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Division of Workplace Programs
Center for Substance Abuse Prevention
Substance Abuse and Mental Health Services Administration, HHS

RE: Docket No. 04-7984

Proposed Revisions to Mandatory Guidelines for Federal Workplace Drug Testing Programs, Substance Abuse and Mental Health Services Administration, HHS

The following comments are based on more than 30 years of experience in the drug abuse field with the primary focus on drug testing. Having been directly involved in the writing and implementation of the original HHS Mandatory Guidelines for Federal Workplace Drug Testing Programs, I fully appreciate the time, effort and good intentions required to promulgate government guidelines and regulations aimed to eliminate the use of drugs in the Federal workforce and the extension of such rules to private sector workforces, e.g., those covered under separate regulations of the Department of Transportation and the Nuclear Regulatory Commission. The HHS Guidelines are also used as a model template for most private sector workplace drug testing programs.

Myself and others that work with various types of employers welcome the overall thrust of these proposed guidelines, which will provide necessary standards for the inclusion of alternate specimen testing for all work environments. It is with this broader view of world-wide drug testing programs, beyond the public sector, that I make the following comments and recommendations in order to make these new approaches acceptable alternatives to traditional testing programs limited to urine.

My comments focus on two areas: oral fluid tests and point-of-collection tests (POCT). These are summarized as:

Oral Fluid Test (OF) - I strongly object to the following proposed requirements: limiting "saliva" collections to spitting; the collection of a urine specimen along with a "saliva" specimen; and the exclusion of return-to-duty and follow-up testing.

Point of Collection Test (POCT) - I recommend clarification of: what constitutes a POCT device, the frequency of periodic inspections of POCT sites, and the number of PT samples to be submitted quarterly to POCT sites. Also, comments on the daily quality control requirements.

COMMENTS

Oral Fluid Test (OF)

1. Proposed Guideline

Section 2.5(b) Oral Fluid: 2 mL collected as a "neat specimen" (divided as follows: at least 1.5 mL for the primary specimen and at least 0.5 mL for the split specimen)

Comment

Having been directly involved with studies utilizing saliva, it can be stated that this is one of the most objectionable specimens to collect and handle. Unfortunately, the proposed Guidelines limit the collection of saliva to expectoration, commonly known as spitting. The proposal calls this "oral fluid," which is in contradiction to nomenclature guidelines from experts in the field of saliva analysis and collection. Namely, in a 1992 conference on "Saliva as a Diagnostic Fluid" (published as an entire issue of the Annals of the New York Academy of Sciences: Saliva as a Diagnostic Fluid, Ann. N.Y. Acad. Sci., **694**, (1993)), a consensus panel proposed the following nomenclature and collection guidelines:

* Whole Saliva: The fluid obtained from the mouth by expectoration (mixed saliva).

* Parotid Saliva: The fluid secreted by the parotid glands and obtained directly from a parotid duct orifice (parotid fluid).

* Submandibular Saliva: The fluid secreted by the submandibular glands and obtained directly from a submandibular duct orifice when there is objective evidence (e.g., sialography) that the sublingual glands do not secrete fluid into the same duct (submaxillary saliva, mandibular saliva).

* Submandibular/Sublingual Saliva: The fluid secreted mainly by the submandibular and sublingual glands and obtained from the floor of the mouth in the vicinity of the submandibular duct openings when secretions from the parotid and minor salivary glands are prevented (by use of absorbent swabs) from gaining access to this region or when specific collection devices are employed.

* Minor Salivary Gland Secretions: The fluids secreted by the minor salivary glands and obtained directly from the duct openings. The location of the glands should be indicated (e.g., labial, palatine, etc.) because there are differences in the secretions.

* Gingival Crevicular Fluid: The fluid that gains access to the oral cavity via the gingival crevice.

*** Oral Fluid: The fluid obtained by insertion of absorptive collectors into the mouth.**

* Unstimulated Saliva: The basal secretion; saliva secreted in the absence of exogenous gustatory, masticatory, or mechanical stimulation.

* Stimulated Saliva: Saliva secreted in response to mechanical, pharmacologic, or gustatory stimulation.

The proposal is really limited to the collection to "whole or mixed saliva" not "oral fluid" using accepted medical terminology. To call spit "oral fluid" creates confusion in the field of saliva's use in the diagnostic field.

