

# DADE BEHRING

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2003D-0522-1-005

February 27, 2004

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

**RE: FDA Docket No. 2003D-0522: Draft Guidance for Industry and FDA Staff; Premarket Submission and Labeling Recommendations for Drugs of Abuse Screening Tests; Availability**

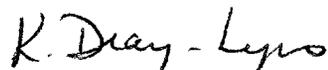
Dear Sir or Madam:

Dade Behring Inc., a manufacturer of *in vitro* diagnostic devices, respectfully submits comments to the Draft Guidance: Premarket Submission and Labeling Recommendations for Drugs of Abuse Screening Tests. The availability of the guidance document was announced in the Federal Register Vol. 68, No. 231, December 2, 2003.

Dade Behring supports FDA's efforts in development of such a guidance. Our comments are provided in Attachment 1. Dade Behring appreciates this opportunity to provide comments and hopes that FDA will find them constructive. We look forward to issuance of the guidance in its final form.

If you have any questions or require additional information, please do not hesitate to contact me personally at 781.826.4551 or by email: [kathleen\\_dray-lyons@dadebehring.com](mailto:kathleen_dray-lyons@dadebehring.com).

Sincerely yours,



Kathleen A. Dray-Lyons  
Regulatory Affairs and Compliance Manager

2003D-0522

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# Attachment 1

Reference in Draft Guidance Doc	Comment and Proposed Re-wording	Draft Guidance Document Wording
<p>I. Introduction Page 1</p>	<p><b>Comment:</b> FDA has assumed that the quality of test results will vary based on where the device is used. While we agree that it is necessary to differentiate single use from traditional laboratory or multiple use settings, we disagree that the quality of results from automated test systems will differ significantly. Performance based site differences should not be expected as these systems are designed with the user in mind. Requiring manufacturers to perform testing in all types of settings and at varying skill levels will be overly burdensome.</p> <p>We agree that the label should clearly indicate where studies are performed. However, including the experience and training of the users who participated in studies to characterize performance should not be necessary in the case of laboratory professionals, healthcare professionals or trained staff as both CLIA and SAMHSA regulations mandate training and experience for these personnel.</p> <p><b>Proposed Re-wording:</b> For example, if a test is intended for use in a laboratory setting or workplace or other repetitive testing sites (outside of laboratories), we recommend that the data provided in your submission be based on use of the test by laboratory professionals, health care professionals, or trained staff. For a test intended for occasional testing of individual subjects by untrained users (e.g., home users), the data should be based on use by untrained users. In both situations, you should write your labeling in a manner appropriate to the type of user. We recommend that your label clearly indicate where the studies to characterize the analytical performance of your test were conducted. In addition, your labeling should note that performance may be negatively impacted if the test is performed by inexperienced or untrained users.</p>	<p><b>Original Wording:</b> For example, if a test is intended for use in a laboratory setting, we recommend that the data provided in your submission be based on use of the test by laboratory professionals, healthcare professionals, or trained staff. For a test intended for occasional testing of individual subjects by untrained users (e.g., home users), the data should be based on use by untrained users. In both situations, you should write your labeling in a manner appropriate to the type of user. Similarly, if a test is intended for workplace or other repetitive testing sites (outside of laboratories), you should provide data reflecting the intended use, the use setting, and the likely end users. We recommend that your label clearly indicate the experience or training of the users who participated in the studies to characterize the analytical</p>

