

Department of Health and Human Services (HHS)  
Substance Abuse and Mental Health Services Administration (SAMHSA)  
**Center for Substance Abuse Prevention (CSAP)**

**Drug Testing Advisory Board**

**September 19, 2017**  
**Minutes – Open Session**

**SAMHSA’s CSAP Drug Testing Advisory Board (DTAB) convened on September 19, 2017**

**In accordance with the provisions of Public Law 92-463, the meeting was open to the public on September 19, 2017 from 9:30 a.m. to 12:45 p.m.**

**Table of Contents**

Board members in attendance.....1  
Call to order.....2  
Welcome and Introductory Remarks.....2  
Mandatory Guidelines for Federal Workplace Drug Testing Programs – Updates.....2  
Results from the Opioid Implementation PT samples.....4  
Oral Fluid Pilot PT Program: Lessons Learned.....5  
Stability of DNA in Urine and Oral Fluid (A Pre-study).....5  
Detection of Opioid Glucuronides (metabolites) in User Hair.....6

**Board Members in Attendance**

- Mr. Ronald R. Flegel, Chairman
- Ms. D. Faye Caldwell
- Mr. Randal Clouette
- Dr. Jennifer A. Collins
- Dr. James L. Ferguson
- Dr. David Green.
- Mr. Paul Harris
- Dr. Courtney Lias
- Ms. Patrice Kelly
- Dr. Christine M. Moore
- Ms. Madeline Montgomery (remote)
- Dr. Buddha D. Paul
- Dr. Michael Schaffer

## **Call to Order**

### **Brian Makela, (DFO), DTAB, CSAP, SAMHSA**

Brian Makela, the Designated Federal Official of SAMHSA's CSAP Drug Testing Advisory Board (DTAB) called the meeting to order at 9:30 a.m.

Mr. Makela welcomed the Board members, Division of Workplace Programs (DWP) staff, federal partners (Department of Transportation – DOT, Department of Defense – DoD, Office of General Counsel – OGC, Nuclear Regulatory Commission - NRC, and the Office of National Drug Control Policy – ONDCP), contractors, invited guests, and members of the public. Mr. Makela stated that the morning session was an open meeting with presentations from the Division of Workplace Program staff and from personnel at RTI International. Topics will include information on mandatory guidelines for the Federal Workplace Drug Testing Programs; results from the opioid implementation PT samples; lessons learned in the oral fluid PT pilot program; a briefing on a pre-study of stability of DNA in urine and oral fluids; and detection of opioid glucuronides (metabolites) in user hair.

Mr. Makela announced that public comment was on the agenda, announced prior to the meeting, but there had been no requests to comment. The remaining sessions of the two-day meeting would be closed. Proposed revisions to the mandatory guidelines would be discussed, as would practices and procedures, and future planning of board activities. Only board members and invited guests may participate in the closed session.

Mr. Makela announced the next four quarterly meetings of DTAB in FY 2018: December 6, 2017; March 20-21, 2018; June 12-13, 2018; and September 22 (the first and last via web/teleconference only). A notice of topics to be discussed, and whether the meetings would be open or closed, will be published in the Federal Register about two weeks before each meeting. Mr. Makela invited Mr. Ron Flegel, Director of the Division of Workplace Programs and chair of DTAB, to make opening remarks.

## **Welcome and Introductory Remarks**

### **Ron Flegel, DWP, CSAP, SAMHSA**

Ron Flegel, B.S., MT(ASCAP), M.S., Director of DWP and DTAB Chair, added his welcome to DTAB members, ex officio members, industry representatives and members of the public, expressing his appreciation for their contribution of time and expertise. He noted that, during the day, the agenda would include an update on the mandatory guidelines for urine and oral fluid, and the progress on the guidelines for hair. There are also several presentations on the agenda – the opioid implementation proficiency testing data, a pre-study on the stability of DNA in urine and oral fluid, and some information on data regarding opioid metabolites in hair.

