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Conechem research, llc

Drug Delivery Systems, Pharmaceutics, Pharmacology, Forensic Drug Testing

July 9, 2003

Dr. Walter F. Vogl
SAMHSA
5600 Fishers Lane
Rockwall II, Suite 815
Rockville, MD 20857

Dear Dr. Vogl:

Re: docket number (04-7984)

I would like to offer comments on the Proposed Mandatory Guidelines for Workplace Drug Testing Programs published in the April 13, 2004 "Federal Register".

Issue #1

The Proposed Guidelines require collection of an oral fluid specimen be accompanied by a urine specimen (Section 2.3; Section 8.3). In the event of a confirmed positive oral fluid test for marijuana, the laboratory must not report the result for the oral fluid specimen but, instead test the primary (Bottle A) urine specimen and report that result in accord with the rules for urine testing for marijuana.

The logic for this unusual requirement is expressed in the Preamble of the Proposed Guidelines as follows:

"Science shows that opiates, PCP, amphetamines and cocaine and most drugs including prescription medications enter oral fluid through passive diffusion of the drug from the blood stream into the oral fluid. However, the active component of marijuana (delta-9-tetrahydrocannabinol (THC)) does not diffuse into oral fluid. The only way to detect marijuana use is through the presence of the parent drug (THC) in the oral fluid because the parent drug was present in the oral cavity. Unfortunately, further scientific study is needed to be able to differentiate between whether the parent drug was present in the oral cavity due to drug use or environmental contamination, i.e. the individual was present in a room when others smoked marijuana, for example. In order to protect Federal workers from incorrect test results for marijuana, the Department proposes that a second biological specimen, a urine specimen, will need to be collected under the current Guidelines at the same time the oral fluid specimen is obtained, primarily for the purpose of testing for marijuana when the oral fluid specimen is positive for marijuana. The Department will revise the Guidelines when the science is available to differentiate between actual use and environmental contamination."

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The assertion of "incorrect results for marijuana" is surprising and inappropriate. This assertion should not be associated with oral fluid testing given the vast amount of scientific data available regarding the accuracy of oral fluid testing for marijuana.

The stated basis for requirement of an accompanying urine test with oral fluid test for marijuana is as follows:

1. Lack of diffusion of THC and metabolites into oral fluid
2. Oral contamination by THC during active usage
3. Lack of scientific evidence that shows that passive exposure to marijuana smoke cannot be discriminated from active marijuana use

General Comments on Issue #1

Oral fluid collection and testing should be unencumbered by the requirement for a positive urine test.

The efficacy for detection of marijuana usage has been shown to be equivalent or better than urine testing in a large scale database study involving approximately seventy-seven thousand oral fluid tests [Cone, E.J. et al., (2002). Oral Fluid Testing for Drugs of Abuse: Positive Prevalence Rates by Intercept™ Immunoassay Screening and GC-MS-MS Confirmation and Suggested Cutoff Concentrations. J. Anal. Toxicol, 25: 130]. Further, oral fluid testing offers significant advantages to urine testing in marijuana detection. As indicated in the Proposed Guidelines, urine testing is subject to such limitations as adulteration, dilution and substitution; whereas oral fluid testing overcomes these problems. The addition of oral fluid testing to the armamentarium of tools in Federal Workplace testing programs is a clear improvement in these programs' ability to adapt to the changing nature of our nation's drug abuse problems. However, the requirement of a positive urine test for marijuana to accompany an oral fluid test is counter-productive to implementation of oral fluid testing. Further, the concerns expressed in the Preamble regarding oral fluid testing have been addressed by industry and researchers.

SAMHSA makes the assertion in the Preamble that "In order to protect Federal workers from incorrect test results for marijuana, the Department proposes that a second biological specimen, a urine specimen, will need to be collected under the current Guidelines at the same time the oral fluid specimen is obtained, primarily for the purpose of testing for marijuana when the oral fluid specimen is positive for marijuana."

The following sections address the current scientific evidence regarding the concerns expressed by

SAMHSA.

Specific to the issues addressed in the Preamble of the Proposed Guidelines I offer the following comments.

