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DADE BEHRING

Dade Behring Inc.
P.O. Box 6101
Newark, DE 19714

July 9, 2004

Division of Dockets Management (FR Doc 04-7984)
Atten: Walter F. Vogel, PhD
5600 Fishers Lane
Rockwall II, Suite 815
Rockville, MD 20857

RE: FR Docket No. 04-7984: Substance Abuse and Mental Health Services Administration Mandatory Guidelines for Federal Workplace Drug Testing Programs

Dear Dr. Vogel:

Dade Behring Inc., a manufacturer of validity tests and *in vitro* diagnostic devices for drug testing, respectfully submits comments to the Substance Abuse and Mental Health Services Administration Mandatory Guidelines for Federal Workplace Drug Testing Programs. The availability of the mandatory guidelines was announced in the Federal Register Vol. 69, No. 71, April 13, 2004.

Written comments are provided in Attachment 1 and supporting information is provided in Attachment 2 of this correspondence. Dade Behring appreciates this opportunity to provide comments and hopes that the agency will find them constructive. We look forward to issuance of these mandatory guidelines in their final form.

If you have any questions or require additional information, please do not hesitate to contact me personally at 302-631-9454 or by email: taskeram@dadebehring.com.

Sincerely yours,

Andrea M. Tasker
Regulatory Affairs and Compliance Manager

FR Docket No. 04-7984: Substance Abuse and Mental Health Services Administration Mandatory Guidelines for Federal Workplace Drug Testing Programs

Attachment 1- Comments

1. Reference in Published Guidelines:
Background Supplementary Information: General Topic: Subpart C - Drug and Validity Tests – Major Change

Wording from Guidelines:
The Department is specifically interested in obtaining information on the ability of the various immunoassay test kits to detect MDMA, within the amphetamine class of drugs. The Department is aware that DoD drug tests members of the uniformed services for MDMA using an additional initial test focused on that drug. Based on this experience from DoD, if drug testing is proposed at the cutoffs in this document, the Department believes that the only sensitive and specific manner to perform the initial test for methamphetamine, amphetamine, and MDMA is to use two separate initial tests, one for methamphetamine and amphetamine and a second initial test for MDMA. Recommendations on using a single amphetamine test kit or the need to use separate test kits are requested.

Comment:
We support the Department's approach of requiring two separate initial tests, one for methamphetamine and amphetamine and a second initial test for MDMA.

Design and manufacture of a single initial test that demonstrates equivalency for MDMA, amphetamine, and methamphetamine at the required cutoff would be technically difficult. Such an assay would require three antibodies to be employed. Each antibody for the specific drug would have some cross-reactivity to the other two drugs making assay optimization difficult. Furthermore, a combination assay would be more prone to undesirable interference from over-the-counter amphetamine-like substances.

See the Supporting Information in Attachment 2 from Dade Behring Amphetamine assays. Dade Behring has an MDMA assay under development (Confidential) and can share preliminary data with the Department on request.

2. Reference in Published Guidelines:
Mandatory Guidelines, Section 3.15 What Criteria are Used To Report a Urine Specimen as Adulterated? (c)

Wording from Guidelines:
(c) The presence of chromium (VI) is verified using either a general oxidant colorimetric test (with a greater than or equal to 50 mcg/mL chromium (VI)-equivalent cutoff) or a chromium (VI) colorimetric test (chromium (VI) concentration greater than or equal to 50 mcg/mL) for the initial test on the first aliquot and a different confirmatory test (e.g., multi-wavelength spectrophotometry, ion chromatography, atomic absorption spectrophotometry, capillary electrophoresis, inductively coupled plasma-mass spectrometry) with chromium (VI) concentration greater than or equal to the limit of detection (LOD) of the confirmatory test on the second aliquot.

Proposed Action and Comment :
The chromium cutoff changed from at least 20 mcg/mL in the proposed guidelines published in August 2001 to 50 mcg/mL in the proposed guideline published on April 13, 2004. No reason for this change was included in the proposed guidelines supplementary information and currently, most commercial oxidant tests do not employ a 50 mcg/mL cutoff.

We respectfully request a scientific reason or rationale for this change be included in the guidelines.

3. Reference in Published Guidelines:
Mandatory Guidelines, Section 11.25 What Are the Requirements for Conducting Each Validity Test on a Urine Specimen? (b) The requirements for measuring specific gravity are as follows:

Wording from Guidelines:
(1) The refractometer shall report and display the specific gravity to four decimal places. The refractometer shall be interfaced with a laboratory information management system (LIMS), computer, and/or generate a hard copy of the digital electronic display to document the numerical result.
(2) The initial and confirmatory specific gravity tests must have a calibrator or control at 1.0000; and
(3) The initial and confirmatory specific gravity tests must have the following controls:
(i) One control targeted at 1.0020;
(ii) One control in the range of 1.0040 to 1.0180; and
(iii) One control greater than or equal to 1.0200 but not greater than 1.0250.