		performance of your test. In addition, your labeling should note that performance may be negatively impacted if the test is performed by users with less experience or training.
<p><b>III. Performance Characteristics</b>  <b>A. Overview</b>  Page 6</p>	<p><b>Comment:</b> Performance study testing should be representative of the possible settings, but not necessarily inclusive of all settings, in which a test may be used. Including all types of settings would be redundant and economically burdensome for a manufacturer. For automated systems, test results should not be affected by the test setting or the skill of the operator performing the test. Such systems are designed with the end user in mind. Requiring performance testing to be conducted in a manner that reflects how the device will be used seems in conflict with the design validation requirement of the Quality System Regulations where testing under simulated use conditions is acceptable.</p> <p><b>Proposed Re-wording:</b>  Performance testing should be conducted in a manner that is representative of how the device will be used.</p>	<p><b>Original Wording:</b>  We recommend that you conduct performance testing in a manner that reflects how the device will be used. For example, in laboratory settings.....</p>
<p><b>III. Performance Characteristics</b>  <b>C. Specific Performance Studies</b>  2. Specificity and Cross-reactivity  Page 9</p>	<p><b>Comment:</b> In the Content section, the list in the example of recommended cross-reactants to be tested for amphetamine and methamphetamine assays specifies a racemic mixture be tested for MDMA, MDA and MDEA. Testing these compounds in a pure form (d and l) is a more standard approach.</p> <p><b>Proposed Re-wording:</b>  For example, we recommend that submissions for amphetamine and methamphetamine assays evaluate:  d-amphetamine  l-amphetamine  d-methamphetamine  l- methamphetamine  d-MDMA (3,4-Methylenedioxymethamphetamine)  l-MDMA (3,4-Methylenedioxymethamphetamine)  d-MDA (3,4-Methylenedioxyamphetamine)  l-MDA (3,4-</p>	<p><b>Original Wording:</b>  For example, we recommend that submissions for amphetamine and methamphetamine assays evaluate:  d-amphetamine  l-amphetamine  d-methamphetamine  l- methamphetamine  d,l-MDMA (3,4-Methylenedioxymethamphetamine)  d,l-MDA (3,4-Methylenedioxyamphetamine)  d,l-MDEA  (Methylenedioxyethylamphetamine)</p>

	<p>Methylenedioxyamphetamine)  d-MDEA  (Methylenedioxyethylamphetamine)  l-MDEA  (Methylenedioxyethylamphetamine)</p>	
<p><b>II. Performance Characteristics</b>  <b>C. Specific Performance Studies</b>  3. Interference  Page 11</p>	<p><b>Comment:</b> Under study design, the section regarding altering pools to reflect the full range of physiological conditions within the body seems relevant to only urine while in section I., other matrices are mentioned. Consider rewording for clarity.</p> <p><b>Proposed Re-wording:</b>  To evaluate the effects of variable physiological conditions, you may alter the same two pools of specimen to reflect the full range of physiological conditions that might exist within the body. For example, you may alter the pH of urine pools so they span the pH range of 3 to 9, run each sample, and look for a change in the expected result. For urine specimens, we recommend you examine the performance under varying pH and specific gravity conditions.</p>	<p><b>Original Wording:</b>  To evaluate the effects of variable physiological conditions, you may alter the same two pools of specimen to reflect the full range of physiological conditions that might exist within the body. For example, you may alter the pH of the pools so that they span the pH range of 3 to 9, run each sample, and look for a change in the expected result. We recommend that you examine the performance under varying pH and specific gravity conditions.</p>
<p><b>III. Performance Characteristics</b>  <b>C. Specific Performance Studies</b>  5. Method Comparison  Page 12</p>	<p><b>Comment:</b> We recommend the Study Design section regarding how many samples must be run on the reference method when comparing to a predicate device, be revised for clarity.</p> <p><b>Proposed Re-wording:</b>  For well established assays, when comparing to a predicate device, we recommend that you also analyze all positive and 10% of the negative samples using a reference method.</p> <p>If the analyte, matrix, or method is not well characterized, or the reference method is being run in lieu of another predicate device, we recommend that you compare all samples to a reference method, and that you increase the sample size of the study.</p>	<p><b>Original Wording:</b>  For well established assays, we recommend that you analyze all positive and 10% of the negative samples using a reference method. If the analyte, matrix, or method is not well characterized, we recommend that you compare all samples to a reference method, and that you increase the sample size of the study.</p>

