100
0
pg/mg
6-AM 4
6-AM 3
6-AM 2
Sample
Reference mean
Group mean
Lab
Lab
28


Performance with Codeine
700
600
500
400
300
200
100
0
pg/mg
COD 4
COD 3
COD 2
COD 1
Sample
Reference mean
Group mean
Lab
Lab
29


Performance with PCP
900
800
700
600
500
400
300
200
100
0
pg/mg
PCP 3
PCP 2
PCP 1
Sample
Reference mean
Group mean
Lab
Lab
30


Performance with 9 Carboxy-THC
1.400
1.200
1.000
0.800
0.600
0.400
0.200
0.000
pg/mg
THCA 4
THCA 3
THCA 2
THCA 1
Sample
Reference mean
Group mean
Lab
Lab
31


Performance with Opioids in User Hair
25000
20000
15000
10000
5000
0
pg/mg
MOR
6-AM
Compound
Reference mean
Group mean
Lab
Lab
32

Performance Testing and Certification of Hair Testing Laboratories

Proposed Guidelines as released for public comment
(Fed Reg Vol 69 April 2004)

33

Section 9.6 What Are the PT Requirements for an Applicant Laboratory to Conduct Hair Testing?

- (a) An applicant laboratory that seeks certification to conduct hair testing must satisfy the following criteria on 3 consecutive sets of PT samples:
  - (1) Have no False Positive Results
  - (2) Correctly identify and confirm at least 90 percent of the total drug challenges on the 3 sets of PT samples

34

PT Requirements for an Applicant Hair Testing Laboratory Section 9.6(a) (cont)

- (3) Correctly determine the quantitative values for at least 80 percent of the total drug challenges to be within ± 20% or ±2 standard deviations of the calculated reference group mean
- (4) Have no quantitative value on a drug concentration that differs by more than 50 percent from the calculated reference mean, and

35

PT Requirements for an Applicant Hair Testing Laboratory Section 9.6(a) (cont)

- (5) For an individual drug, must correctly detect and quantify at least 50 percent of the total drug challenges

36

Laboratory Performance Compared to Section 9.6(a) PT Requirements

- (1) No False Positives; however all analytes were directed for only confirmation by analyte class (initial testing not conducted)
- (2) Two labs correctly identified 90% of analyte challenges over 3 cycles
  - For AMP,MAMP,BE, MOR,6-AM, COD, PCP, THCA
    - 5 laboratories met this criterion
  - For COC,NCOC,CE,MDMA,MDA,MDEA
    - 2 laboratories met this criterion

37

Laboratory Performance Compared to Section 9.6(a) PT Requirements

- (3) No laboratory quantitated 80% of analyte challenges within 20% of group mean
- (4) All laboratories had one or more 50% quantitation errors
- (5) No laboratory quantitated 50% of all individual analytes within 20% of the mean

38

Pilot Hair PT Program

- Purposes are:
  - To provide information on the state of the hair testing science to help guide the development and implementation of the expanded Mandatory Guidelines
    - To develop appropriate PT materials for the National Laboratory Certification Program
  - To provide opportunity for interested labs to develop accurate and precise test procedures before implementation of the expanded Guidelines

39

Variation in Hair Pilot PT Results I

- Large variation exists among labs
  - Possible reasons:
    - Labs have a variety of methods for preparing hair for analysis (powder, snippets, solubilization)
    - Labs have widely varying methods for extraction of drugs from the solid hair matrix
    - Labs are conducting confirmatory testing with a wide array of instruments, some of which do not have the necessary sensitivity.

40

Variation in Hair Pilot PT Results II

- Large variations exist within labs
  - Possible reasons:
    - Reference materials are not commercially available
    - Labs have not developed procedures that are accurate and precise
      - Sample measurement
      - Best extraction procedures
      - Best instrumentation

41

Variation in Hair Pilot PT Results III

- PT sample composition may account for some of the variability.
  - Spiked PT samples appear to have uniform drug concentrations based on segment analysis and ability of some labs to provide results with CVs <10%
  - Values for BZE and THCA in spiked hair appear to change over time.

42

Variation in Hair Pilot PT Results IV

- Lab quality control procedures may largely account for the variability.
  - Standards used to calibrate do not contain drug analytes at concentrations required for workplace drug testing
  - Controls included in test batches do not ensure accuracy and precision of the testing process

43

Road Map for Successful Implementation of Guidelines

1. Increase the dialogue between the NLCP and participant labs to produce an exchange of ideas and solutions
   - Use webcast meetings, conference calls and/or teleconferencing to provide feedback as soon as possible after each PT event
   - Review test results with participant labs, encouraging group development of improved methods and solutions to observed analytical problems

44

Road Map (cont)

2. Obtain commitment from labs to use future hair pilot PT program resources to develop and improve testing accuracy and precision
3. Use future cycles to resolve sample and lab variation
4. Facilitate the development of appropriate calibrator and control materials

45

NLCP Oral Fluid Pilot Performance Testing (PT) Program Update

Cycles 4 Thru 6

Drug Testing Advisory Board
March 7, 2006

John M. Mitchell and Francis M. Esposito

Objectives

- Review the Design and Results of Oral Fluid Pilot PT Cycles 4 Thru 6
- Compare Test Results to Requirements of Proposed Guidelines of April 2004
- To Disseminate Future Plans

Pilot Oral Fluid PT Program: Design of Cycles 4 Thru 6

NLCP

Pilot PT of Oral Fluid: Cycle 4 Thru 6

- New Production of All Analytes
  - AMP, MAMP
  - MDA, MDMA, MDEA
  - COC
  - BE
  - 6-AM, COD, MOR
  - PCP
  - THC
- 3 Concentrations for Each
  - 50% Cutoff
  - Cutoff
  - 200% Cutoff (except THC, COC, & BE = 300%)

NLCP

Pilot PT of Oral Fluid: Cycles 4 Thru 6

- Confirmatory Testing Only
- Included in Shipment:
  - 21 NLCP spiked Oral Fluid Samples
  - Each challenge: 2 mL aliquot
- Results Submitted by Labs within 10 Working Days

NLCP

Pilot PT of Oral Fluids: Cycles 4 Thru 6

- Samples Shipped Oct 2003 – Jan 2004
- 3 Shipments- Alternate Months
- 12 Labs Participated
- Analyses of Results Were Provided to Labs at End of Study (after cycle 6)

NLCP

Cycles 4 Thru 6 of Pilot Oral Fluid PT Program: Confirmation Analysis

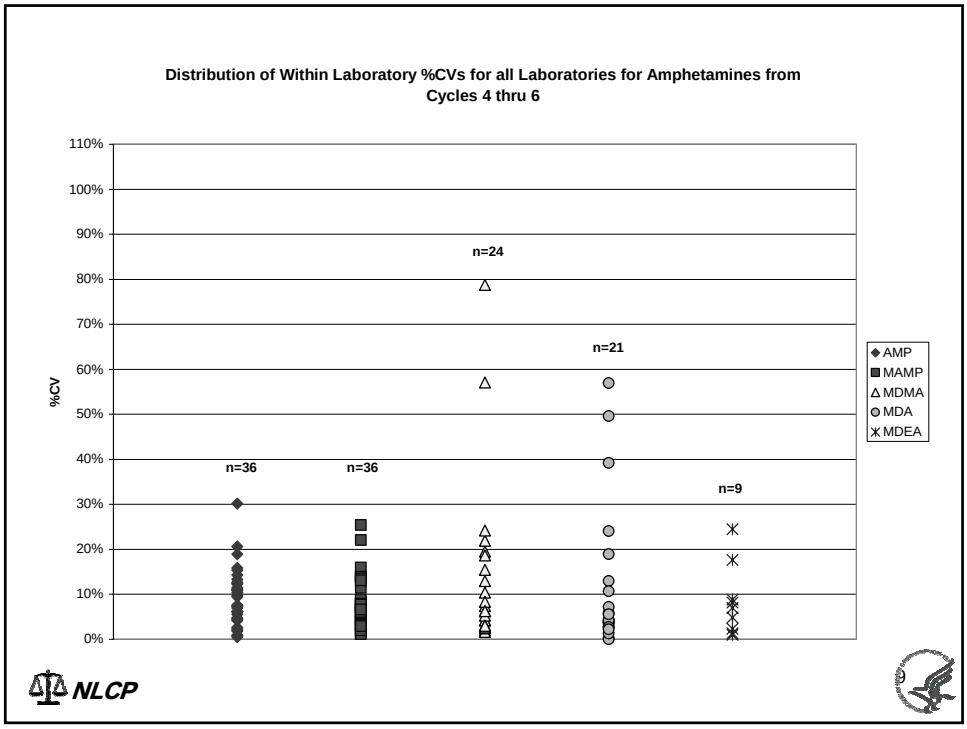
Laboratory	Specimen Required per Drug Class Tested (mL)	LOQ ≤ HHS Proposed Cutoff	Current Urine Analytes Analyzed	Proposed New Analytes Analyze
E	0.25 (THC = 0.1)	Y	Y	No: MDMA, MDEA, MDA
F	0.2 (OPI, PCP = 0.3)	6-AM = 5 ng/mL	Y	No: COC, MDEA
G	0.4 (OPI = 0.1)	Y	Y	Y
H	0.05 (OPI, THC = 0.125)	Y	Y	Y
J	1	Y	Y	No: MDMA, MDEA, MDA
L	0.25	Y	Y	Y
N	0.066 (Amps, OPI = 0.033)	Y	Y	No: COC, MDEA
O	0.25	Y	Y	No: MDEA
P	0.25 (Amps, COC =0.125)	Y	Y	Y
R	0.2	Y	Y	No: COC, MDEA
S	1 (PCP = 0.5)	Y	Y	Y
T	0.25	Y	No: Opiates	No: Opiates