Lack of diffusion of THC and metabolites into oral fluid

Comment: The conclusion that THC and metabolites do not diffuse into oral fluid is not likely to be correct. The literature citations that relate to this issue arise from unpublished study results [personal communication by M. Perez-Reyes cited in Reference #31 of the Proposed Guideline, Hawks R.L. (1982). The constituents of cannabis and the disposition and metabolism of cannabinoids. In Hawks RL (Ed): The Analysis of Cannabinoids in Biological Fluids, NIDA Research Monograph Series 42; U.S. Government Printing Office; Washington, DC; p. 125]. The other citations repeat the same reference. An additional source of this information that is somewhat more complete is published in another monograph series [M. Perez-Reyes (1990). Marijuana smoking: factors that influence the bioavailability of tetrahydrocannabinol. In Chiang CN and Hawks RL (Eds): Research Findings on Smoking of Abused Substances, NIDA Research Monograph Series 99; U.S. Government Printing Office; Washington, DC; p. 42]. Neither of these publications were peer-review articles, nor is there sufficient detail to assess the validity of the conclusions that THC does not diffuse into oral fluid (saliva). For example, details are missing regarding when saliva specimens were collected, sensitivity of the assay, number of subjects tested, or dosage. Further, it is a scientifically accepted principle that passive diffusion of lipophilic drugs through biological membranes occurs readily. The degree of penetrance of drugs from blood to saliva is related to the drug concentration in plasma, the extent of protein binding, and membrane characteristics. In the absence of conclusive scientific information, there is no reason to believe that THC will not diffuse into saliva, albeit at low concentrations, because of its high protein binding characteristics.

2. Oral contamination by THC during active usage

Comment: I agree that oral contamination of the oral mucosal cavity occurs during the course of marijuana usage. The majority of THC detected in oral fluid after usage most likely results from THC deposited in oral fluid and from THC "depots" in the oral mucosal cavity. A scientific article that is currently in press co-authored by M.A. Huestis and myself discusses this issue [Huestis, M.A. and Cone, E.J. (in press, 2004). Relationship of Δ9-tetrahydrocannabinol in oral fluid to plasma after controlled administration of smoked cannabis. J. Anal. Toxicol.]. This study demonstrated that the deposition of THC in oral fluid followed a similar time course as plasma THC following smoked cannabis administration under controlled dosing conditions. Considerable scientific evidence is available that demonstrates that THC in the oral cavity can be absorbed into the bloodstream, thereby linking THC in oral fluid to blood. The data from the above cited study also suggest that transmucosal absorption into blood occurs both during and after smoked cannabis

administration that contributes to existing blood THC concentrations, thereby explaining current observations that oral fluid THC levels mimic plasma THC concentrations.

The formation of a THC depot in the oral cavity during cannabis use does not rule out the possibility that a portion of THC measured in oral fluid arises from secretion from blood. Careful controlled scientific study would be needed to determine the relative contributions from these sources. However, none of these issues serve as reasons that oral fluid testing for marijuana usage is not a valid detection methodology for marijuana usage.

3. Lack of scientific evidence that shows that passive exposure to marijuana smoke cannot be discriminated from active marijuana use

Comment: I present scientific evidence that demonstrates that passive exposure to marijuana smoke can be discriminated from active marijuana use by oral fluid tests. This study was recently completed and is currently accepted pending final review for publication in the Journal of Analytical Toxicology [Niedbala et al. Journal of Analytical Toxicology, accepted, 2004]. This entire article is appended as a separate file to this communication and is discussed below. Briefly, the study involved an assessment of the risk of positive oral fluid tests from passive cannabis smoke exposure. The study was conducted by housing four cannabis-free volunteers in a small, unventilated and sealed room with an approximate volume of 36 m^3. Five active cannabis smokers also were present in the room and each smoked a single cannabis cigarette which contained an average of 1.75% THC. Cannabis smoking occurred over the first 20 minutes of the study session. All subjects remained in the room for approximately 4 hrs and provided oral fluid at designated times. Oral fluid specimens were collected with the Intercept DOA Oral Specimen Collection Device before the start of the session and periodically throughout the session. All oral fluid specimens were screened by enzyme immunoassay (EIA) for cannabinoids (cutoff concentration = 3 ng/mL) and tested by GC-MS-MS for THC (LOQ/LOD = 0.75 ng/mL). A total of eight oral fluid specimens (collected 20 to 50 min following initiation of smoking) from the four passive subjects screened and confirmed positive for THC at concentrations ranging from 3.6-26.4 ng/mL. Two additional specimens from one passive subject, collected at 50 and 65 min, screened negative but contained THC in concentrations of 4.2 and 1.1 ng/mL, respectively. All subsequent specimens for passive participants tested negative by EIA and GC-MS-MS for the remainder of the 4 hr session. In contrast, oral fluid specimens collected from the five cannabis smokers generally screened and confirmed positive for THC throughout the session at concentrations substantially higher than observed for passive subjects. A biphasic pattern of decline for THC was observed in oral fluid specimens collected from cannabis smokers, whereas a linear decline was seen for passive subjects suggesting that initial oral fluid contamination is cleared rapidly and is followed by THC sequestration in the oral mucosa. Thus, the risk of positive oral fluid tests from passive cannabis smoke inhalation was limited to a period of approximately 30 minutes following cannabis exposure. Further, the positive tests were only obtained during the period passive subjects were present in the sealed room with the marijuana smoke. Even before subjects emerged from the smoky room, THC

