Draft Guidance for Industry and FDA Staff

Premarket Submission and Labeling Recommendations for Drugs of Abuse Screening Tests

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
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This document was previously issued as two draft guidances on November 14, 2000: "Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications" and "Over the Counter (OTC) Screening Tests for Drugs of Abuse: Guidance for Premarket Notifications. "

C·D·R·H
Center for Devices and Radiological Health

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety

Preface

Comments and suggestions regarding this draft document may be submitted at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register* and the exact title of the document. For questions regarding this document contact Jean Cooper, D.V.M. at (301) 594-1243 or by email joc@cdrh.fda.gov.

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Contains Nonbinding Recommendations
Draft - Not for Implementation

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Premarket Submission and Labeling Recommendations for Drugs of Abuse Screening Tests

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed in the preface to this guidance.

I. INTRODUCTION

This document provides the Food and Drug Administration's (FDA's) guidance for premarket notification submissions and labeling for *in vitro* diagnostic (IVD) devices intended to screen for drugs of abuse. These recommendations are based on current science, clinical experience, and FDA review experience.

The devices discussed in this document are assays intended for the qualitative and semi-quantitative measurement of drugs of abuse in single-use (i.e., home testing), traditional laboratory use, and multiple-use settings (i.e., workplace or similar settings). These screening tests may be designed to detect drugs of abuse in urine, hair, saliva, or other matrices. The tests may be read by automated analyzers or they may be visually interpreted. This document focuses on screening tests for amphetamines, cocaine, methamphetamine, opiates, cannabinoids, and phencyclidine.

FDA previously issued two draft guidances addressing premarket submissions for drugs of abuse tests. These documents elicited concerns from industry and others because they included recommendations to bundle the cost of screening with the cost of confirmatory testing and because they stated that FDA would expect premarket submissions for tests used

in workplace and other sites performing repetitive testing[1] to include the same type of information as submissions for screening tests intended to be used in home settings.

The agency has evaluated the comments received and is issuing a new draft guidance to replace the earlier documents. In this new draft, FDA is clarifying that premarket notification submissions for drugs of abuse screening tests used in workplace and other repetitive testing sites may not require the same types of data as submissions for screening tests that are intended for sale directly to untrained users who perform these tests on an occasional basis (e.g., home use).

This draft also recognizes that the risk of getting an inaccurate or unreliable result in a repetitive-use environment (like the workplace) will vary depending upon a number of factors. The actual setting, the training of testing personnel, the volume of use, and access to trained medical review officers (MROs) will all impact the quality of results. Furthermore, we recognize that this risk may be addressed in ways other than bundling a proportionate cost of confirmatory testing into the costs of screening tests. Labeling and other performance controls may help mitigate the risk of inaccurate or unreliable results, and may do so at less cost to the manufacturer and consumer.

This document is intended to provide information on data and labeling that we recommend to support 510(k) submissions for drugs of abuse screening tests. The document will distinguish between submissions for screening tests that are intended to be used in a laboratory setting, screening tests intended to be used in the workplace or other repetitive testing sites, and screening tests that are intended to be used at home.

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, 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.

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 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.

[1] For the purpose of this document, "workplace and other repetitive testing sites" (or similarly worded phrases) include settings such as sports, schools, insurance, and rehabilitation centers where multiple individuals are tested.

At this time, FDA will continue to defer oversight of the use of these tests in the forensics (law enforcement) setting to the existing system of legal controls, such as the rules of evidence in judicial proceedings and other protections afforded through the judicial process.

This document is an adjunct to FDA's regulations and to the agency's guidance document entitled "In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions" available at http://www.fda.gov/cdrh/manual/ivdmanul.html. It does not supersede those publications, but is designed to provide additional guidance and clarification concerning information that we recommend be provided to FDA in premarket notification submissions for *in vitro* diagnostic devices. You may wish to consult with the Division of Chemistry and Toxicology Devices (DCTD) before beginning studies involving new technologies, analytes, or matrices.