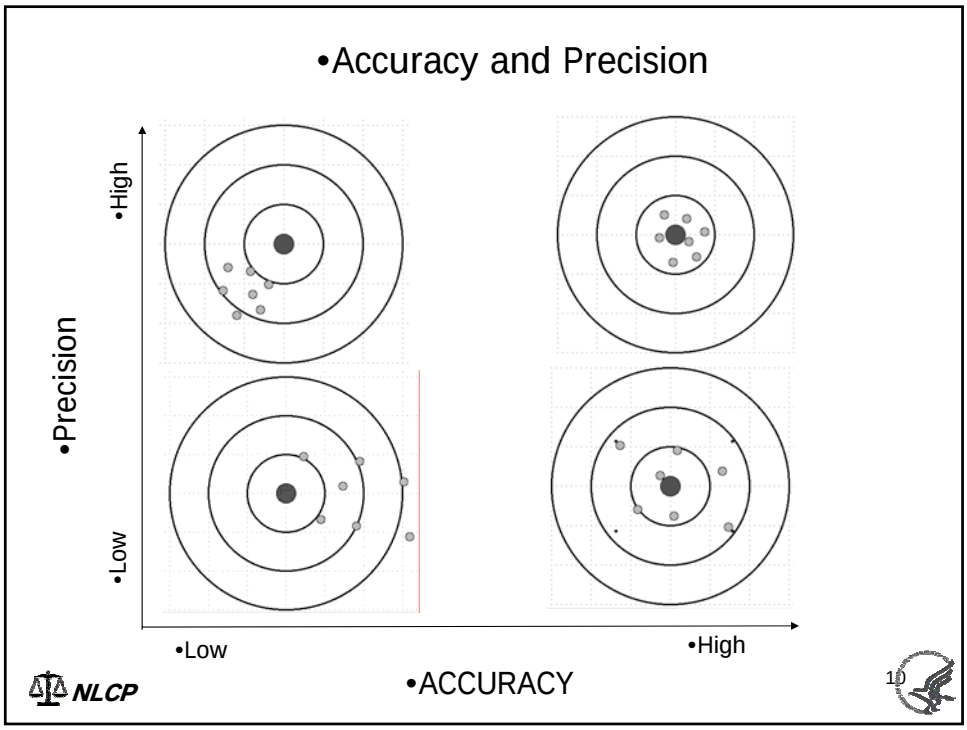
NLCP

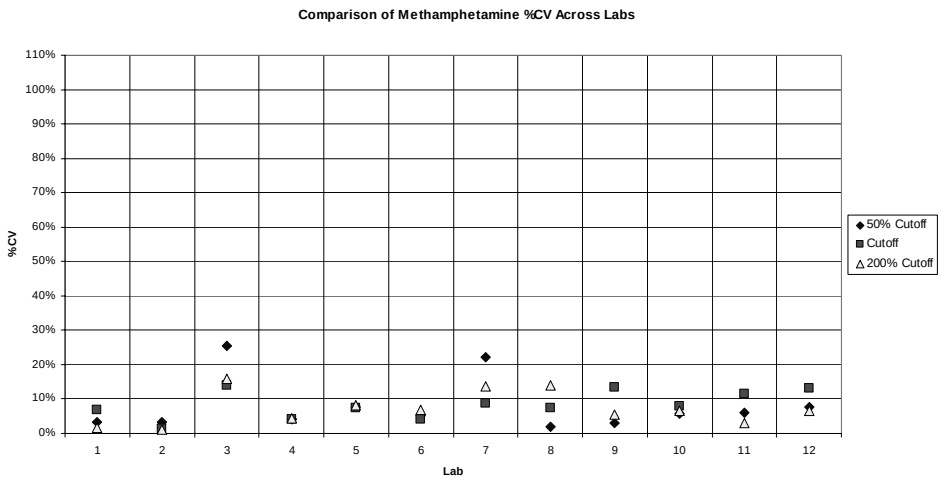
Cycles 4 Thru 6 Highlights

- Quantitative Variation
  - Within Lab Variation
  - Accuracy and Precision
- Performance of Selected Participants

NLCP

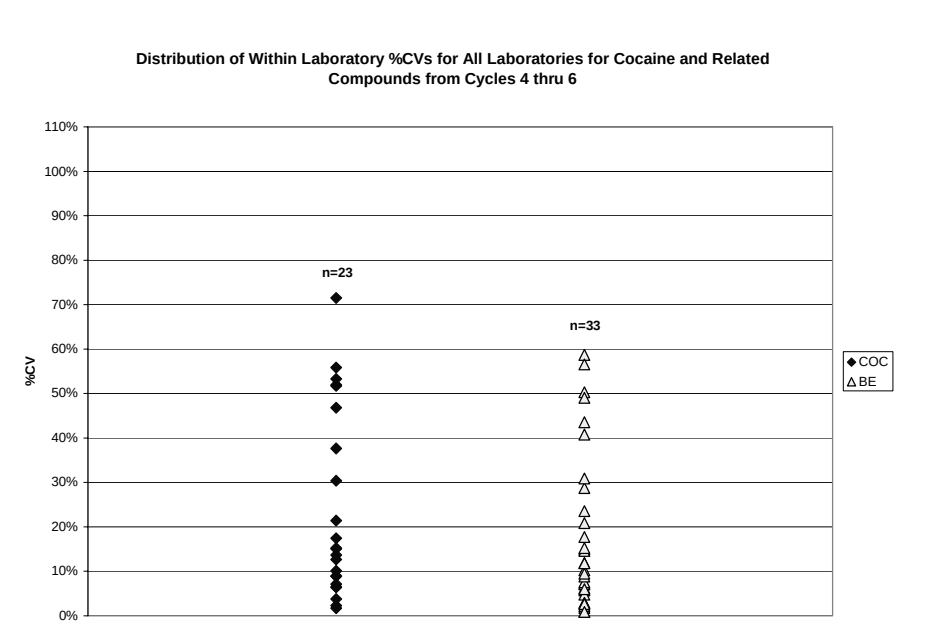

Distribution of Within Laboratory %CVs for all Laboratories for Amphetamines from Cycles 4 thru 6
110%
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
%CV
n=36
n=36
n=24
n=21
n=9
AMP
MAMP
MDMA
MDA
MDEA
NLCP
9