A quote from one of the Annals'chapters summarizes a common opinion on saliva collection:

> "However, concerns about the obtaining of the correct specimen (not infrequently, sputum specimens were received), the fact that subjects found dribbling distasteful, the frequency of receiving specimens with insufficient volume, the possible contamination of the outside of the receptacle used to collect the specimen, and the difficulty in pipetting

untreated saliva all led instead to the adoption of proprietary saliva collection devices."[1]

This report also presents the performance characteristics of dribbled saliva (an alternative method to spitting, but with the same concerns) with foam swabs and three commercial collection devices. It found that one of the commercial devices was superior based on the measurement of IgG concentrations. The author also pointed out the necessity of setting minimum IgG concentrations to establish specimen validity. Of the 4,111 specimens tested in one study, 0.6% had IgG levels less than 0.1 ug/mL, indicating the efficiency of a collection device using an absorbent pad. The author's work was performed at the Public Health Laboratory Service, London.

> In the same Annals, a study on the quantitative comparison of serum and saliva (actually oral fluid) concentrations of theophylline showed a mean difference of 0.06 ug/mL (std. dev. 2.1 ug/mL, 95% confidence limits +/- 4.2 ug/mL) over a range of 1.6 to 27.9 ug/mL for 118 adults and 0.4 ug/mL (95% confidence limits +/- 2.0 ug/mL) for 10 pediatric patients using the same collection device cited in the above study. The device utilizes an absorbent pad that is placed in a preservative. It illustrates that acceptable quantitative concentrations can be obtained using collection devices.[2]

Beyond the opinions based on such medical studies, spitting is not a commonly accepted practice and has unsanitary stigma. Fear of contagious infections, whether warranted or not, will create an unwillingness to conduct such collections by collectors. Moreover, the thought of a collector trying to split an untreated whole saliva specimen is preposterous, in light of the difficulties in handling such specimens. The net result of these factors will seriously limit the acceptability of using whole saliva collections by spitting. This would be a serious blow to the significant advantages of using saliva over urine in drug testing programs. The potential for dilution and adulteration, the most serious limitation to urine testing, will be considerably less likely with saliva, as noted in the Background discussion of the proposed Guidelines. In addition, the Background discussion also recognizes these concerns: "*To avoid saliva stimulation, some recommend spitting into a cup, but some donors may be opposed to spitting, especially when observed, and may experience dry mouth.*" Repeated spitting also stimulates saliva flow.

It appears that the decision to limit saliva testing to spitting is over concern about the variability in the amount of whole saliva collected, whether by spitting or with a collection device approved or cleared by the FDA for quantitative clinical decisions. If one compares this variability with the tremendous variability in drug concentrations in urine, there is no rational basis for this concern. In a widely used FDA cleared collection device, an absorbent pad is inserted in the mouth for two minutes. It has been evaluated extensively to collect approximately 0.4 mL of whole saliva. It is placed in 0.8 mL of preservative fluid. If one assumes variability in collection of saliva of +/- 0.2 up to +/- 0.8 mL (which is far in excess of the observed variability), a specimen that contains 10 ng/mL of a drug would range from 2 to 5 ng/mL in the final liquid, a 2.5-fold difference. True, this might cause the specimen to be negative if the cutoff was 3 ng/mL. In contrast, the existing Guidelines permit unlimited ranges for urine. E.g., if a urine specimen contains 50 ng/mL of drug with an "average" creatinine level of 150 mg/dL, the concentration would be 1.6 ng/mL if diluted to a creatinine level of 5 mg/dL and 83.3 ng/mL if concentrated to a creatinine level of 250 mg/dL. This is more than a 50-fold difference, yet no sanctions are affixed to the specimen other than being reported as a negative dilute specimen at the low end.

Recommendation

The Guidelines should require the use of FDA-cleared collections devices, period. Such devices are available for the collection of "whole saliva" (i.e., by spitting or drooling) or for the collection of "oral fluid" using an adsorbent pad, which may or may not be placed in a preservative fluid. The Guidelines could establish acceptable limits to the variability in the volume of "oral fluid" collected by such devices, but, as noted above, even with a large variation of +/- 100% in volumes there are small variations in the drug concentrations.