This document includes several references to information contained in guidelines issued by the Substance Abuse and Mental Health Services Administration (SAMHSA). Among its responsibilities, SAMHSA has established and implements the Mandatory Guidelines for Federal Workplace Drug Testing Programs. Although this guidance refers to certain elements of SAMHSA's guidelines, we do not suggest that the SAMHSA guidelines apply to the screening tests addressed in this guidance. This guidance document addresses submissions made by entities seeking to market tests for use in a variety of settings. The system of controls that SAMHSA has implemented in the federal workplace setting may or may not be appropriate in other workplace and non-workplace settings. Therefore, we have sought to identify the least burdensome method through which manufacturers can provide information sufficient for us to determine whether 510(k) clearance is appropriate.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing and revising the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should contact the Office of In Vitro Diagnostics at (301) 594-5084, following the procedures outlined in the “A Suggested Approach to Resolving Least Burdensome Issues” document. It

is available on our Center web page at:
http://www.fda.gov/cdrh/modact/leastburdensome.html.

II. DEVICE DESCRIPTION

The device panel, review method, regulations, and product codes for the assays addressed in this guidance document are listed below.

Panel: Toxicology (91)
Class: II
Review Method: Premarket Notification (510(k))
Regulations and Product Codes: (See below.)

21 CFR 862.3100 Amphetamine Test System

Product Codes:
DKZ Enzyme Immunoassay, Amphetamine
DJL Free Radical Assay, Amphetamine
DOD Gas Chromatography, Amphetamine
DNI Liquid Chromatography, Amphetamine
DJP Radioimmunoassay, Amphetamine
DPJ Radioimmunoassay, Amphetamine(^{125}I), Goat Antibody, Ammonium Sulfate Sep
DIT Thin Layer Chromatography, Amphetamine

21 CFR 862.3250 Cocaine and Cocaine Metabolite Test System

Product Codes:
JXO Enzyme Immunoassay, Cocaine
DIO Enzyme Immunoassay, Cocaine And Cocaine Metabolites
DIR Free Radical Assay, Cocaine
DNG Free Radical, Benzoylecgnonine
DIN Gas Chromatography, Cocaine
DLN Hemagglutination, Cocaine Metabolites (Benzoylecgnonine)
LAC High Pressure Liquid Chromatography, Cocaine And Cocaine Metabolites
KLN Radioimmunoassay, Cocaine Metabolite
DOM Thin Layer Chromatography, Benzoylecgnonine
DMN Thin Layer Chromatography, Cocaine

21 CFR 862.3610 Methamphetamine Test System

Product Codes:
LAF Gas Chromatography, Methamphetamine
LAG High Pressure Liquid Chromatography, Methamphetamine
DJC Thin Layer Chromatography, Methamphetamine

21 CFR 862.3650 Opiate Test System

Product Codes:
DJG Enzyme Immunoassay, Opiate
DKT Free Radical Assay, Opiates
DJF Gas Chromatography, Opiates
DLT Hemagglutination, Opiates
LAH High Pressure Liquid Chromatography, Opiates
LAI Thin Layer Chromatography, Opiates

21 CFR 862.3870 Cannabinoid Test System

Product Codes:
LDJ Enzyme Immunoassay, Cannabinoids
LAT Radioimmunoassay, Cannabinoids
DKE Reagents, Test, Tetrahydrocannabinol

Unclassified Phencyclidine Test System

Product Codes:
LCM Enzyme Immunoassay, Phencyclidine
LCL Radioimmunoassay, Phencyclidine
LCK Thin Layer Chromatography, Phencyclidine

Unclassified Over the Counter Drugs of Abuse Test System

Product Code:
MVO Test Kit, Multiple Drugs of Abuse, Over the Counter.

III. PERFORMANCE CHARACTERISTICS

A. OVERVIEW

Your 510(k) should provide evidence that your device is substantially equivalent to a predicate device legally marketed in the United States. We recommend that you also establish the performance of a new device by comparing the device, where possible, to an applicable reference method. Reference methods are well defined higher order laboratory methods, such as gas chromatography/mass spectroscopy (GC/MS), which are considered to provide definitive results for an analyte of interest.

FDA's recommendations for performance data depend on:

- the test analyte,
- the intended use,
- whether the test is semi-quantitative or qualitative,
- whether the test involves a new or well established matrix or methodology, and
- the expertise level of the intended user.

