

February 24, 2004

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Docket # 2003D-0522

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) and the National Academy of Clinical Biochemistry (NACB) welcome the opportunity to comment on the Food and Drug Administration's (FDA's) draft guidance, entitled "Premarket Submission and Labeling Recommendations for Drugs of Abuse Tests," which sets forth the agency's current views on how to regulate drugs of abuse screening tests. Our comments follow:

III. Performance Characteristics;

In general, we believe the sections on cutoff, specificity, and interference are inadequate to describe the output of each evaluation. We urge that each section state unequivocally that the performance characteristics of drugs in each class be documented in two ways: (1) the level of each drug that is equivalent to the cutoff level for the primary calibrator; and (2) the dilution characteristics of each drug in terms of signal linearity when diluted with negative urine. This will allow the user to differentiate between a member of the class and other potential cross-reactants without the need for a more specific procedure such as GC-MS.

III. Performance Characteristics; C. Specific Performance Studies; 1. Cutoff Characterization

Most drugs of abuse testing performed by clinical laboratories are conducted in emergency rooms, rehabilitation programs and other clinical settings to diagnose and/or treat patients. We are concerned that this document does not sufficiently address the distinctions among these settings. Instead, the guidance document recommends SAMHSA cut-off levels as if those levels apply to all settings in all situations. They do not. In fact, the use of SAMHSA cut-off levels in clinical settings can lead to the misinterpretation of results by treating physicians, since results below the cut-off thresholds are reported as 'negative,' which most physicians interpret to mean 'no drug present.' For example, many clinical laboratories routinely set lower cut-off levels to detect drug levels in newborns or determine exposure levels in individuals. AACC and NACB recommend that the agency modify the document to reflect these differences.

Specifically, the agency states on page eight: "We encourage the use of threshold cutoff concentrations identified by the Substance Abuse and Mental Health Services Administration (SAMHSA) for the following classes of drugs of abuse in urine...":

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We suggest that this statement be modified to recognize that the SAMHSA guidelines were specifically set up to support workplace testing and not clinical toxicology. Thus, we recommend that the sentence be rewritten to state:

"For assay kits supporting workplace substance abuse testing, we encourage the use of threshold cutoff concentrations identified by the Substance Abuse and Mental Health Services Administration (SAMHSA) for the following classes of drugs of abuse in urine..."

After the listing, a note should be added that states: "The SAMHSA cutoff concentrations may not be appropriate for clinical toxicology testing."

We also recommend that the FDA add a statement under the "Special Notes" section that states: "Cutoff concentrations may differ from SAMHSA recommended concentrations for clinical purposes. Therefore, when developing a clinical assay for amphetamines, cocaine, opiates, cannabinoids or phencyclidine you may use your own clinical studies or scientific literature to support your cutoff." This statement is consistent with our earlier recommendation that allows for clinically relevant cutoffs of the "SAMHSA" five drugs for clinical toxicology.

III. Performance Characteristics; C. Specific Performance Studies; 2. Specificity and Cross-reactivity & 3. Interference

We also want to bring to your attention two issues regarding specificity and cross-reactivity pertinent to the use of these tests within the clinical setting. The first relates to the designation of target compounds to represent drug classes. As with the cut-off issues discussed previously, SAMSHA established these target compounds based upon prevalence of use within the workplace setting using metabolites affording long windows of detection. The generic use of these has led to the use of assays that fail to detect compounds of clinical interest. For example, few opiate immunoassays detect oxycodone, few amphetamine assays detect MDMA, and similar problems exist with assays for benzodiazepines and barbiturates. Again, the inability of current assays to identify these compounds can, and has, led to misinterpretation of results by treating physicians. We believe the agency should encourage manufacturers to develop assays with broader class applications for use in clinical settings.

Second, the sections on specificity and interference discuss the potential cross-reaction of drugs with similar structures, but does not venture into the issue of co-administered drugs, regardless of structure. We urge the FDA to include a statement requiring that drugs commonly co-administered within the therapeutic (not molecular) class be evaluated for cross-reactivity as well. For example, other approved anti-epileptics can be used in evaluating barbiturate assays.

III. Performance Characteristics; C. Specific Performance Studies; 3. Interference, Study Design

The agency recommends that manufacturers assess the effect of an interferent by diluting pools of the target drug (at two levels) and, if there is a change from the expected result, diluting the interferent with drug-free urine. Since the test specimens already contain the target drug, dilution with drug-free urine changes the concentration of both the target and the interferent, thus confounding the interpretation of the signal. We recommend that this procedure be changed to perform the dilution with urine containing the target drug at constant concentration, so that the difference in signal reflects solely the change in the interferent concentration .

IV. Labeling Considerations; 4. Quality Control

The numerous references to SAMHSA in the document overly emphasize the SAMHSA cutoff limits. For example, on page 19 the document states: "If you used alternative levels of controls, you should clearly indicate the levels used in the label along with a statement that these differ from SAMHSA levels." Alternative levels of controls could be tighter than the SAMHSA levels due to improved precision of an assay and a better total error. If the manufacturer can claim a total error of no more than 10%, then the system should be challenged at that claim, rather than SAMHSA levels, and there should be no need to justify a lower percentage against SAMHSA levels. We recommend that the above statement be rewritten as follows: "If you used alternative levels of controls, you should clearly indicate the levels used in the label. If the alternative level of control exceeds 25% above or below the cutoff concentration of the assay an explanatory statement should be included as to why the 25% threshold was exceeded."

V. Labeling Considerations; 3. Understanding the Test Result

The information regarding the calculation of false positives is based upon SAMHSA criteria for the identification and quantification of specific target analytes. In the clinical setting, these may not be false positives if another clinically relevant drug of that class is indeed present. For example, in workplace drug testing an opiate screen would be considered a false positive if, on confirmation, oxycodone was found instead of morphine, codeine or 6-acetylmorphine. Similarly, the criteria for a confirmed amphetamine/methamphetamine positive are quite stringent in the workplace setting requiring specific quantities of each to be present.

V. Labeling Considerations; 6. Performance Characteristics; Specificity and Cross-reactivity

The comments and recommendations in this section are correctly stated, but should also include a recommendation that when the manufacturer lists “. . . all compounds tested

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and . . . the lowest concentration of each compound that generated a positive result," that it also identify the amount of drug generally required to be ingested in order to produce the concentration noted. For example, it is of little value to state that 500 ng/mL dextromethorphan produces a positive PCP result, without knowing whether 500 ng/mL is a typical dose, or if it requires the patient to consume two or three bottles of a dextromethorphan-containing syrup to achieve the stated level.

By way of background, AACC is the principal association of professional laboratory scientists--including MDs, PhDs and medical technologists. The AACC provides national leadership in advancing the practice and profession of clinical laboratory science and its application to health care. The NACB is the Academy of the AACC and is dedicated to advancing the science and practice of clinical laboratory medicine through research, education, and professional development. It publishes Laboratory Medicine Practice Guidelines for the application of clinical biochemistry to medical diagnosis and therapy. Our two organizations look forward to working with you as you refine this document. If you have any questions, please call Thomas Moyer, PhD, AACC's President, at (507) 284-3480, D. Robert Dufour, MD, NACB's President at (202) 745-8285 or Vince Stine, AACC's Director of Government Affairs, at (202) 835-8721.

Sincerely,



Thomas Moyer, PhD
President
American Association for Clinical Chemistry



D. Robert Dufour
President
National Academy of Clinical Biochemistry