In addition, along with the provision for splitting a spit specimen (which will be difficult), the Guidelines should permit the collection of two simultaneous "oral fluid" specimens using two collection devices. One would serve as the primary and the other as a split specimen.

2. Proposed Guideline

Section 2.3(a) When an oral fluid specimen is collected, a urine specimen must also be Collected.

Section 8.3(a)(16) After completing the oral fluid specimen collection procedure, the collector must also collect a urine specimen following the procedures described in section 8.5.

Comment

The collection of a urine specimen along with a "whole saliva" or "oral fluid" specimen, as stated in the proposed Guidelines, is based on concern over the possibility of passive exposure to marijuana smoke. The existing HHS Guidelines (59 FR 1994) recognized the potential of passive exposure producing detectable levels of cannabinoids in urine testing, stating: "The Department does not believe that passive inhalation is a reasonable defense or that significant exposure can occur through passive inhalation to cause a urine specimen to be reported positive." This opinion was based on published studies on passive exposure to marijuana smoke, most notably those conducted by Dr. Edward Cone, then at NIDA's Addiction Research Center. Those studies placed subjects under two exposure conditions that produced detectable levels of THC-9-carboxylic acid (THCA), with many above the 50 ng/mL screening cutoff for THCA in urine and as high as 12 ng/mL in confirmation under the more extreme of the two conditions (exposure to 16 marijuana cigarettes over one hour on six consecutive days). Under the less extreme condition (using 4 cigarettes), levels were considerably lower.

It must be noted that many drug testing programs outside of the deterrence-based HHS and DOT programs, e.g., those under NRC and the private sector, use screening cutoffs for THCA of 20 ng/mL and confirmation cutoffs as low as 5 ng/mL. These programs deal with the passive exposure issue through an MRO.

I have been provided with a copy of a summary of a new study, also conducted by Dr. Cone, in which four subjects were exposed during a single session to the smoke of five active smokers each smoking one marijuana cigarettes in the same or identical sealed, small chamber used in the above cited urine study. At 30 minutes following exposure, only one of the specimens collected was positive at a screening cutoff of 3 ng/mL (confirmation, 3.6 ng/mL) and none gave positive responses at 45 minutes. In contrast to the above cited urine study, there was no need to perform exposures over multiple days as the half-life of THC in saliva (whole saliva or oral fluid) is limited to a few hours, negating day-to-day accumulation. This study has been submitted to the

Journal of Analytical Toxicology for publication.

It is obvious that the same extreme conditions are required to produce positive test results in oral fluid as with urine, so the cited rationale for including testing for the use of Cannabis products in the current HHS Guidelines prevails in the proposed Guidelines. These data illustrates that a donor would have to had left a closed, marijuana smoked-filled room 30 to 45 minutes prior to providing a specimen even to have a less than 25% chance of testing positive. I do not know of any MRO that would find that as an acceptable "medical explanation," as required by the current and proposed HHS Guidelines.

The dual collection requirement also raises several other complicating and conflicting factors. With published studies and available data documenting the wide variability on drug concentrations in urine due to unintentional and especially intentional dilution of urine, it would be highly likely that many initial whole saliva or oral fluid specimens would give positive results, but would have negative results in concomitantly collected urine specimens. If a drug testing program, in any sector, was utilizing whole saliva or oral fluid testing (but required to follow this proposed condition) to overcome the known limitations of urine testing, coupled with the fact that cannabinoids are the most frequently encountered positives, they would soon lose confidences in the use of saliva, abandoning it for less effective urine testing alone. Thus, this somewhat overzealous attempt to eliminate *any* possibility of passive exposure to marijuana smoke under *any* conditions, no matter how extreme, would cripple and eventually deter the use of "saliva" testing.

Recommendation

The requirement for collecting a urine specimen along with a whole saliva or oral fluid specimen be deleted.

3. Proposed Guideline

Section 2.2 Under what circumstances can the different types of specimens be collected? Oral Fluid... Pre-employment, random, reasonable suspicion/cause, postaccident

Comments

The exclusion of return-to-duty and follow-up testing for whole saliva or oral fluid makes no sense. The timeframes for drug use and possible attempts to subvert drug tests is no different for return-to-duty tests than for pre-employment tests, which are permitted. As discussed above, due to the typically pre-announced times for these tests, a donor has ample opportunity to produce a dilute urine specimen, even with very recent use, whereas the donor would have to refrain from drug use for some period of time prior of providing a "saliva" specimen.