We recommend that you conduct performance testing in a manner that reflects how the device will be used. For example, in laboratory settings (e.g. hospital lab, physician office lab, emergency room), trained laboratory workers, health care professionals without laboratory backgrounds, and/or trained lay users perform drugs of abuse screening using instrument systems or single-use devices. In these settings, a physician ordinarily reviews preliminary and confirmatory results and considers other information about the patient in drawing conclusions.

In contrast, in home settings, untrained users perform drugs of abuse tests with single-use devices. Home users are not expected to be proficient in testing and may or may not understand the limitations of screening tests for drugs of abuse and the potential for both false positive and false negative results.

In the workplace setting, testing is often performed repetitively. As a result, users may become proficient in testing. In some cases, testing programs include access to MROs. In situations where MROs are available, decisions about the accuracy and reliability of any given result can be made in the context of additional medical information about the testing subjects.

Because of the different use settings, you may obtain data to support performance for your test using a variety of different options. To ensure that the user of your product has accurate information, your labeling should clearly indicate how you evaluated the performance of your test, and the conditions for appropriate use.

B. GENERAL STUDY CONSIDERATIONS

The following table outlines the types of studies we recommend for evaluating drugs of abuse tests for different settings:

Table 1.

	Laboratory Use	**Home Use**	**Workplace/ Repetitive Use**
Cutoff characterization	Yes	Yes	Yes
Specificity and cross–reactivity	Yes	Yes	Yes
Interference	Yes	Yes	Yes
Precision	Yes	Yes	Yes
Method comparison	Yes	Yes	Yes
Stability	Yes	Yes	Yes
Specimen collection, handling, and storage	No studies necessary unless claims are novel	No studies necessary unless claims are novel	No studies necessary unless claims are novel

	Laboratory Use	**Home Use**	**Workplace/ Repetitive Use**
Clinical investigation	No studies necessary unless claims are novel	No studies necessary unless claims are novel	No studies necessary unless claims are novel
Studies by trained users	Depends on claims made about who should perform tests	No	Depends on claims made about who should perform tests
Home use (untrained lay use studies)	No	Yes	Depends on claims made about who should perform tests

In your submission, we recommend that you provide a description of your study design for evaluating each performance parameter (where applicable), such as:

- number of samples in the study
- pre-screening of samples or selection criteria used to obtain samples
- concentrations of specimens and method used to determine those concentrations
- number of replicates
- number of days over which the analysis occurred
- number of operators involved in the study
- masking techniques, randomization of samples, and any other efforts taken to minimize operator bias
- description of the testing facility(ies)
- educational backgrounds of the individuals performing the tests
- type of specimen, for example:
  - unaltered clinical samples,
  - clinical samples diluted with known negative human urine,
  - control material, or
  - prepared specimens.

When describing the type of specimen, please specify the matrix of the material as well as any compound added to the matrix (e.g., "Benzoyleconine was added to human urine known to be drug-free to a targeted concentration of 250 ng/mL. The concentration was verified by gas chromatography/mass spectroscopy (GC/MS) to be within 10% of the targeted concentration."). When various isomers of an analyte are possible, indicate the isomer form in the description (e.g., indicate the "d" or "l" form of amphetamine, or the delta 8 or delta 9 form of tetrahydrocannabinol (THC)).

C. SPECIFIC PERFORMANCE STUDIES

The following sections describe in more detail the types of information that should be provided in support of the studies that we identified in the table above.

1. Cutoff Characterization

Definition: The cutoff concentration of an assay is the specific concentration of drug or drug metabolite in the sample that distinguishes a presumptive positive from a negative test result. Samples with concentrations above the cutoff level are presumptive positive and samples with results below are negative.

We recommend that you identify the cutoff concentration of your assay and provide an estimate of performance (i.e., accuracy and precision) around the cutoff level.

In the case of a class of drugs, such as benzodiazepines, barbiturates, or tricyclic antidepressants, we recommend that you identify the specific drug against which the assay is calibrated. Secobarbital, for instance, might be the drug targeted in a barbiturate assay.

We encourage the use of threshold cutoff concentrations identified by SAMHSA for the following classes of drugs of abuse in urine:

- amphetamines
- cocaine
- opiates
- cannabinoids
- phencyclidine

You can find SAMHSA guidelines at their internet address (http://workplace.samhsa.gov).