<p><b>III. Performance Characteristics</b>  <b>C. Specific Performance Studies</b>  5. Method Comparison  Page 12</p>	<p><b>Comment:</b> FDA's suggestion in the Content section that clinical specimens from subjects taking the specific drug be obtained and tested when the assay targets a class of drugs will be unnecessarily burdensome for the manufacturer. Drugs of abuse samples are typically collected from an uncontrolled subject population. It is difficult to obtain reliable information on what the subject was taking and would therefore, be difficult to separate in a method comparison study. Accuracy can be assured by further characterizing the specimen with a reference method.</p> <p><b>Proposed Re-wording:</b>  <b>Remove this paragraph.</b></p>	<p><b>Original Wording:</b>  Because varying drugs within a drug class (e.g., barbiturates) have different levels of cross- reactivity, pooling data from samples.....</p>
<p><b>III. Performance Characteristics</b>  <b>C. Specific Performance Studies</b>  5. Method Comparison  Page 12</p>	<p><b>Comment:</b> We recommend you include more specific dilution guidelines in the Content section such as a procedure for diluting samples, i.e., use of individual drug-free specimen vs. a drug-free pool.</p> <p><b>Proposed Re-wording:</b>  We recognize that you may find it difficult to obtain clinical samples near the cutoff concentrations for certain drugs, such as PCP. If you must supplement your study with diluted specimens, they should be prepared by diluting a patient sample of a higher concentration with a drug free specimen. Use of specimen pools is not allowed. We recommend that you analyze these samples by a reference method to determine their concentrations after dilution. The number of diluted specimens and the method of dilution should be documented in the submission and in the labeling.</p>	<p><b>Original Wording:</b>  We recognize that you may find it difficult to obtain clinical samples near the cutoff concentrations for certain drugs, such as PCP. In these instances, you may supplement your study with clinical samples of higher concentrations diluted with drug- free specimen. We recommend that you analyze these samples by a reference method to determine their concentrations after dilution. In the submission, you should indicate which samples you diluted and describe the protocol you followed.</p>

<p><b>III. Performance Characteristics</b>  <b>C. Specific Performance Studies</b>  5. Method Comparison  Page 12</p>	<p><b>Comment:</b> We recommend that the Study Design section include an example of an actual breakdown of the study sample numbers to provide clarity.</p> <p><b>Proposed Additional Wording:</b>  For example:  Total number of samples: 120  Number of samples between cutoff and 50% above the cutoff = 12  Number of samples between cutoff and 50% below the cutoff = 12  Number of samples evenly distributed between 50% above the cutoff and upper assay range = 48  Number of samples evenly distributed below 50% of the cutoff and the lower assay range = 48</p>	<p><b>Original Wording:</b>  None</p>
<p><b>III. Performance Characteristics</b>  <b>C. Specific Performance Studies</b>  9. Studies in the Workplace and Other Sites Performing Repetitive Testing  Page 14</p>	<p><b>Comment:</b> In the Study Design section, FDA recommends that the intended user (i.e., trained or untrained) perform method comparison and precision studies in the environment where the product ultimately will be used. This should not be necessary for tests run on automated systems. For automated systems, test results should not be affected by the test setting or the skill of the operator performing the test. Such systems are designed with the end user in mind. Requiring performance testing to be conducted in a manner that reflects how the device will be used seems in conflict with design validation requirement of the Quality System Regulations where testing under simulated use conditions is acceptable.</p> <p><b>Proposed Re-wording:</b>  We believe that studies done to characterize the performance of a device should be representative of how the device will be used.</p>	<p><b>Original Wording:</b>  We believe that studies done to characterize the performance of a device should reflect how the device will be used. We therefore recommend .....</p>