•Accuracy and Precision
•Precision
•High
•Low
•Low
•High
•ACCURACY
NLCP
10



NLCP

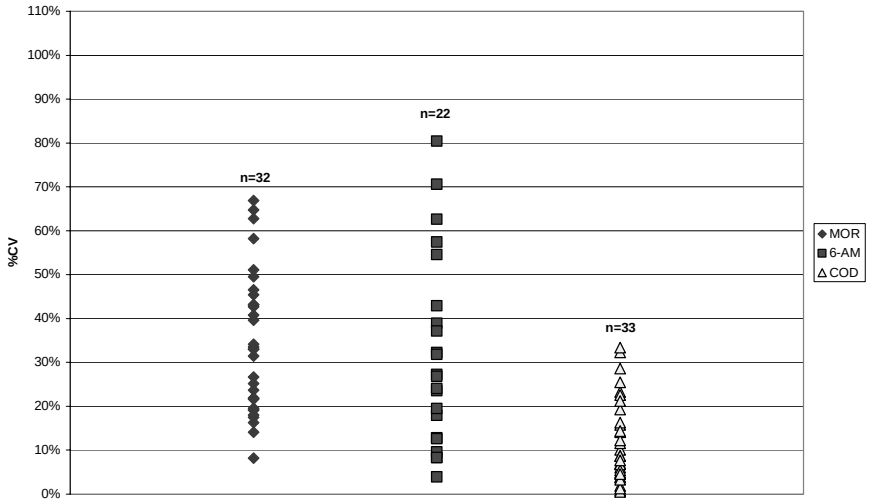
11



NLCP

12

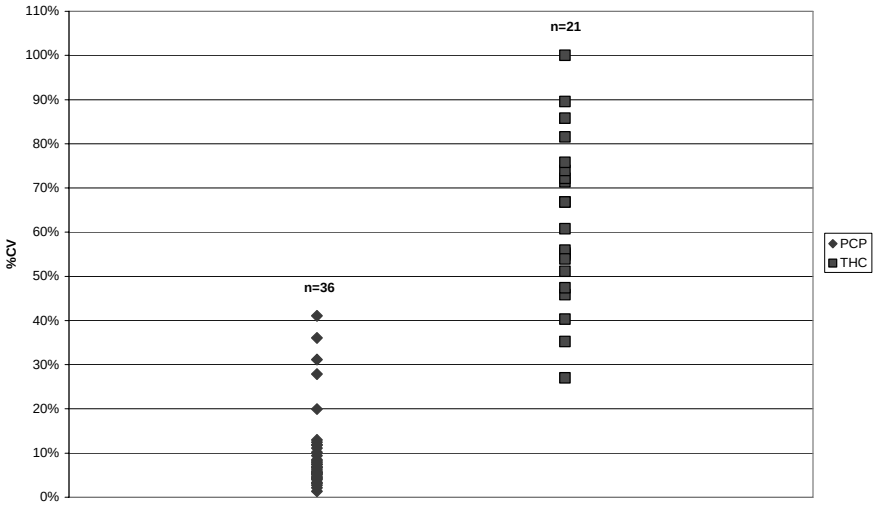
Distribution of Within Laboratory %CVs for All Laboratories for Opioids from Cycles 4 thru 6



NLCP

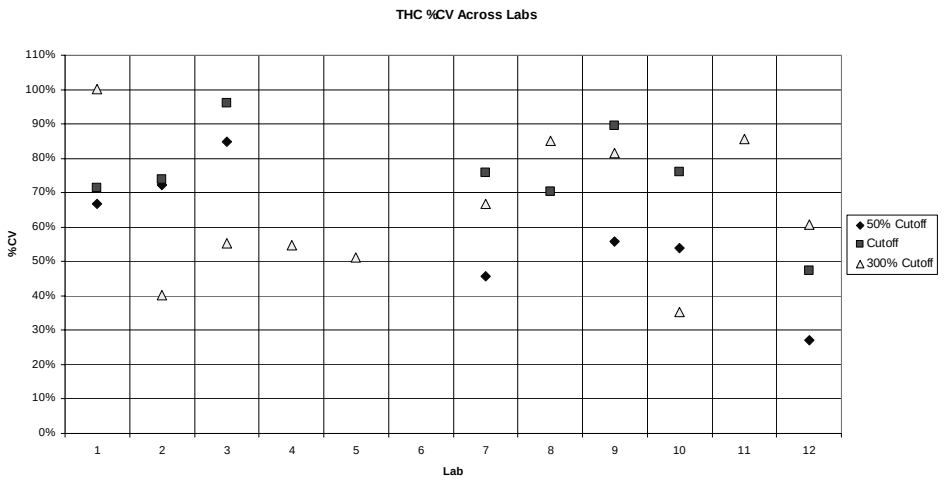
13

Distribution of Within Laboratory %CVs for All Laboratories for PCP and THC from Cycles 4 thru 6