Performance of visually read self-contained devices, particularly around the cutoff, is dependent on the visual acuity and interpretive skills of the operator, as well as the manufactured lot of the devices. Therefore, we recommend that you incorporate multiple lots of product and multiple operators in studies to characterize performance of these devices. For example, for visually read devices, we recommend that a minimum of three different individuals read different lots of tests.

Cut-off Validation Study Design: We recommend that you analyze a statistically significant number of samples at each of the following concentrations: the cutoff concentration minus 25% of the value, the cutoff concentration, and the cutoff concentration plus 25% of the value. To obtain the recommended concentrations, you might prepare samples by adding the targeted drug to a known amount of drug-free specimen. Alternately, you may use samples with concentrations determined by GC/MS or an equivalent analytical method. We recommend that you randomize and mask samples from study participants to avoid bias. If results are not all negative at concentrations 25% below the cutoff, or not all positive at

concentrations 25% above the cutoff concentration, we recommend that you extend the study to include concentrations 50%, 75%, or 100% below and above the cutoff as needed.

Special Notes:

- If no other legally marketed device exists that utilizes the same cutoff concentration as your device, you may use your own clinical studies or scientific literature to support your cutoff. We recommend that you provide a rationale for selecting your cutoff.

- For semi-quantitative tests, you should establish cutoff levels far enough above the background noise of the test to permit accurate and reproducible results.

- For semi-quantitative tests, we recommend that you also characterize the linear range of the assay by evaluating samples whose concentration levels are known relative to each other. Evaluation of the Linearity of Quantitative Analytical Methods, Proposed Guideline NCCLS Document EP6-P, describes a protocol for sample preparation and value assignment as well as a format for stating performance characteristics.

- For visually read devices, you may design your experiments to combine the cutoff characterization and precision studies.

2. Specificity and Cross-reactivity

Definition: Analytical specificity is a measure of the ability of a method to exclusively determine certain drugs and/or drug metabolites, without cross-reacting with other related substances. Cross-reactivity refers to the ability of an analyte other than that being measured to cause falsely elevated results.

Content: We recommend that you perform analytical specificity studies on all drugs and drug metabolites within the same class of drugs, or with similar molecular structures that may cross-react.

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)

Study Design: You may add drug compounds to a drug-free specimen and then perform the assay. We recommend that you prepare concentrations of compounds so that the levels are comparable to the highest expected level in a subject. If a compound generates a positive result, serially dilute the sample until you observe a negative result.

3. Interference

Definition: Interference is the effect that an externally ingested compound (or group of compounds), or that an internally existing physiological condition, has on the accuracy of test measurement.

Content: We recommend that you evaluate whether commonly ingested medications or substances, or varying physiological conditions, affect test results, such as:

- Acetaminophen, Acetylsalicyclic Acid, and Ibuprofen
- Dextromethorphan (Phencyclidine)
- Ephedrine (Amphetamines)
- Pseudoephedrine (Amphetamines)
- Ascorbic Acid
- Ranitidine (Amphetamines)

We recommend that for each item, you evaluate the potential for both positive and negative effects.

NCCLS document EP7[2] describes how you may determine the appropriate level of intereferents for testing and how to conduct interference testing. In addition, a listing of drugs and how they interfere with many tests is also available.[3]

You may not need to conduct a study if it has been previously established that a particular compound interacts with a test. However, in these circumstances we recommend that you place a warning or limitation statement in the labeling either in the interference or limitation sections. (NOTE: This statement would be in addition to any other limitations presenting with the assay).

Study Design: We recommend that you add relevant concentrations of each compound to two pools of specimen: one with the lowest concentration of the targeted drug known to consistently render positive results (to assess negative interference effects), and the other with the highest concentration of targeted drug known to consistently render negative results (to assess positive interference effects). If you observe a change from the expected result, we suggest that you serially dilute the interferent with a drug-free specimen until you no longer observe the effect.

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[2] EP7: Interference Testing in Clinical Chemistry; Proposed Guideline (1986), NCCLS, 1986.
[3] Young, D.S. Effects of drugs on clinical laboratory tests. 4th Ed. Washington, DC, AACC Press, 1995

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. If your device is visually read, we recommend that you also evaluate the effects of photochromic substances such as hemoglobin, myoglobin or other artificially or naturally occurring food colorings or medications.