Similarly, follow-up testing is conducted randomly, so what makes it different from "random" testing? The rationale, which is only stated in the "Subpart B--Specimens--Major Change" discussion section of the proposed Guidelines, is because "of the short detection window" for "saliva." Although random and follow-up-testing are identical in nature and provide the donor with less opportunity to dilute or adulterate a specimen for a urine test, there should be equally less opportunity to cease using the drug or drugs of choice. Of course, this presumes the random or follow-up test is conducted properly, i.e., with little notice.

In a published study of prevalence rates, the positive rates across the five drug classes were nearly identical for "oral fluid" tests (using a commercial collection device, Intercept) and federally-mandated and general workforce populations, with the overall positive rate slightly higher for oral fluid (reference 21 in the proposed Guidelines). This included over 77,000 oral fluid results and over six million urine results. Clearly, for all of the reasons discussed above, whole saliva or oral fluid testing is comparable to urine testing regardless of the circumstances for conducting the test.

Recommendation

Include all reasons to test for whole saliva *and* oral fluid.

Point of Collection Test (POCT)

1. Proposed Guideline

Point of Collection Test (POCT). A drug or validity test conducted at a collection site to obtain a preliminary result as to whether a specimen may contain a drug/drug metabolite or is not a valid specimen.

Section 12.4 What types of POCT devices are there? POCT devices are:

(a) Non-instrumented for which the endpoint result is obtained by visual evaluation (i.e., read by human eye); or

(b) Instrumented for which the result is obtained by instrumental evaluation (e.g., densitometer, spectrophotometer, fluorometer).

Section 12.5 What must a POCT device manufacturer submit to the Secretary to have its POCT device initially included on the list of SAMHSA-certified POCTs?

(e) A total of 100 POCT devices and related testing procedures in representative numbers from all currently available manufactured lots of the device for HHS testing to evaluate the performance of the POCT device(s) for drug and validity testing; and

Comments

As president of Duo Research Inc., I have been responsible for a contract for oversight of a nation-wide drug testing program that conducts over 100,000 POCTs per year. These involve devices that fit the POCT definition and include both types of devices named above under Section 12.4 of the proposed Guidelines. However, the language in Section 12.5 is limited to only non-instrumented drug test (NIDT) devices. For testing sites that utilize instrumented systems, clearly it is not the Department's intent for them to send their Hitachi 717 or whatever other on-site instrument they are using to be evaluated. Also, in the case of at least one other computerized instrumented system that utilizes lateral flow immunoassay devices, how does the computer and instrument portion be provided in order to test the lateral flow test strips? In the program monitored by Duo Research, the instrumented and non-instrumented sites receive performance test samples and are inspected periodically. The performance of the NIDT devices is monitored by periodic reviews of the confirmation rates from the testing laboratories.

Recommendation

These two sections and any others that fail to distinguish between POCT instruments and POCT NIDT devices need to be modified. I would strongly object to the "easy way out" by the exclusion of POCT instrumented devices as these provide more accurate results and are more cost effective for large numbers of drug tests.

2. Proposed Guideline

Section 12.8 What are the responsibilities of a Federal agency that wishes to conduct POCT? A Federal agency which seeks to conduct POCT as part of its Federal Workplace Drug Testing Program must:

(e) Inspect the POCT sites periodically to ensure compliance with these Guidelines

Comments

The proposed Guideline frequency of "periodic inspections" of POCT sites leaves too much latitude, basically to the interpretation and discretion of the Federal agency.

Recommendation

I recommend that "periodic" be defined, for example, as not more often than 12 months or less than 18 months.

3. Proposed Guideline

Section 12.8 What are the responsibilities of a Federal agency that wishes to conduct POCT? A Federal agency which seeks to conduct POCT as part of its Federal Workplace Drug Testing Program must:

(f) Ensure that on a quarterly basis sets of HHS-contractor prepared PT samples (that satisfy the requirements in section 12.9) are submitted to challenge the performance of each POCT drug and validity test device at each site;

Comment

Although these PT samples are to be submitted by the HHS contractor, as with the other forms of testing, there is no indication of the number of PT samples that will be submitted on a quarterly basis. The Department appears to want to change the number of PT samples from time to time for all forms of testing. However, in the case of POCTs, where relatively few specimens may be tested, it would seem beneficial for Federal agencies and others that may fall under these Guidelines, to have some indication of how many PT samples might be expected. This could be a significant factor in the cost analysis of advantages and disadvantages of conducting POCTs.