## **Mandatory Guidelines for Federal Workplace Drug Testing Programs – Update**

### **Ron Flegel, DWP, CSAP, SAMHSA**

SAMHSA seeks to improve the quality of services for forensic workplace drug testing, assess the science of drug analysis, improve quality of lab services and systems of drug testing and formulate standards for certification for testing labs. A certification workshop was recently held to provide information to the labs on National Laboratory Certification Program (NLCP). The DWP works with federal laws, testing issues, especially with regard to state legislation, state laws, and contracts and legal issues. DWP's immediate objective is implementation of the revised urine Mandatory Guidelines, gaining approval for oral fluid as an alternate specimen in the DWP program. The next project is writing the proposed hair guidelines, and implementing the semi-synthetic opioid testing in the regulated programs. The semi-synthetic opioids include hydrocodone, oxycodone, hydromorphone, and oxymorphone.

Mr. Flegel stated that a Federal Register Notice was published January 23, 2017, on urine mandatory guidelines, with an implementation date of October 1, 2017. The changes included the added semi-synthetic

opioids mentioned before, removal of MDEA and added MDA, as an initial testing analyte, a raised pH cutoff for adulterated specimens (from 3 to 4), and several wording changes to accommodate alternative specimens (oral fluid) when authorized. Mr. Flegel noted that HHS-certified labs are on track to meet the implementation date, and agency drug program coordinators have been advised that the Drug-Free Workplace Program (DFWP) has been revised to be consistent with the Mandatory Guidelines. He added that the previous 2014 CCF has been extended until June 1, 2018, by which time the new CCF should be in effect.

For Oral Fluid Mandatory Guidelines, the THC/THCA issue has been covered by a number of technical and scientific peer reviewed articles that have been published and a list of those, prepared by NLCP, have been sent to the directors, MROs and inspectors, and will be made available to the Board and to the public, hopefully on the DWP web site. Mr. Flegel expressed appreciation to Drs. Ed Cone and Ryan Vandrey (Johns Hopkins) for developing those studies. The present target for implementation of the guidelines is 2018. The inclusion of oral fluid as a matrix in the federal program is important since it will provide an alternate specimen now. HHS continues to look for options for the use of marijuana analytes since there is no single immunoassay that detects both THC and THCA at the proposed cutoffs. However, the guidelines allow labs to use an alternate method (other than immunoassay). The testing for THC is important when looking at driving under the influence of drugs. Finally, HHS does not accept passive exposure as a reason for testing positive.

Mr. Flegel provided an update on the hair mandatory guidelines. DWP staff is now writing the draft proposed guidelines and there are some proposed research studies on unique metabolites. The Secretary approved DTAB's recommendation to consider hair as an alternative specimen, and the scientific and technical issues must be addressed before completing the guidelines for hair. Two issues are decontamination of hair specimens and the influence of hair color. There are additional challenges within the division to consider. The first is implementing oral fluid guidelines since the program has used only urine since 1988, and the funding must be resolved to address future evaluation of program activities. The technical and scientific studies must be reviewed to rule out any issues with external contamination. Finally, emerging issues related to marijuana, opioids, synthetic drugs, and the impact of state laws must be addressed.

There are positive outcomes to anticipate: implementation of guidelines for urine that include the synthetics; oversight and standardization of regulated industry in testing for synthetic opioids; deterrence of illegal use of drugs and prescription opioids; implementation of oral fluid as an alternative specimen (which should decrease the number of substituted and adulterated specimens); and providing a noninvasive alternative to urine testing. Mr. Flegel showed a graphic of the steps (up to 17) that it takes to reach Federal Register publication of a mandatory guideline, including an implementation date. The MRO Guidance Manual, including subpart M, Section 13, specifically for MROs, has been released and should be on the DWP web site within days. It covers the four synthetic drugs previously discussed; the change of hydrocodone combination drugs to Schedule II; and help for MROs in identifying a valid prescription drug under the DWP.

Mr. Flegel noted several ongoing and future studies, including:

- A postponed cannabidiol study should begin in 2018.
- Two presentations (postponed with the rescheduling of SOFT 2017) that cover disposition of cannabinoids in oral fluid and whole blood after vaporized and smoked cannabis, and pharmacodynamic comparison of acute cannabis effects following oral, smokes and vaporized administration.
- A retrospective analysis of 520 re-identified specimens tested under the current guidelines (revealing one positive for morphine) and under the revised guidelines, revealing nine positives in semi-synthetic opioids, a significant tenfold increase.
- About five studies of marijuana in science have been released, including a cannabis vaporization study and a cannabis brownie study.
- Studies that may lead to guidelines and policy related to oral fluid as a testing matrix for driving under the influence of drugs and other federal workplace testing programs.
- A study that demonstrated the dramatic difference in the effect timeline of smoking cannabis (which is

relatively short, less than an hour) and ingesting cannabis brownies (as many as four to five hours).