4. Precision

Definition: Precision is the ability of a test to produce the same value during repeated measurements.

Content: Studies should characterize the precision or random error associated with use of the device. The appropriate study design is dependent on the type of test, such as whether the assay is qualitative, semi-quantitative, visually read, automated, or whether there are pre-analytical steps involved. We recommend that you incorporate the pre-analytical steps into the precision study when they have a potential to affect the final test result.

You may use spiked samples or control materials (prepared in the same matrix for which the device is intended) for evaluating the precision of an assay. We do not consider stripped matrices appropriate (e.g., charcoal-filtered urine). We recommend that your study materials challenge the cutoff concentration. If the pre-analytical steps change the chemical composition or binding state of the analyte in the sample, we recommend that you use actual clinical samples.

NCCLS recommends an analysis-of-variance experiment for estimating imprecision (EP5-A).[4]

5. Method Comparison

Definition: Method comparison refers to comparative studies in which a series of patient samples are analyzed by both the test device and a comparative device. The results are assessed to determine whether differences exist between the two devices. You may establish comparative performance of your assay by comparing your device to a predicate device legally marketed in the U.S. If you compare your device to a predicate device, we recommend that you choose a device with the same cutoff concentration. You may also establish comparative performance using an accepted reference method, e.g., GC/MS. When you compare to a reference method, you do not have to compare your device to a predicate device.

[4] EP5-A: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (1999). NCCLS, 1999.

Comparisons between two immunoassays provide limited information on device performance because of the variable reactivity of antibodies to clinically active drug compounds. For this reason, we recommend that you perform some portion of your comparative studies against a reference method (especially those samples with concentrations near the assay cutoff).

Content: Because varying drugs within a drug class (e.g., barbiturates) have different levels of cross-reactivity, pooling data from samples containing more than one drug within the class may cause false characterization of a device. Therefore, when the assay targets a class of drugs, we suggest that you study only clinical samples containing the specific drug against which the assay is calibrated. If you choose to include samples containing different drugs with varying levels of cross-reactivity within that family, we recommend that you separate each set of comparison data.

You may use reference laboratories to ensure that the selected clinical samples span the appropriate range for testing and adequately challenge the cutoff point. As some drugs deteriorate in specimens over time (especially benzoyleconine), we suggest that you minimize the time between the reference (e.g., GC/MS) measurement and analysis on the new device.

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.

We recommend that you present the data from your studies in a table showing the results of your assay, the results of the reference method, and the results from a predicate device (if performed). To facilitate our review of your submission, you may wish to sort the data in ascending order of total GC/MS results. We recommend that you provide the individual values of drugs or drug metabolites that are contributing to the total GC/MS result, and demonstrate that you evaluated an adequate number of samples near the cutoff.

Study Design: We recommend that you evaluate a statistically significant number of positive and negative clinical samples.

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.

We recommend that you evaluate drug concentrations in the samples over the range of possible results. For example you might study 10% of the total number of samples between

the cutoff and a concentration 50% above the cutoff, and another 10% of the total number of samples between the cutoff and a concentration 50% below the cutoff. You may determine these concentrations through a reference methodology using SAMHSA guidelines for testing. In the absence of SAMHSA recommendations, you should combine all drugs or metabolites known to significantly cross-react to determine the total drug concentration. Please note that GC/MS may not be the preferred method for all drugs. For example, High Performance Liquid Chromatography (HPLC) is the accepted standard method for measuring tri-cyclic antidepressants.

6. Stability

We recommend that you provide a summary of the stability study used to establish the expiration dating of your product, as tested under the suggested storage conditions. We recommend that your summary include a description of:

- the material tested,
- the concentration of the drug levels in relation to the cutoff concentration,
- testing frequency, temperature and humidity conditions, and
- acceptance criteria for the study.

7. Specimen Collection, Handling, and Storage

In general, collection devices should be durable, leak-proof, and constructed of non-absorbing and non-leaching materials. When particular requirements for the sample exist, we recommend that you explain the specifications for the collection device and any applicable special instructions in the package insert. Ordinarily, data will not be necessary to support collection devices unless such devices are novel or support new matrices.