levels were below detectable levels and no further positives were produced.

Based on the controlled marijuana dosing study described above, the risk of passive inhalation of marijuana smoke clearly was limited to a period of approximately 30 minutes after exposure. Thus, the only scenario that can be imagined for passive inhalation to result in false positive oral fluid test would be if the individual undergoing testing were transported in an unventilated car to the test site while being accompanied by a number of individuals smoking numerous marijuana joints. Based on current scientific data, it appears unlikely that even this scenario would result in a positive oral fluid test once the individual was removed from the marijuana smoke environment.

The above defined risks of passive inhalation on oral fluid testing are not unlike the risks faced with all other types of specimens. Passive inhalation to marijuana smoke has been shown scientifically to produce positive urine tests [Cone et al., Journal of Analytical Toxicology, 11: 89-96, 1987]. The risks of passive marijuana smoke exposure to hair and sweat testing remains unknown; however, no requirements for additional specimen collection and testing for these specimens are specified in the Proposed Guidelines. Consequently, it seems prudent to conclude that the risk of passive inhalation of marijuana smoke on oral fluid tests as compared to urine testing is of equal, if not substantially lesser magnitude.

Thus, the restrictions on oral fluid do not make scientific sense and they do not make practical sense. Drug testing programs will not go to the added expense of collection of two separate specimens for transport and testing. By mandating this requirement, SAMHSA essentially eliminates the possibility of use of oral fluid as a media for testing in Federal Workplace drug testing programs.

Based on all of the above reasons, I see no valid scientific reason for the required restrictions on oral fluid testing for marijuana. The Guidelines should be modified to remove the restriction of collection of an accompanying urine specimen with an oral fluid specimen and the necessity of testing urine when a positive result is obtained by oral fluid testing.

Issue #2

Requirement for collection of two milliliters of neat oral fluid (Section 2.5).

Presumed basis for 2 mL volume requirement:

1. Use of oral fluid collection device may alter pH and thereby alter drug concentration

Comment: The pH of oral fluid is dynamic and pH changes with flow, regardless of whether a device is used for collection or expectoration is employed. As saliva flow increases, excretion of bicarbonate increases with a concomitant increase in pH. This phenomenon is well recognized and documented in scientific literature. Movement of the jaw during expectoration is a stimulus to saliva flow. The physiology of saliva production dictates that oral fluid production is dynamic rather than static. Hence, all oral fluid collections except passive draining (which is not practical) produces stimulus to salivary glands and alters flow and pH.

2. Requirement for exact volume measure of oral fluid specimen during analysis

Comment: Spitting into a tube is unsanitary, cumbersome, unpleasant and not necessary. Bacteria and viruses appear in oral fluid of infected individuals. Spitting into a tube increases the risk of disease transmission through direct contact with oral fluid and aerosol formation of infected droplets of oral fluid that are released to the environment. Collection staff and other individuals present during "spitting" would be subjected to the risk of infection. The use of FDA cleared devices for oral fluid collection provides a suitable alternative that eliminates this risk. The volume of oral fluid collected by these devices can be standardized within acceptable limits to provide exact concentrations to be measured. Such devices have been shown to be sanitary, convenient to use, and acceptable to individuals undergoing collections in workplace drug testing settings. Further, use of hair, sweat, and urine specimens face equal challenges in determining exact concentration. With sweat, there is no means of obtaining a volume measurement with the "patch" device. With hair, drug is distributed unevenly in a hair strand and expressions of concentration that are reported represent an "averaged" concentration across the entire hair strand. With urine, concentration is under direct control of the donor and is determined by the amount of fluids ingested. Consequently, all specimens, to a greater or lesser extent, only provide an "approximate" drug concentration.