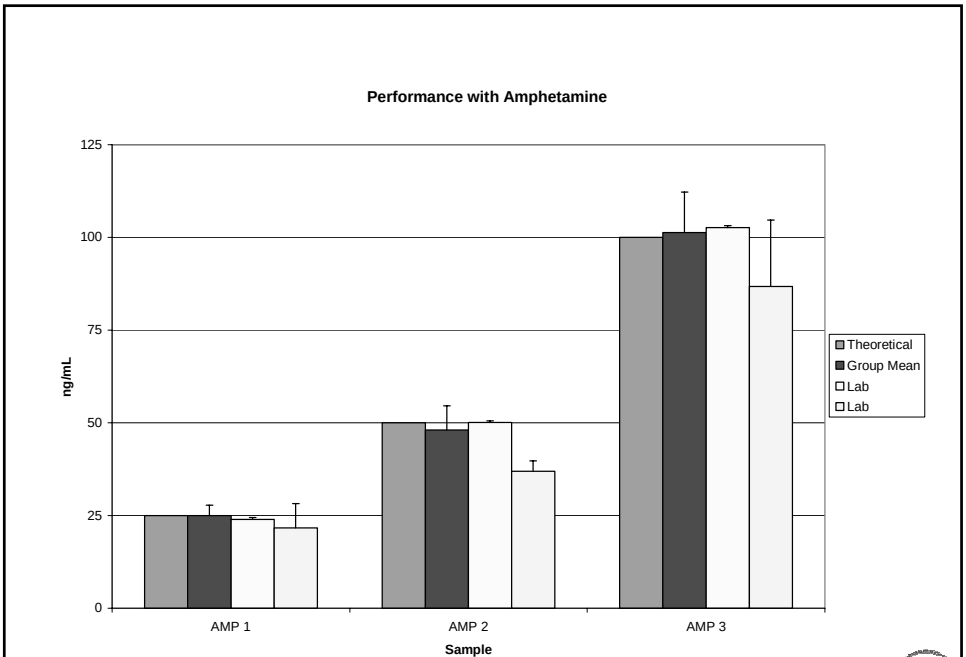
NLCP

14



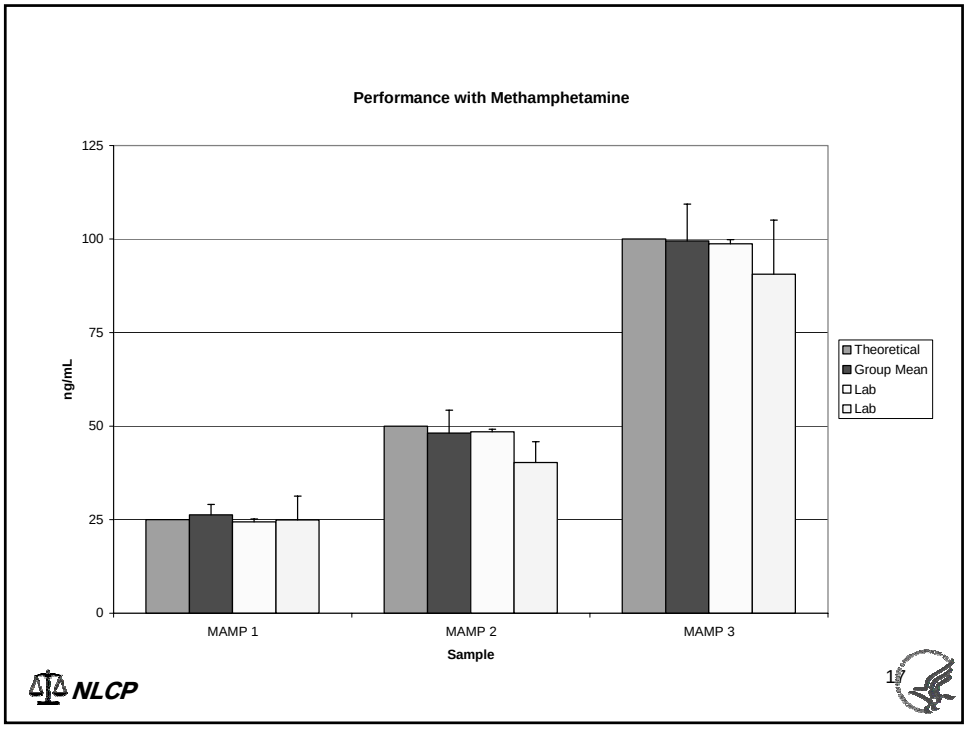
NLCP

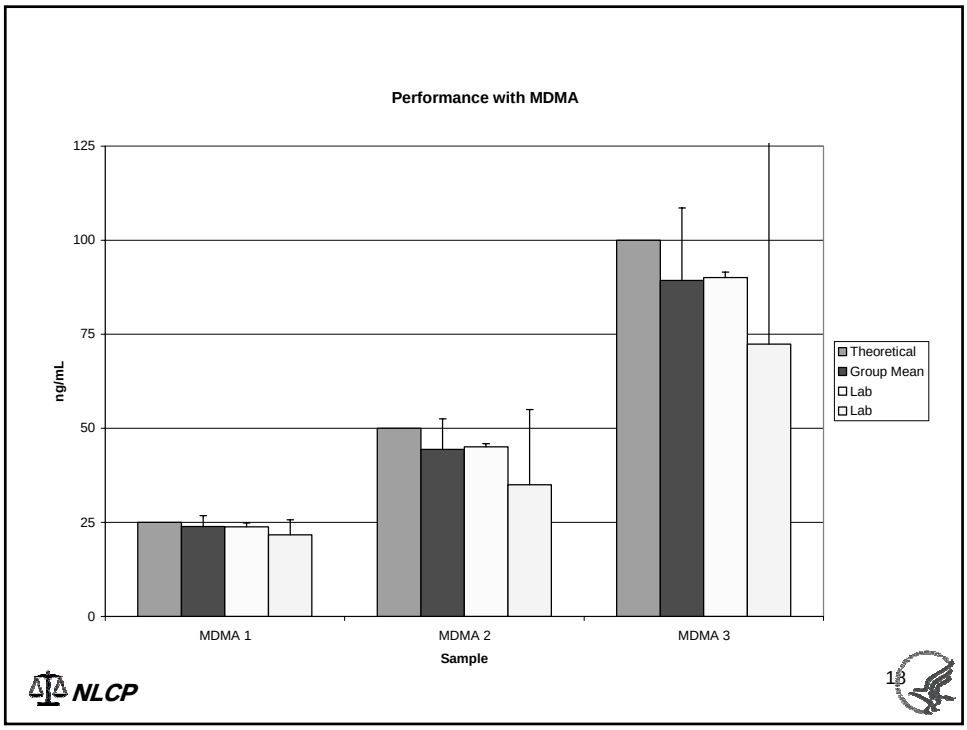
15

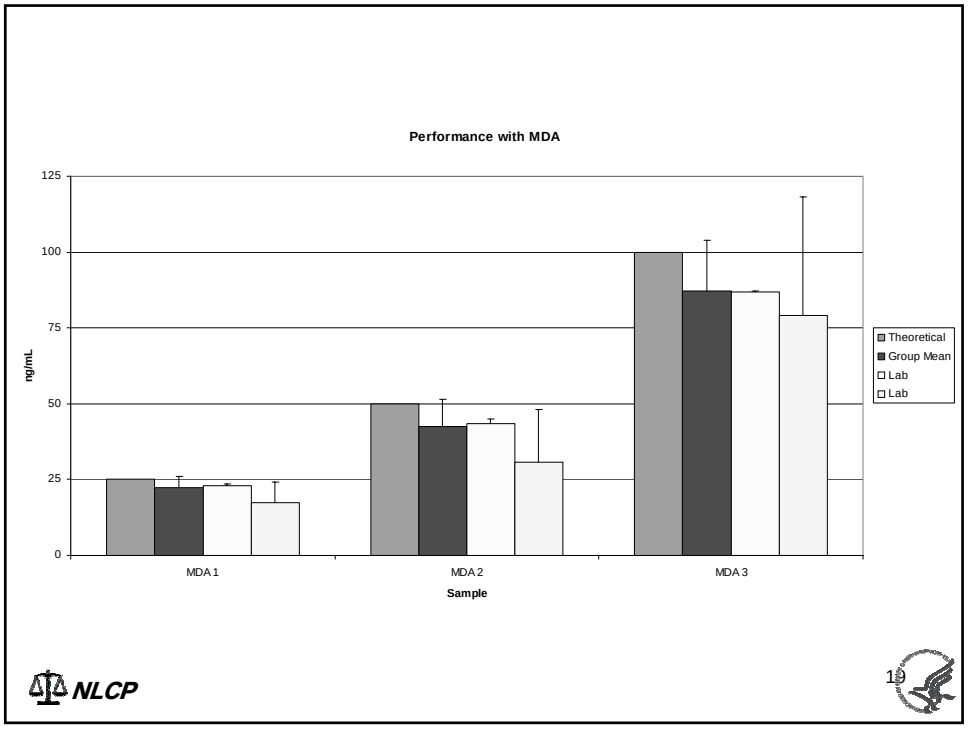


NLCP

15

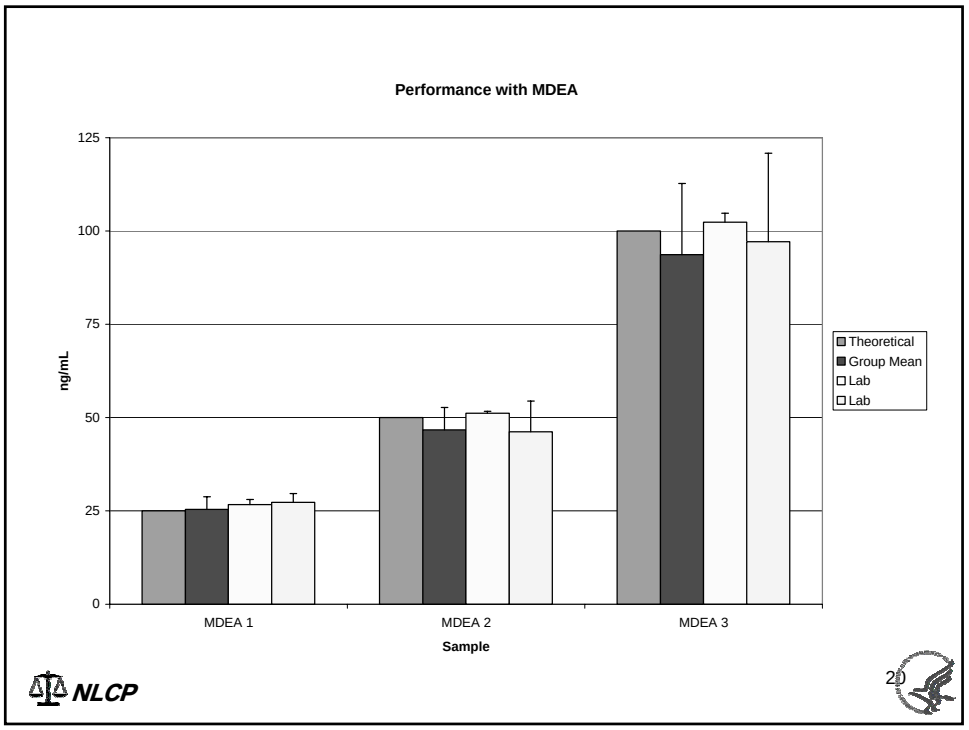

Performance with Methamphetamine
125
100
75
50
25
0
ng/mL
MAMP 1
MAMP 2
MAMP 3
Sample
Theoretical
Group Mean
Lab
Lab
NLCP
17


Performance with MDMA
125
100
75
50
25
0
ng/mL
MDMA 1
MDMA 2
MDMA 3
Sample
Theoretical
Group Mean
Lab
Lab
NLCP
18