When the collection device is an integral part of the test system, data may be necessary to demonstrate that instructions are adequate to ensure proper collection and handling of the sample. For example, in some tests the collection device may serve as the reaction chamber and require the addition of diluent or manipulation of sample, or may be used to house the testing unit. Please consult with DCTD if you have any concerns about your particular device.

8. Clinical Investigations

In certain instances, you may need clinical data to establish substantial equivalence of your device to a predicate device if your device uses a new methodology or technology, a new or uncharacterized matrix, a new or unstable analyte, or a new cutoff. We recommend that you consult us before proceeding with these studies.

9. Studies in the Workplace and Other Sites Performing Repetitive Testing

Definition: Workplace studies are method comparison and precision studies done to characterize the performance of a device intended for use in environments such as work, insurance, and school settings. In some cases, testing by untrained lay users occurs on an

infrequent and sporadic basis, resembling home use. In others, employers may utilize trained lay users, health care professionals without laboratory training, and/or trained laboratory professionals to perform tests.

***Study Design*:** We believe that studies done to characterize the performance of a device should reflect how the device will be used. We therefore recommend that the intended user (i.e., trained or untrained) perform the test in the method comparison and precision studies in the environment where the product ultimately will be used. We recommend that you provide a summary of the sites, the educational background of the operators, and the instructions (written and verbal) and training given to the study participants.

If your device is semi-quantitative, we suggest that you take replicate measurements of each of the assay calibrators. We recommend that you include this information in the labeling only if there is overlap between calibrator results.

For visually read single-use tests that involve well characterized analytes and well established technologies, the study described in section C.1, Cutoff Characterization, is appropriate for characterizing precision when performed at three different workplace sites with representative operators.

10. Home Use Consumer Studies

Definition: Home use consumer studies demonstrate that untrained users are able to follow the labeling instructions, obtain acceptable test results, correctly interpret test results, and understand the limitations of test results.

Study Design: We recommend that you select a statistically significant number of consumers who are representative of the target user population with regard to age, education, and geographic regions to permit extrapolation of observations from the sampled group to the intended user population, and to demonstrate accuracy and precision in the hands of the untrained user. We recommend that you divide the number of samples equally over at least three sites. Since accuracy data is most meaningful when the concentrations of the samples are near the cutoff, we recommend that you test samples distributed over a variety of concentrations. For example, you might study the following:

- low negative concentrations
- at 50% below cutoff concentration
- at 25% below the cutoff concentration
- at 25% above the cutoff concentration
- at 50% above the cutoff concentration
- high positive concentrations

Your study may use drug-free (but not charcoal filtered) sample pools spiked with known amounts of drug. We recommend that you confirm the concentrations of drug or metabolite

in each sample pool using a reference method, such as GC/MS. Untrained users may then evaluate multiple aliquots from each sample pool.

If you are evaluating several drugs in the study, the number of samples can sometimes be reduced by having sample solutions contain combinations of two drugs. We recommend that you prepare samples with different concentrations of drugs, and that you characterize performance of the product for home use by:

1. Evaluating instructional materials that you will provide in the final labeling;

2. Having a study administrator observe or monitor the studies without providing assistance to the participants;

3. Prohibiting participants from interacting with each other; and

4. Masking the collation and recording of all test results from the users.

You may summarize the results of your consumer study by presenting a table of results for each drug that includes the following data:

1. the number of samples at each targeted concentration;

2. the reference values (i.e., GC/MS) of each specimen pool;

3. the number of positive and negative results generated from each pool; and

4. the percentage of correct results generated at each concentration.

You may pool data from the three sites if there are no significant differences between sites. You do not need to provide the raw data from the study; however, you should keep the data on file.

Surveys and Labeling Assessments: To ensure that the untrained user is able to understand the labeling, we recommend that the difficulty level of the material not exceed the 7th grade reading level. The NCCLS document, "Labeling of Home-Use In Vitro Testing Products: Approved Guideline: GP-14A[5]," describes how you can evaluate the level of your reading material.

We recommend that you evaluate how users comprehend your labeling by having untrained users complete questionnaires after they have performed the test and recorded their results. The questionnaires should give users the opportunity to state whether any part of the package insert is confusing. For example, you may ask questions such as: “What should you do if

[5] Write It Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care. HHS Publication FDA 93-4258, 1993.

there is no line in the test window? " "What does it mean if you see a very light line in the test window?" or "Can cold medicines affect my test result?" We prefer these types of questions to Yes/No questions, such as "Do you understand the meaning of the test results?"