Recommendation

Consider the inclusion of some anticipated range of PT samples that could be expected, for example, not less than 6 or more than 12, etc.

4. Proposed Guideline

Section 12.19 What are the quality control requirements when conducting POCTs?

(a) For drug POCTs:

(1) Each day testing is performed using devices with visually read endpoints (i.e., a color appearing or disappearing that indicates a positive result using that device), each individual performing drug tests using these devices must test at least one negative control (i.e., a sample certified to contain no drug or drug metabolite) and one positive control (i.e., a sample with the concentration of the drugs or metabolites in the range of 25 percent above the cutoff concentration) before donor specimens are tested. These quality control samples must be tested and the results interpreted with the positive control testing positive and the negative control testing negative before donor specimens are tested and reported each day.

(2) Each day testing is performed using devices with semi-automated or automated testing devices with machine read endpoints (i.e., spectrophotometer), at least one negative control (i.e., a sample certified to contain no drug or drug metabolite) and one positive control (i.e., a sample with the concentration of the drugs or metabolites in the range of 25 percent above the cutoff concentration) must be tested on each device used. These quality control samples must be tested and the results interpreted with the positive control testing positive and the negative control testing negative before donor specimens are tested and reported each day.

Comment

As co-chairperson of the POCT working group that assisted in the evolution of these proposed Guidelines, it was quite a surprise to see the above proposed quality control requirements. There was considerable discussion about the most appropriate means of assessing the day-to-day, lot-to-lot variations with non-instrumented drug test (NIDT) devices. Experience with several different manufacturers' devices strongly indicated a potential bias towards positive results at concentrations below the claimed cutoffs (see reference 58 in the proposed Guidelines). Such devices would very likely meet the weak control standards in the proposed Guidelines. That is, negative samples would be negative and QC samples at 25% above the Guideline cutoffs would be positive. This would not evaluate the true cutoff of the device. In addition, as found in the studies in References 56 and 58 in the proposed Guidelines and a previous one conducted for the Administrative Office of the U.S. Courts,[3] many of the positive NIDT results were not confirmed. There were considerable variations from one drug class to another.

It was the final recommendation of the POCT working group to set the controls to 50% above and below the cutoffs in order to better assess the performance of the devices at the required cutoffs. Consideration of controls at 25% above and below the cutoffs, similar to those for laboratory-based testing, was rejected as several of the manufacturer representatives stated that it was not possible, at least with current manufacturing methods, to consistently produce lots that could meet the more stringent 25% requirement. Thus, devices that are at the cutoff will likely fail on the +25% control. Although 50% may appear to broad in comparison to instrumented systems, which can be calibrated prior to use, the symmetrical 50% requirement provides a better control over variations in manufacturing, storage, etc.

The Department may have considered that the requirement that devices be certified prior to their use with controls grouped around the cutoffs may satisfy the symmetrical assessment of their performance. However, this does not account for variations in devices in the same lot,

storage issues, and, most importantly, the performance of the POCT tester.

Recommendation

The QC requirements should be changed to require controls at 50% above and below the cutoffs.

SUMMARY

The long awaited publication of these proposed changes to the HHS Guidelines will have a significant impact on how drug testing is conducted in all forms of workplace settings. They will provide greater flexibility in how and when testing can be conducted. The Department has taken the bold step of moving workplace drug testing into a new era. It is the fervent desire of all working in various aspects of drug testing to assure applicants and employees with the highest accuracy possible and at the same time provide employers, federal and non-federal, with the means to have drug testing programs that are realistic, usable and effective. These comments and recommendations are intended to contribute too the forthcoming deliberations on the final HHS Guidelines.

Respectfully,

(via email)

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[1]References

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[3] R.E. Willette and K.J. Kadehjian, "Drugs-of-Abuse Test Devices," in "On-Site Drug Testing," A.J. Jenkins and B.A. Goldberger, eds, Humana Press, Totowa, NJ, 2002.