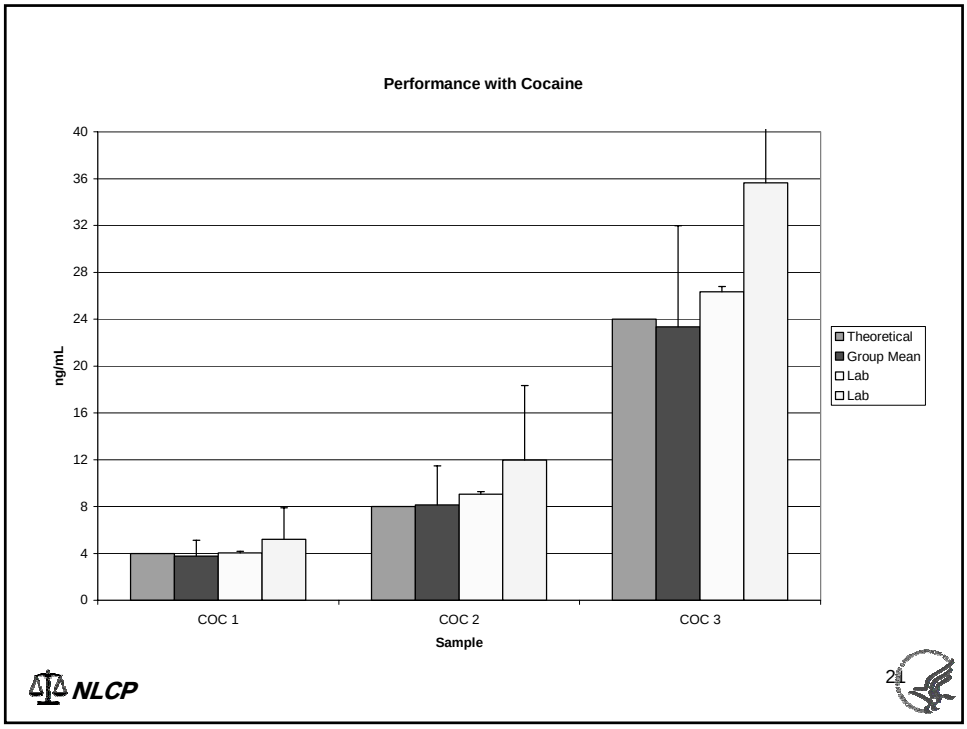
NLCP

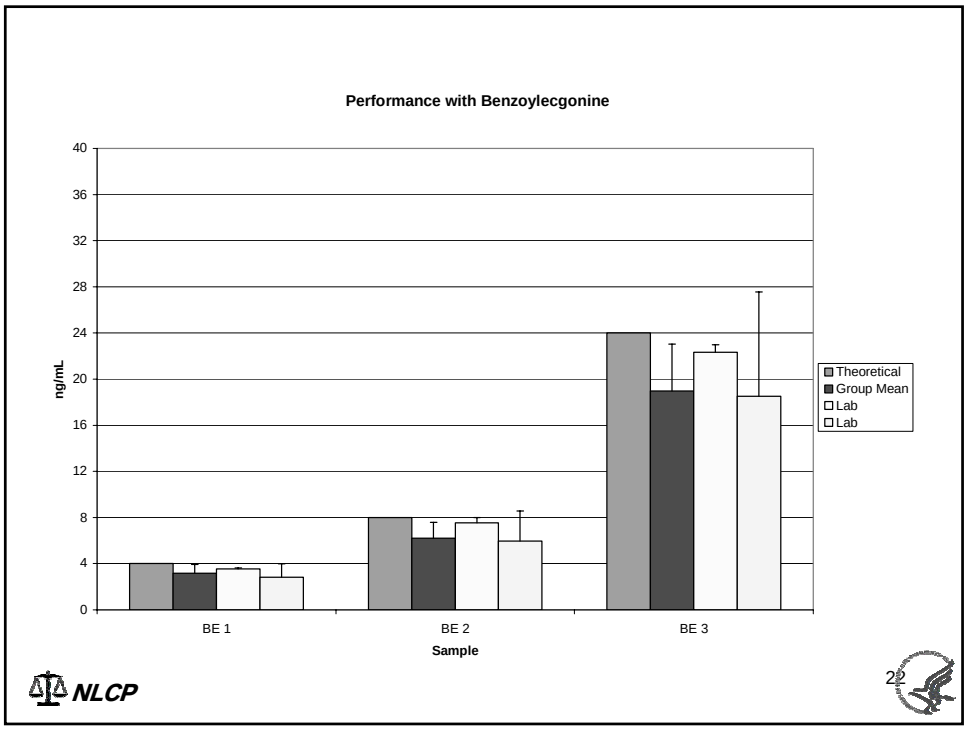
19

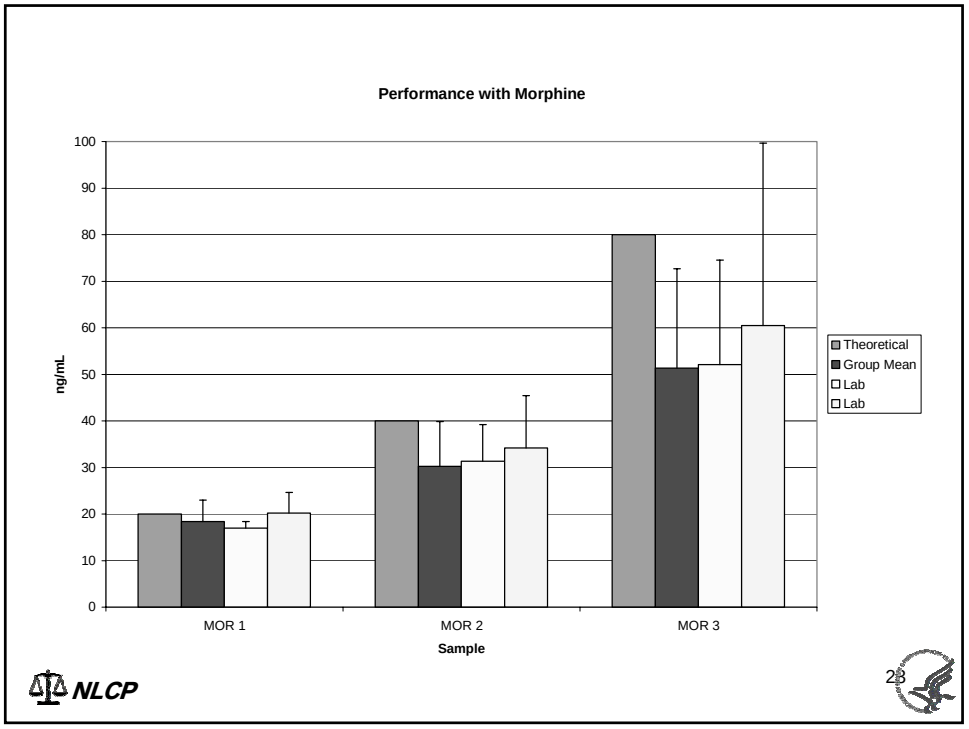


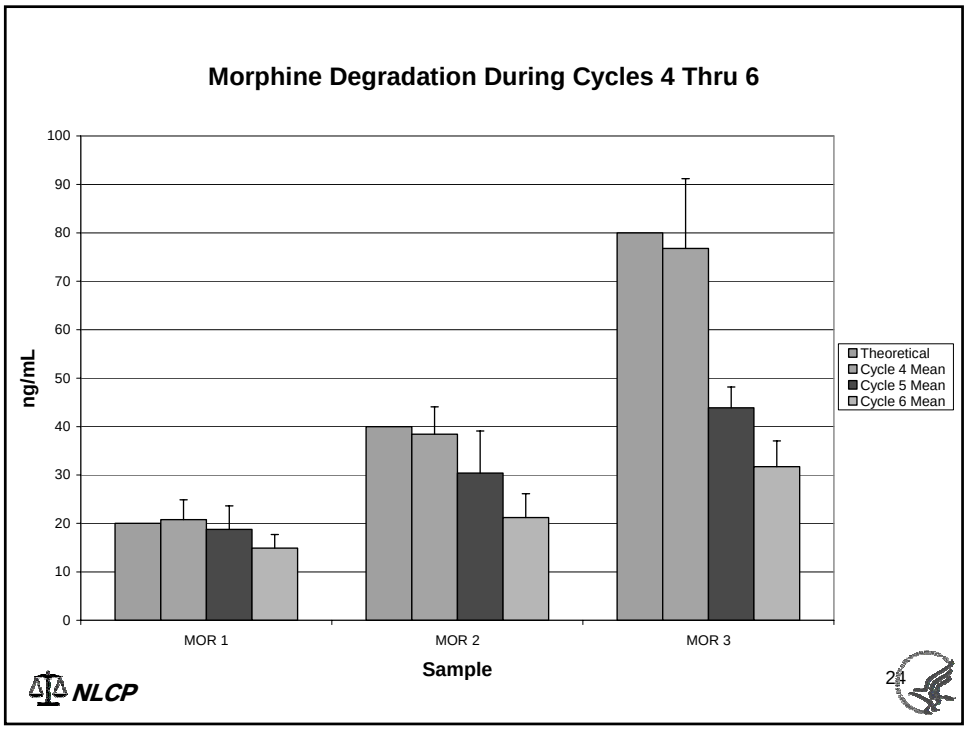
NLCP

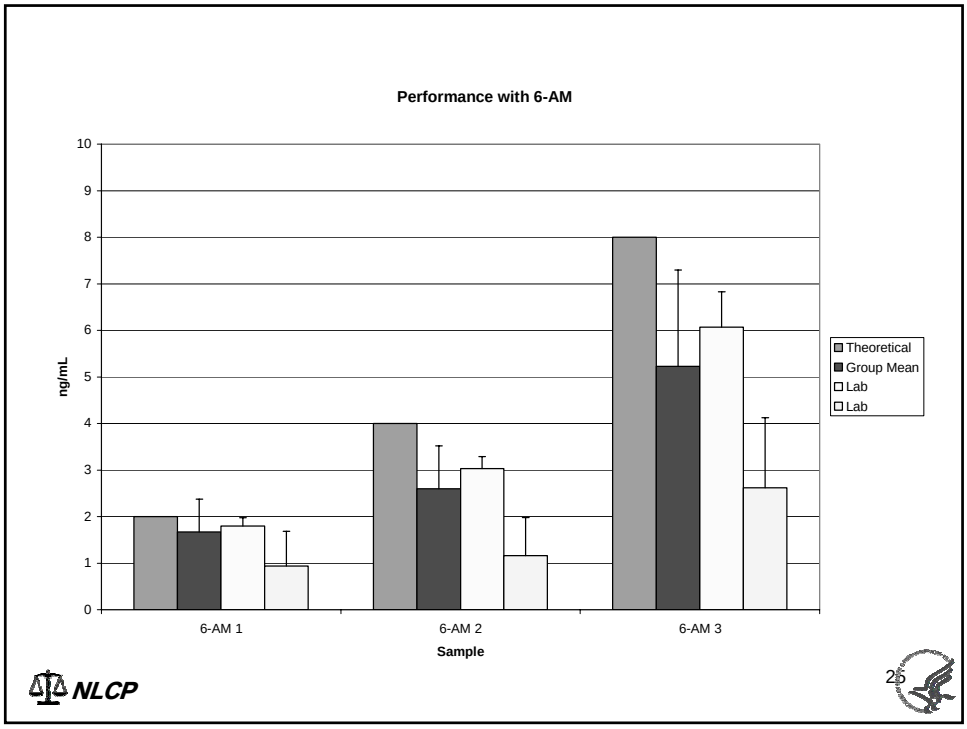
20

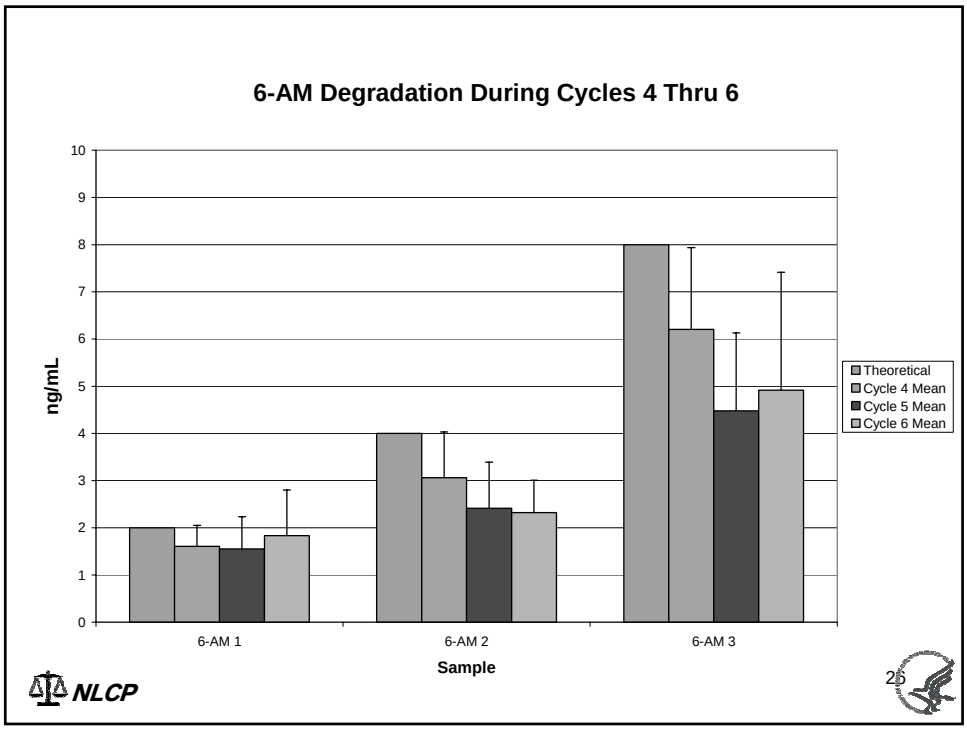

Performance with Cocaine
40
36
32
28
24
20
16
12
8
4
0
ng/mL
COC 1
COC 2
COC 3
Sample
Theoretical
Group Mean
Lab
Lab
NLCP
21


Performance with Benzoylecgonine
40
36
32
28
24
20
16
12
8
4
0
ng/mL
BE 1
BE 2
BE 3
Sample
Theoretical
Group Mean
Lab
Lab
NLCP
22

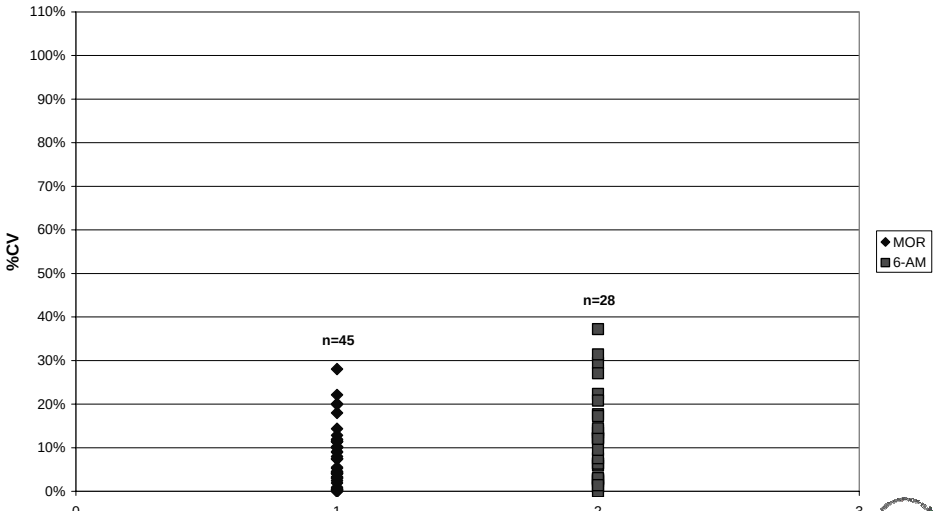

Performance with Morphine
100
90
80
70
60
50
40
30
20
10
0
ng/mL
MOR 1
MOR 2
MOR 3
Sample
Theoretical
Group Mean
Lab
Lab
NLCP
23


Morphine Degradation During Cycles 4 Thru 6
100
90
80
70
60
50
40
30
20
10
0
ng/mL
MOR 1
MOR 2
MOR 3
Sample
Theoretical
Cycle 4 Mean
Cycle 5 Mean
Cycle 6 Mean
NLCP
24


Performance with 6-AM
ng/mL
10
9
8
7
6
5
4
3
2
1
0
6-AM 1
6-AM 2
6-AM 3
Sample
Theoretical
Group Mean
Lab
Lab
NLCP
25


6-AM Degradation During Cycles 4 Thru 6
ng/mL
10
9
8
7
6
5
4
3
2
1
0
6-AM 1
6-AM 2
6-AM 3
Sample
Theoretical
Cycle 4 Mean
Cycle 5 Mean
Cycle 6 Mean
NLCP
25