We recommend that you include a copy of the questionnaire in your submission and summarize the results, and that you identify how you determined the reading level of the labeling.

IV. LABELING CONSIDERATIONS

Because there are a variety of ways to support your submissions for drugs of abuse tests, your labeling should accurately reflect what you have or have not done to establish the performance of the test. Your labeling must comply with section 502 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR 809.10. The following recommendations are intended to assist you in complying with these provisions.

A. GENERAL LABELING FOR DRUGS OF ABUSE SCREENING DEVICES

1. Intended Use

Your intended use statement should describe:

- the training level of the user (i.e. trained or non-trained) and the 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

A sample intended use statement is:

> *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.*
>
> *Minimum training for operators is defined as those individuals who have received instructions for drugs of abuse testing from a physician or medical review officer.*

Operators may be lay users with no prior experience in running laboratory tests, but who are expected to perform at least 5 tests per week. Training should cover a variety of topics such as the value of confirmation testing, how to obtain confirmation testing, false positive results, false negative results, and quality control procedures. We recommend that operators take a written and practical exam before performing any testing and that employers keep documentation of the training.

We recommend that you provide a warning following the intended use statement that addresses the presumptive nature of screening test results, such as:

This assay provides only a preliminary result. Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly in evaluating a preliminary positive result. To obtain a confirmed analytical result, a more specific alternate chemical method is needed. Gas chromatography/mass spectroscopy (GC/MS) is the recommended confirmatory method.

2. Summary and Explanation of the Test

We suggest that you present a general description of the drug that the test is designed to detect and the clearance rates for the drug. You may wish to indicate that clearance rates are dependent on many factors such as frequency of drug use, the amount of drug taken, metabolism rates, and even body fat content. Examples are presented in Table 2.

Table 2. Clearance Rate Examples

Drug	Drug may be present within	Drug is likely to persist up to
Pot/Marijuana (Cannabinoids)	1 to 3 hours	1 to 7 days
Crack (Cocaine)	2 to 6 hours	48 to 72 hours
Heroin (Opiates)	2 to 6 hours	24 to 72 hours
Speed/Uppers (Amphetamine/methamphetamine)	4 to 6 hours	48 to 72 hours
Angel Dust/PCP (Phencyclidine)	4 to 6 hours	7 to 14 days

3. Understanding the Test Result

Your labeling should explain that drugs of abuse tests are not always accurate. We recommend that the following (or similar) labeling language be placed under this section:

A positive test result does not always mean a person took illegal drugs and a negative test result does not always mean a person did not take illegal drugs. There are a number of factors that influence the reliability of drug tests. Certain drug of abuse tests are more accurate than others.

For Preliminary Positive Tests: In general, the Substance Abuse and Mental Health Services Administration (SAMHSA) reports the accuracy of drug tests as[a]:

60 out of 100 times a "preliminary positive" result from an opiate test is a "false preliminary positive" result. A "false preliminary positive" result means that the result of the first test was "preliminary positive" even though the person did not take an illegal drug.
50 out of 100 times a "preliminary positive" test result from an amphetamine or methamphetamine test is a "false preliminary positive" result.
50 out of 100 times a "preliminary positive" result from a PCP (phencyclidine) test is a "false preliminary positive" result.
10 out of 100 times a "preliminary positive" result from a marijuana test is a "false preliminary positive" result.
2 out of 100 times a "preliminary positive" result from a cocaine test is a "false preliminary positive" result.

[a] *Data was generated from laboratory tests that have the following cutoff concentrations: Marijuana, 50 ng/mL; Cocaine, 300 ng/mL; Phencyclidine, 25 ng/mL; Opiates, 2000 ng/mL; Amphetamines, 1000 ng/mL. In general, the rates of false preliminary positive results will increase as the cutoff concentration of the test is lowered.*

Note: FDA believes that the contents of the table accurately reflect the false positive rate of drugs of abuse screening tests, and that communication of these limitations will help ensure that operators properly interpret results from drugs of abuse screening tests. If you wish to modify this information because you believe your assay performs in a superior manner, you should provide information to support the modification in the 510(k). If you choose to use a screening cutoff different than those used by SAMHSA, labeling should reflect how this will impact performance.