3. Split specimen requirement

Comment: Simultaneous collection of oral fluid specimens with two devices has been shown to meet all requirements for split specimen collection. For example, Niedbala et al. [Journal of Analytical Toxicology, 25, 289-303, 2001] showed that simultaneous collection with the Intercept® device produced nearly identical results in studies of oral fluid testing for marijuana. Simultaneous collection of dual specimens met all SAMHSA requirements for split collection, much in the same way as dual collection of hair specimens. Consequently, a provision for simultaneous collection should be allowed in the guidelines as a valid means of split specimen collection.

Issue #3

Because of the short detection window, oral fluid is not suited for return to duty, and follow-up testing.

Comment: The detection time for drugs in oral fluid is generally comparable to urine detection times. Detection time of drugs in oral fluid and urine are based on single dose studies that involve unrealistically low doses as compared to doses administered by illicit and recreational drug users. Recent studies of over 77,000 oral fluid test results in workplace settings demonstrated that oral fluid testing was equally effective and in some cases better for drug detection than urine testing. These data provide substantial evidence that drug detection by oral fluid testing is equivalent in power to urine testing. An additional benefit of oral fluid testing is that it detects recent use and does not detect drug use that occurred weeks before. The purpose of return to duty and follow up testing is to detect recent drug use not historical drug use. Consequently, oral fluid testing for return to duty and follow up cases will provide the employee with the assurance that their former drug use will not be confused with new use. The value of drug treatment diminishes significantly when employees, who have responded to treatment, are falsely accused of continued use. The use of oral fluid testing will provide treatment providers with the confidence that the employee is following the required treatment plan. Consequently, oral testing is well suited for use in return to duty and follow up testing.

Issue #4

It (oral fluid) may be least suited for random testing if prior notice (greater than 24 hours) is given.

Comment: All forms of testing lose effectiveness when prior notice is given before a drug test. This is especially true for random testing. Allowing an individual prior notice before a urine test is likely to result in the drug user attempting to subvert the test by substitution, adulteration and dilution means. These methods have clearly been shown to be effective in "beating urine tests" as documented in many scientific studies. Oral fluid testing is less susceptible to these means of subverting drug tests and is superior to urine testing in this regards. Consequently, this restriction should not be placed on oral fluid testing.

Issue #5

There are many unresolved scientific and administrative issues regarding the use of hair testing, sweat testing, and POCTs in the Federal workplace.

Comment: An organized meeting of scientists, laboratory personnel, and device manufacturers should be convened to assess the current state of knowledge regarding testing with hair, sweat and POCTs. Such a meeting could determine what scientific data is needed to bring these test methods into required compliance with SAMHSA requirements for drug testing of Federal workers. Hair testing has unresolved issues regarding the potential for environmental contamination and false positive generation. Scientific studies should be required that demonstrate that test methods can clearly differentiate environmental contamination from active drug use. The issue of hair color bias must be resolved such that individuals with different hair color are treated equitably. Sweat testing currently is limited to a single collection device and sweat concentration can not be determined directly, but must be expressed as drug amount on the device. Other collection means should be explored to provide additional scientific information on sweat testing. POCT devices are abundant and their performance characteristics change frequently. A means of monitoring the performance of these devices should be established that tracks the performance of these devices. The issue of how quality control methods will be enforced should be established for POCTs. In general, all of these test methods have the potential for producing accurate results, but clearly, there are many unresolved issues that should be evaluated by unbiased, scientific means.

In closing, I would like to thank SAMHSA for providing me with the opportunity to comment on the proposed Guidelines.

Sincerely,

Edward J. Cone, Ph.D.

Appended Scientific Data

(Separate File)

"Passive Cannabis Smoke Exposure and Oral Fluid Testing"

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