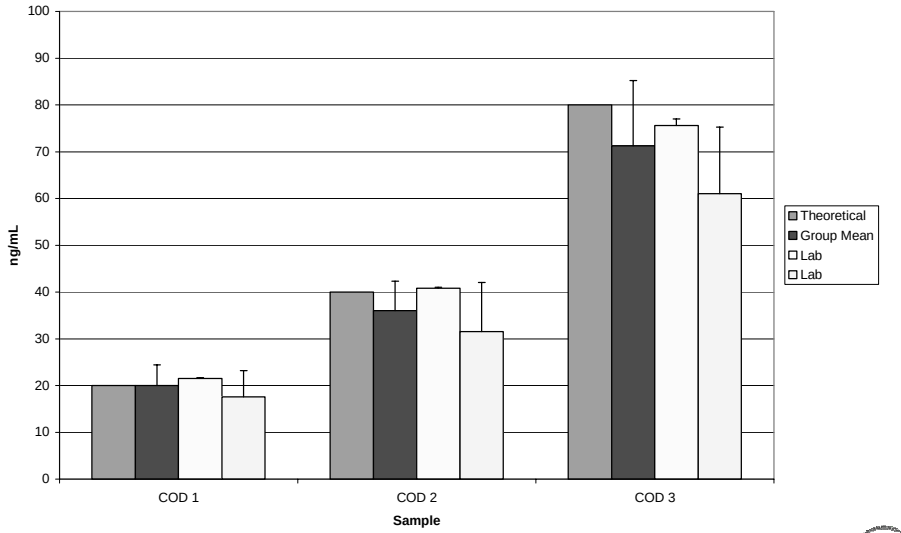
Distribution of Within Laboratory %CVs for All Laboratories for Opioids from Cycles 8 and 9