<p><b>IV. Labeling Considerations</b></p> <p><b>A. General Labeling for Drugs of Abuse Screening Devices</b></p> <p>1. Intended Use Page 16</p>	<p><b>Comment:</b> It is recommended that the manufacturer provide a description of the testing facility(ies) and educational backgrounds of the individuals performing the tests in the intended use of the labeling.</p> <p>Including such information for automated systems should not be necessary. The level of skill and training should be left to the individual testing facility and not prescribed by the manufacturer. Adequate training can be demonstrated by equivalent performance during the validation of the assay and through a Quality Control program.</p> <p>In the traditional laboratory setting or multiple use setting, the level and nature of training is mandated by CLIA and SAMHSA respectively.</p> <p>Rather than including a description of the testing facility(ies) and educational backgrounds of the individuals performing the tests in the labeling, we suggest including a warning recommending that operator training is required for all users. This is described adequately in CLIA §493.156 - Control requirements for the subspecialty of Toxicology of the State Operations Manual -- Appendix C, Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services. We recommend that wording similar to this be included in "Understanding the Test Results" section of the labeling.</p> <p>Including "for in vitro diagnostic use" with the intended use is inconsistent with the order specified in 21 CFR 809.10 where this statement is to be included with warnings and precautions.</p> <p><b>Proposed Re-wording:</b>  <b>A. GENERAL LABELING FOR DRUGS OF ABUSE SCREENING DEVICES</b>  <b>1. Intended Use</b>  Your intended use statement should describe:</p> <ul style="list-style-type: none"> <li>• whether your device is qualitative</li> </ul>	<p><b>Original Wording:</b>  <b>A. GENERAL LABELING FOR DRUGS OF ABUSE SCREENING DEVICES</b>  <b>1. Intended Use</b>  Your intended use statement should describe the training level of the user (i.e. trained or non-trained) and the</p>
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	<p>or semi-quantitative</p> <ul style="list-style-type: none"> <li>• the targeted drug/metabolite</li> <li>• the cutoff concentration</li> <li>• any special instrument requirements</li> <li>• the type of recommended specimen.</li> </ul> <p>A sample intended use statement is:  <i>ABC's cannabinoid test is intended for qualitative measurement of cannabinoids (THC) in human urine at a cutoff concentration of 50 ng/mL.</i></p>	<p>extent or nature of training (e.g., medical technologist, medical laboratory technician, lay user that has received training from a qualified health care provider) the setting of use (e.g., laboratory, home, workplace or other repetitive setting) whether your device is qualitative or semi-quantitative  the targeted drug/metabolite  the cutoff concentration  any special instrument requirements  the type of recommended specimen.</p> <p><i>ABC's cannabinoid test is a prescription assay intended for use in drug rehabilitation clinics and physician offices by trained users. It provides qualitative screening results for cannabinoids (THC) in human urine at a cutoff concentration of 50 ng/mL.  For In vitro Diagnostic Use.</i></p> <p><i>Minimum training .....</i></p>
<p><b>IV. Labeling Considerations</b>  <b>A. General Labeling for Drugs of Abuse Screening Devices</b>  3. Understanding the Test Result  Page 17</p>	<p><b>Comment:</b> FDA's suggested wording regarding accuracy of drugs of abuse tests is misleading and likely to confuse the user. The recommended wording regarding SAMHSA's reports of accuracy of drug tests is not a fair and accurate reflection of the actual performance of any individual assay. Users are not accustomed to seeing this type of general performance information in a manufacturer's Instructions for Use and it will most likely be viewed as a performance claim for the specific test.</p> <p>We also recommend including additional wording in this section of the labeling as a warning in lieu of including specific training requirements in the intended use.</p> <p><b>Proposed Re-wording:</b>  Remove this section and include a bibliography reference to the Substance Abuse and Mental Health Services Administration (SAMHSA) reports on accuracy.  We recommend that the following precaution statement be included:</p>	<p><b>Original Wording:</b>  <i>For Preliminary Positive Tests: In general, the Substance Abuse and Mental Health Services Administration (SAMHSA) reports the accuracy of drug tests as a :</i></p> <p><i>60 out of 100 times a "preliminary positive" .....</i></p>

	<p><i>Operator performance, including improper specimen preparation and handling, incorrect test interpretation, and failure to follow manufacturer's test system instructions may affect the accuracy and precision of the preliminary test result.</i></p> <p><i>Operator training is required prior to beginning testing and competency assessments over time are necessary to ensure continued accurate test performance.</i></p>	
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