Finally, Mr. Flegel touched on emerging issues, such as those related to marijuana and the new synthetic drugs. During discussion, asked about the issues related to federal and state regulations, Mr. Flegel stated that there was some progress in that FDA has kept marijuana on Schedule I, and in two legal cases employers in states where marijuana is legal have been supported in testing employees and terminating them if any test positive. With regard to fentanyl, a small study is planned to see if testing is feasible and to assess prevalence in the regulated sector. Asked about public comments on the MRO manual, Mr. Flegel suggested that the manual is a guidance document and, although comments and inquiries are welcome, public comment is not solicited.

### **NLCP Opioid Qualifying Performance Testing (PT) Results** **Cynthia Lewallen, M.S., RTI International**

Ms. Lewallen explained that all HHS-certified labs were required to successfully complete three sets of qualifying PTs to demonstrate readiness for the changes to the Guidelines. On January 23, 2017 revisions to the urine mandatory guidelines were published, with three significant changes, as described by Mr. Flegel in his presentation, addition of four synthetics and MDA, and a change in the cutoff for adulterated specimens. On March 7, NLCP sent the labs 18 practice samples that were identified with a single analyte, target concentrations, and mean concentration from 5 reference labs. The purpose was to allow labs to verify performance of immunoassays and confirmation methods. Labs did not report results for these practice samples. Three qualifying PT samples were shipped between May 1 and July 24, and a maintenance PT set will be shipped on October 9, 2017.

Ms. Lewallen provided specifications for the new analytes (hydrocodone - HYC, oxycodone - OXYC, hydromorphone -HYM, and oxymorphone – OXYM). The initial cutoffs and confirmatory cutoffs were respectively: HYC and HYM, 300 and 100; OXYC and OXYM, 100 and 100. Before the revised guidelines, which included only codeine and morphine, only one of 27 labs were using liquid chromatography and mass spectrometry (LC-MS/MS), and the others were using gas chromatography–mass spectrometry (GC-MS). Labs reported an intention to significantly shift testing under the new Guidelines -- for morphine and codeine, 18 labs will use GC-MS and 9 will use LC-MS/MS, and for the four synthetics, the numbers are 14 and 13 respectively. Finally, additional qualifying PT specifications were included.

Ms. Lewallen noted that the labs received three test sets for the four synthetics. All labs obtained positive results using three methods of analysis. There were also two samples spiked with glucuronide (no free drug) at four times the initial test cutoff and, using the Thermo Fisher DRI technology, all 28 labs obtained a positive initial test result. For the second sample (OXYM), 23 labs using the Thermo Fisher DRI and one lab using Lin-Zhi International technology, obtained positive initial test results. Test performance on all four synthetics revealed only two labs reporting minor errors, one lab reporting minor errors in all four synthetics and the other lab reporting minor errors in HYC and OXYC. As expected, the number of minor errors declined slightly with each successive test set. Only one major error was reported.

Ms. Lewallen reviewed actions taken by the labs to prevent or rectify errors. In Set 1 the most common error was confirming false negatives. One lab changed to LC-MS/MS testing, another validated an alternate GC-MS method, and other labs revised test methods. In Set 2 there were only minor quantitation errors. In Set 3 there was confirmation of false negatives, which was resolved with additional staff training and test methods modifications. There were also quantitation errors blamed on equipment failure, resolved by replacement and possible change from GC-MS to LC-MS/MS. In summary, Ms. Lewallen stated that there were no immunoassay results for the new opioids at 1.25 times cutoff; confirmatory quantitative challenges had minor error rates similar to codeine and morphine. All remedial actions will be completed before October 1; and NLCP inspections began in September to assess validation and qualifying PT data. Therefore, Ms. Lewallen felt that RTI agrees that the labs are prepared for implementation on October 1. There were no questions and

Mr. Makela invited the next presenter to discuss the oral fluid pilot PT program.