NLCP

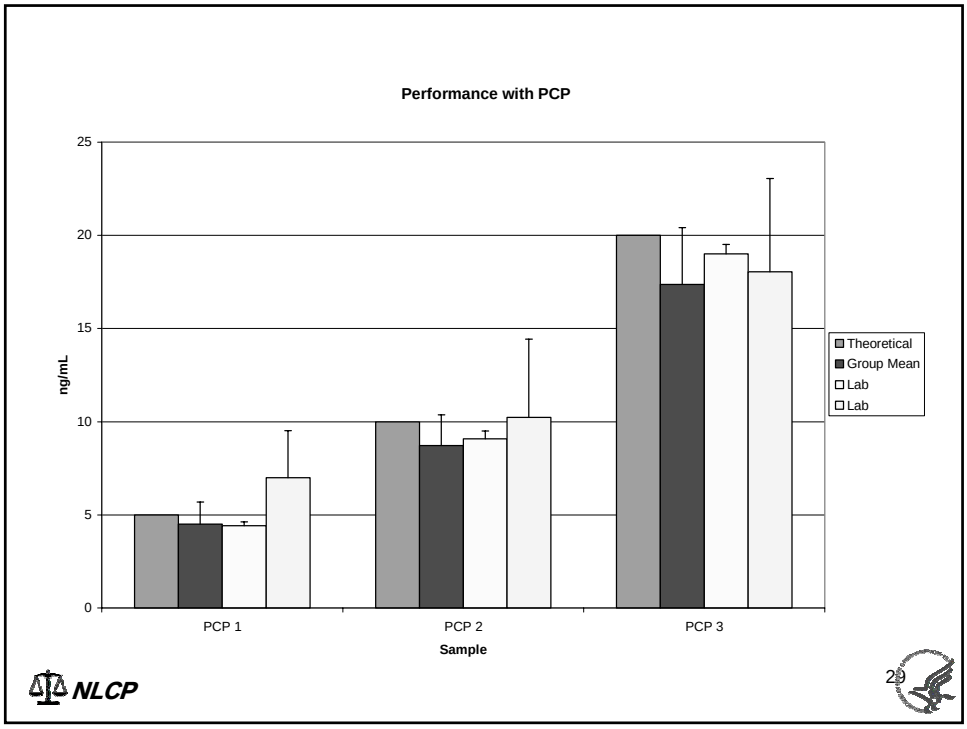
27

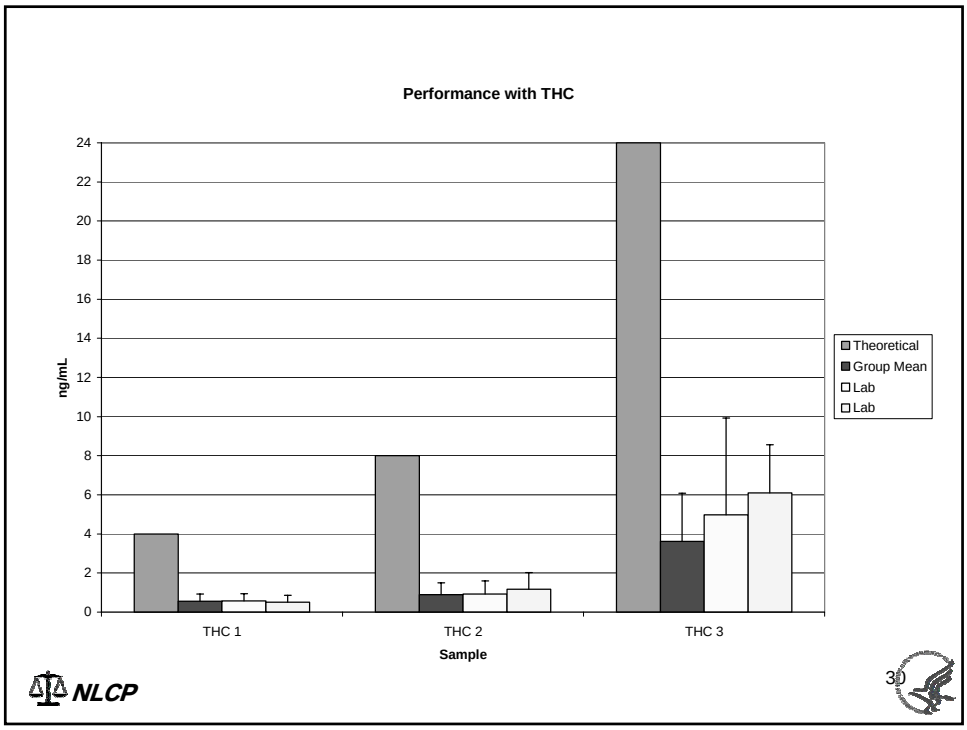
Performance with Codeine

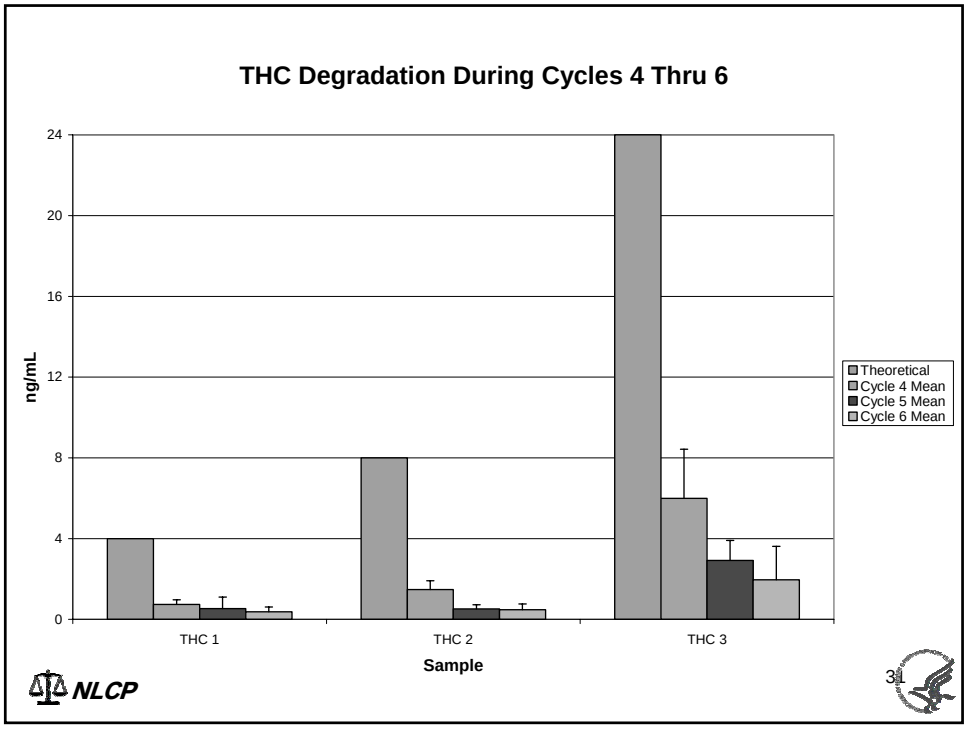


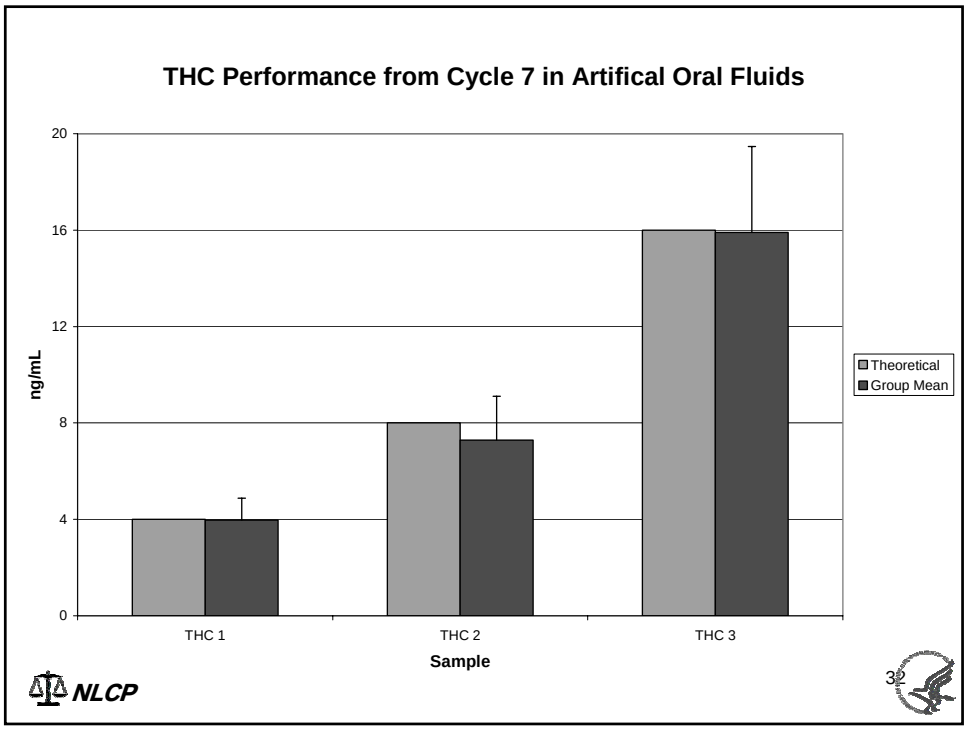
NLCP

28


Performance with PCP
25
20
15
10
5
0
ng/mL
PCP 1
PCP 2
PCP 3
Sample
Theoretical
Group Mean
Lab
Lab
NLCP
29


Performance with THC
24
22
20
18
16
14
12
10
8
6
4
2
0
ng/mL
THC 1
THC 2
THC 3
Sample
Theoretical
Group Mean
Lab
Lab
NLCP
30


THC Degradation During Cycles 4 Thru 6
24
20
16
12
8
4
0
ng/mL
THC 1
THC 2
THC 3
Sample
Theoretical
Cycle 4 Mean
Cycle 5 Mean
Cycle 6 Mean
NLCP
31


THC Performance from Cycle 7 in Artifical Oral Fluids
20
16
12
8
4
0
ng/mL
THC 1
THC 2
THC 3
Sample
Theoretical
Group Mean
NLCP
32

Performance Testing and Certification of Oral Fluid Testing Laboratories

Proposed Guidelines as released for public comment

(Fed Reg Vol 69 April 2004)

NLCP

Section 9.6 What Are the PT Requirements for an Applicant Laboratory to Conduct Oral Fluid Testing?

- (a) An applicant laboratory that seeks certification to conduct oral fluid testing must satisfy the following criteria on 3 consecutive sets of PT samples:
  - (1) Have no False Positive results
  - (2) Correctly identify and confirm at least 90 percent of the total drug challenges on the 3 sets of PT samples

NLCP

PT Requirements for an Applicant Oral Fluids Testing Laboratory Section 9.6(a) (cont)

- (3) Correctly determine the quantitative values for at least 80 percent of the total drug challenges to be within ± 20% or ±2 standard deviations of the calculated reference group mean
- (4) Have no quantitative value on a drug concentration that differs by more than 50 percent from the calculated reference mean

PT Requirements for an Applicant Oral Fluids Testing Laboratory Section 9.6(a) (cont)

- (5) For an individual drug, must correctly detect and quantify at least 50 percent of the total drug challenges

Laboratory Performance Compared to Section 9.6(a) PT Requirements

- (1) No False Positives however all analytes were directed for confirmation by analyte class
- (2) One lab identified 90% of analyte challenges over 3 cycles
  - For AMP, MAMP, BE, MOR, 6-AM, COD, PCP
    - Ten labs met this criterion
    - Without MOR & 6-AM, 12 labs met criterion
  - For COC, MDMA, MDA, MDEA, THC
    - One lab met this criterion
    - Without THC, 2 labs met criterion

NLCP

Laboratory Performance Compared to Section 9.6(a) PT Requirements

- (3) One lab quantitated 80% of all analyte challenges within 20% of group mean. (2 without MOR, 6-AM and THC)
  - For AMP, MAMP, BE, MOR, 6-AM, COD, PCP
    - 7 laboratories met this criterion (Without MOR & 6-AM, 10 Labs met criterion)
  - For COC, MDMA, MDA, MDEA, THC
    - One lab met this criterion (Without THC, 2 labs met criterion)

NLCP

Laboratory Performance Compared to Section 9.6(a) PT Requirements

- (4) Two laboratory had no quantitation error greater than or equal to 50% of group mean on any of the analytes
  - For AMP, MAMP, BE, MOR, 6-AM, COD, PCP
    - Five laboratories met this criterion (Without Mor & 6-AM, 8 labs)
  - For COC, MDMA, MDA, MDEA, THC
    - Three laboratories met this criterion (Without THC, 5 labs)

NLCP

Laboratory Performance Compared to Section 9.6(a) PT Requirements

- (5) No lab quantitated 50% of all individual analyte challenges within 20% of mean
  - For AMP, MAMP, BE, MOR, 6-AM, COD, PCP
    - Two laboratories met this criterion (Without Mor & 6-AM, 9 labs)
  - For COC, MDMA, MDA, MDEA, THC
    - One laboratory met this criterion (Without THC, 3 labs)

NLCP

Pilot Oral FLuid PT Program

- Purposes are:
  - To provide information on the state of the Oral Fluid testing science to help guide the development and implementation of the expanded Mandatory Guidelines
    - To develop appropriate PT materials for the National Laboratory Certification Program
  - To provide opportunity for interested labs to develop accurate and precise test procedures before implementation of the expanded Guidelines

NLCP

41

Variation in Oral FLuid Pilot PT Results I

- Excessive variation exists among labs
  - Possible reasons:
    - Labs are conducting confirmatory testing with a wide array of instruments, some of which may not have the necessary sensitivity
    - Methods for relating analytical results to neat oral fluids may introduce error
    - Failure to use standards from sources outside lab
    - Instability of MOR, 6-AM and THC in PT Samples

NLCP

42

Variation in Oral Fluid Pilot PT Results II

- Large variations exist within some labs
  - Possible reasons:
    - Instability of MOR, 6-AM and THC in PT samples
    - Reference materials are not commercially available
    - Labs have not developed procedures that are accurate and precise
      - Sample measurement
      - Best extraction procedures
      - Best instrumentation

NLCP

Variation in Oral Fluid Pilot PT Results III

- Stability of analytes in some PT samples accounted for some of the variability.
  - Issues with Morphine, 6-AM and THC in oral fluid PT samples appear to have been resolved and improved performance has been demonstrated

NLCP

Variation in Oral Fluid Pilot PT Results IV

- Lab quality control procedures may account for the variability in some labs.
  - Standards and controls from external source should be used to ensure internal QC materials are valid and remain valid

Road Map for Successful Implementation of Guidelines

1. Increase the dialogue between the NLCP and participant labs to produce an exchange of ideas and solutions
   - Use webcast meetings, conference calls and/or teleconferencing to provide feedback as soon as possible after each PT event
   - Review test results with participant labs, encouraging group development of improved methods and solutions to observed analytical problems

Road Map (cont)

2. Obtain commitment from labs to use future Oral Fluid Pilot PT program resources to develop and improve testing accuracy and precision
3. Use future cycles to resolve sample and lab variation
4. Facilitate the development of appropriate calibrator and control materials

NLCP