Comment:
We request that the Department allow use of colorimetric assays for the measurement of specific gravity as an acceptable alternative to refractometry for initial testing of urine specimens for validity. Newer colorimetric assays may be capable of meeting the same requirements as those defined for refractometry. Allowing use of colorimetric assays for initial screening would provide a more convenient, streamlined, automated and economic alternative to refractometry testing for laboratories. Automated instrumentation can be programmed to reflex to additional tests after certain criteria are met allowing the use of a single aliquot. A colorimetric assay for initial screening would also support the philosophy that the initial and confirmatory tests use a different analytical methodology. We respectfully request that the Guidelines allow the use of these next generation colorimetric assays when they become available.

Proposed re-wording:
(1) The initial specific gravity test may be performed using either a colorimetric test method or a refractometer. The confirmatory specific gravity test shall be performed using a refractometer.
(2) The refractometer or colorimetric test must report and display specific gravity to four decimal places. The refractometer or colorimetric test must be interfaced with a laboratory information management system (LIMS), computer, and/or generate a hard copy of the digital electronic display to document the numerical result;
(3) The initial and confirmatory specific gravity tests must have a calibrator or control at 1.0000; and
(4) The initial and confirmatory specific gravity tests must have the following controls:
(i) One control targeted at 1.0020;
(ii) One control in the range of 1.0040 to 1.0180; and
(iii) One control greater than or equal to 1.0200 but not greater than 1.0250.

Attachment 2 - Supporting Information

Specificity Information from the Syva® Emit®II Plus Amphetamines Insert Sheet (Revision 9C122UL.1SL)

Specificity

The Emit® II Plus Amphetamines Assay detects amphetamine compounds in human urine.

Data found in the following tables are representative of the performance of this assay. However, results may vary among reagent lots.

Table 22 lists the concentrations of amphetamine compounds that produce a result that is approximately equivalent to the 300 ng/mL, 500 ng/mL, and 1000 ng/mL calibrator/control cutoffs. Each concentration represents the reactivity level for the stated compound when it is added to a negative urine specimen. These concentrations are within the range of the levels found in urine following use of the compound or, in case of metabolites, the parent compound. If a specimen contains more than one compound detected by the assay, lower concentrations than those listed in Table 22 may combine to produce a rate approximately equivalent to or greater than that of the cutoff calibrator.

Table 22 — Concentrations of Amphetamines that Produce a Result Approximately Equivalent to the 300 ng/mL, 500 ng/mL, and 1000 ng/mL Amphetamine Cutoffs

	Concentration (ng/mL) Giving a Response Approximately Equivalent to the Cutoff		
Compounds	**300 ng/mL Cutoff**	**500 ng/mL Cutoff**	**1000 ng/mL Cutoff**
	444	705	2077
d,l-Amphetamine	617	1037	2138
l-Methamphetamine	726	1318	3630
l-Amphetamine	2185	3739	7237
MDA	1073	1680	3710
MDMA	5193	9150	34274
MDEA	4401	6814	27165

Table 23 lists the concentrations of compounds that produce a result that is approximately equivalent to the 300 ng/mL, 500 ng/mL, and 1000 ng/mL cutoffs. Each concentration represents the reactivity level for the stated compound when it is added to a negative urine specimen. Most of the compounds react at levels much higher than typically found in urine (but which may occasionally occur).[5,8] If a specimen contains more than one compound detected by the assay, lower concentrations than those listed in Table 23 may combine to produce a rate approximately equivalent to or greater than that of the cutoff calibrator.

Table 23 — Concentrations of Compounds that Produce a Result Approximately Equivalent to the 300 ng/mL, 500 ng/mL, and 1000 ng/mL Amphetamine Cutoffs

	Concentration (µg/mL) Giving a Response Approximately Equivalent to the Cutoff		
Compounds	**300 ng/mL Cutoff**	**500 ng/mL Cutoff**	**1000 ng/mL Cutoff**
4-Chloramphetamine	2.6	4.5	12.2
Benzphetamine*	0.4	0.7	1.0
Bupropion	269	487	2221
Chloroquine	2129	2174	4474
l-Ephedrine	426	813	3538
Fenfluramine	24	41.6	155
Mephentermine	8.3	14.5	61.6
Methoxyphenamine	86	157	357
Nor-pseudoephedrine	42	67	169
Phenmetrazine	2.3	3.5	13.4
Phentermine	5.8	9.0	24.9
Phenylpropanolamine	95	165	350
Propranolol	9.9	14.9	90.1
d,l-Pseudoephedrine	1415	2578	8349
Quinacrine	2539	3843	16461
Tranylcypromine	32	58	230
Tyramine	14	21	60