**Oral Fluid Pilot PT Program: Lessons Learned**  
**Dale Hart, RTI International**

Mr. Hart stated that the oral fluid pilot PT program began in April 2000, with 21 occasions, or rounds, completed through 2007. The program was suspended until 2011, completing 24 more occasions for a total of 45. The program is voluntary and open to any lab that submits a letter of commitment and information on test methods. The process involves developing a sample scheme based on NLCP needs, formulating samples a couple of days before shipment, and keeping them refrigerated (frozen) during shipping. Labs receive the samples and a pre-formatted Excel spreadsheet for reporting results and are expected to return the results within two weeks. Results are consolidated and available to participants.

Turning to occasion 45, the most recent, Mr. Hart explained that laboratory performance at low concentrations (40% of confirmation cutoff) was evaluated, as were effects of interfering compounds. Lab results are compared with “paired” samples prepared in both human and synthetic oral fluid. For occasion 45, samples were shipped on February 15, 2017. There were 15 labs, one performing initial testing only, one confirmatory testing only, 13 labs could do both. Reagent manufacturers were represented by three labs. The sample scheme included 15 samples that covered most of the regulated opioids, and were prepared in synthetic oral fluid – THC/THCA, cocaine, benzoylecgonine, PCP, amphetamines, methamphetamines, MDMA/MDA, oxycodone, oxymorphone, hydrocodone, hydromorphone, and acetyl morphine. Some of the samples contained high levels of interfering compounds. Most labs used LC-MS/MS, although GC-MS/MS was used for two PCP tests and one THCA test.

Mr. Hart showed a PowerPoint of results for eight analytes (THC, THCA, cocaine, benzoylecgonine, methamphetamine, amphetamine, MDMA and MDA), which were included in eight samples (1,2,3,6,12,13 and two paired samples 4-7 and 3-14.) The paired samples were prepared in synthetic and human oral fluid containing the same analyte.

Discussing overall trends, Mr. Hart stated that the results for occasion 45 were similar to observations from occasions in the last couple of years, regardless of the drugs included in the sample scheme. Lab performance was good; most labs reported results for most of the samples, including samples at low concentrations. There were 457 results reported, with only seven outliers. Interfering compound appeared to have some impact on data. There were nominal increases in CVs when there were interfering compounds in the sample, and an increase in the number of outliers. Results for paired samples in human and synthetic samples were statistically the same. Therefore, PT samples can be prepared in either matrix. In conclusion, Mr. Hart stated that RTI has eight labs capable of testing oral fluid, achieving the correct results down to the levels required in the 2015 Proposed Guidelines.

Mr. Flegel expressed appreciation to the participating labs and the NLCP in accomplishing the very technical and complex tasks involved. He expressed confidence that the program was ready to implement on October first. He expressed the belief that the labs were ready to begin the initial testing phase for oral fluid. Mr. Flegel announced that his office is working on case studies related to the revised guidelines, which will be published when available. He also invited MROs and testing labs to submit any flow charts currently in use.

**Stability of DNA in Urine and Oral Fluid (A Pre-study)**  
**Robert W. White, Sr., Ph.D., Center for Forensic Science, RTI International (Retired)**

Dr. White stated that he had recently retired from RTI and would be discussing examination of DNA as an identity marker in urine or oral fluid collected for employment-related purposes, which was performed while he was an active employee of RTI. He briefly reviewed the structure and function of DNA, which is the transcription of DNA into RNA into protein. Aberrant proteins may produce the same protein as the wild type

(most common) which are single nucleotide polymorphisms (SNPs). Although over 99% of DNA is identical from human to human, there are elements that are useful in identification. One is called short tandem repeats (STRs), sequences of DNA occurring in noncoding regions found on numerous different chromosomes. When sufficient STRs are identified they are useful in some DNA identity testing. Dr. White described 36 STR markers, explaining the letters and numbers that specifically identify each STR.

Dr. White commented that the proposed study would determine the approximate amount of degradation that might occur in DNA under routine storage conditions typical of a drug testing lab. The study was sponsored by RTI, IRB-approved, included five donors (two females, three males), and all samples (two urine, two oral fluid from each donor) were self-collected. No drug testing was included in the study. Samples were stored at RTI in an air-conditioned office for a couple of days, then transported to a testing lab in North Carolina via car. Commercial carriers, some of which may have used air transport, were not used so there is no data on shipment in that environment. Urine contains nuclear DNA from intact epithelial cells, is hypertonic, and is not a favorable matrix for DNA or intact cells. Samples were tested at 5 days post collection and at 35 days. Generally, there was degradation in DNA collected for the longer interval.

Oral fluid was collected by expectorated saliva and using pad oral fluid collectors, which are placed in the mouth and when sufficient neat oral fluid is absorbed by the pad as indicated by an indicator on the pad, it is removed and placed in a buffer preservative. The samples are electronically analyzed. In summary, for urine, the samples tested after 5-6 days post collection were acceptable. However, a complete profile was not obtained in 40% of cases after freezing the second sample and testing at day 35 post collection. The results were similar with neat oral fluid, except that incomplete profiles resulted in 20% of cases. For pad eluent plus buffer preservative, samples from all donors provided a complete profile five days post-collection.

Whether usable DNA can be extracted from a pad or its buffer/preservative after extended storage need to be the subject of a study that employs a longer storage time. Dr. White concluded his remarks and there were not questions from the committee.

### **Detection of Opioid Glucuronides in User Hair** **Megan Grabenauer, Ph.D., RTI International**

Dr. Grabenauer stated that hair as a desirable test sample because it is less invasive than urine, more easily observed during collection, more difficult to substitute or adulterate and offers a longer window of detection. However, it has issues that may affect the defensibility of analysis results as it does not effectively identify recent use because the hair must grow after use to include detectable drug at the hair root. There is also the issue of external contamination. Drug may be incorporated into the hair for reasons not associated with drug use, such as exposure to second-hand smoke and contact with drug during job-related duties. There are procedures to reduce the risk of contamination, such as extensive washing of hair samples before testing. Drug metabolites may also be tested instead of parent drug, although many metabolites contain manufacturing impurities or degradation products. Normal metabolite ratios may be established to indicate drug use and unique metabolites may be identified that cannot be the result of external contamination. Phase I metabolism changes drugs into compounds that can be easily eliminated. It begins with oxidation, reduction or hydrolysis. Phase II metabolism transforms drug into a glucuronide. Glucuronides are not products of common degradation, not manufacturing impurities, not formed by in vitro reactions on hair, and not commercially available. Research was initiated at RTI to identify metabolites for hair testing that are unambiguous markers of use. RTI developed a validated method for quantification of several opioids and their glucuronides.

The method of extraction consists of washing with isopropanol and phosphate buffer, obtaining a small sample of hair (25 mg), adding 500 microliters of solvent, heating to 100 degrees C for an hour, then cooling prior to SPE. The extraction process uses a solvent, M3 reagent from Comedical, and does not change the morphological characteristics of the hair.

Dr. Grabenauer explained that the samples were analyzed by LC-MS/MS using an Agilent triple quad and an Agilent system of electrospray ionization. The column was C18, flow rate 500 microliters per minute at 50 degrees C. The gradient was from 5% organic to 90% organic in 6.1 minutes. Dr. Grabenauer provided the LC-MS/MS parameters for the analytes. In addition to ruling out interferences from matrix and internal standards, six potential interfering compounds were investigated to determine if they interfered with the analytes of interest – heroin, norcodeine, norhydrocodone, normorphine, noroxycodone, and noroxymorphone. Except for 6-AM being affected by heroin, no other compound produced interference in blank samples or caused any of the quantifications to be out of tolerance. The possibility of glucuronide interference during the extraction process was also investigated, and there was no evidence of interference in any of the analytes of interest. This method was applied to 46 hair samples that had previously confirmed positive for opiates. The most commonly detected analytes were hydrocodone, morphine, oxycodone and 6-acetylmorphine.

In summary, codeine-6-glucuronide, oxymorphone-3-glucuronide, morphine-3-glucuronide, morphine-6-glucuronide, hydromorphone-3-glucuronide are present in drug user hair above the lower limit of quantitation (LLOQ) of 2 pg/mg and generally increase with parent concentration. Glucuronide concentrations generally approximate 1 pg/mg or greater, in samples with greater than 200 pg/mg parent compound present. The validated LLOQ was 2 pg/mg. Maximum relative abundance of glucuronides less than 3% of parents for all but codeine-6-glucuronide (6%). There is room for improvement in extraction method to increase process efficiency and sensitivity. There was not enough data from hair samples containing dihydrocodeine and dihydromorphine to draw conclusions about the presence or absence of their glucuronide metabolites.

A full discussion of the methods and results were submitted to the Journal of Analytical Toxicology. Dr. Grabenauer concluded her remarks. There was no discussion.

**Adjournment:** Mr. Makela adjourned the DTAB open session.