For Negative Tests: A negative result does not always mean a person did not take illegal drugs. For example, you will likely get a negative result if the test is for cocaine when the person tested has only smoked marijuana. There are a number of reasons why you can get a "false negative" test result. A false negative test result means the test result is negative when the person has actually taken the drug that this test is designed to detect. This might happen under the following circumstances:

1. *The drug may not have been in the sample at the time the sample was collected. It takes a while after taking a drug for it to appear in a specimen, and it only stays in the specimen for a limited amount of time. If the sample was taken too early or too late you can get a "false negative" result.*

2. *The person, knowing that they were going to be tested, added something to the specimen to keep it from reacting with the test chemicals. This could cause a false negative result. There are products sold that are specifically advertised for this purpose.*

3. *The drug may be in the specimen because the person took the drug, but it is there at such a low concentration that the drug cannot be detected by the test.*

4. *The test may not be working properly. There are a number of things that could be wrong with any testing product. It might have been damaged during shipment or kept at the wrong temperature, either before or after you received it. Storing a product at temperatures that are too high or too low can damage the chemicals in the test.*

If you get a negative test result but you still suspect someone is taking drugs you should test again at another time, or test for different drugs.

4. Quality Control

We recommend that quality control (QC) materials included with or recommended for your device have target ranges that are traceable to a reference method, such as GC/MS. SAMHSA recommends that the concentration of drug(s) in positive and negative controls be approximately 25% above and below the cutoff concentration of the assay. 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.

If you do not provide QC material with your assay, we suggest that you list recommendations for QC material in the section of the labeling that describes materials not included in the kit, but that are required for use.

We suggest that you include a statement in your labeling such as:

> *Users should follow the appropriate federal, state, and local guidelines concerning the running of external quality controls.*

We recommend that you also include directions for interpretation of results of quality control samples, and information concerning the satisfactory limits of performance.

NOTE: The information on quality control above may not be appropriate for home use labeling. See home use section below.

5. Limitations

We recommend that you list substances known to interfere with your device in the Limitations section of your package insert. If your device is a visually read unitized device suited for workplace setting testing and you have not performed studies in this setting, you should include a statement that accurately indicates performance and limitations in the labeling, such as:

The performance of this device has not been evaluated at school, workplace, insurance, physician office, laboratory, emergency room, or rehabilitation settings.

In addition, we suggest the following limitation:

There is a possibility that other substances and/or factors not listed above may interfere with the test and cause incorrect results (e.g., technical or procedural errors).

6. Performance Characteristics

Cutoff Characterization and Analytical Sensitivity

We recommend that you provide a summary of the study design, including a description of the study materials, including:

- the number of samples
- concentration of the study samples
- the number of operators and lots of product
- the number of testing days
- type of setting where studies were conducted
- the number of positive and negative results obtained at each concentration

You may display results in a table, stratified according to the operator and lot of product. You may pool operator data if there is no significant inter-operator variation observed.

Specificity and Cross-reactivity

We recommend that you summarize your study design. We suggest that study data be presented in tabular form, and that you list all compounds tested and identify the lowest concentration of each compound that generated a positive result. You should include the compound used to calibrate the assay in the table. We recommend that you list concentrations of all compounds in the same units, e.g., ng/mL. Alternatively, you might list the percent cross-reactivity of each compound relative to the drug used to calibrate the assay. You may calculate percent cross-reactivity by dividing the lowest concentration of each compound that generates a positive result by the concentration of the targeted drug that generates a positive result, then multiply by 100.

Interference

We recommend that you present a summary of the study design, reporting the lowest concentration of each compound that caused a change from the expected result and noting whether the observed change was in a positive or negative direction. For studies examining the effects of physiological conditions, you should indicate the range of conditions that have

no effect on test results. If an effect is observed beyond the specified range, you should indicate the point at which the effect was observed, and whether the effect was in a positive or negative direction. If no effect is observed, you may report the highest level of potential interferent that was tested.

Precision

Semi-quantitative or Automated Tests: We recommend that your labeling include a description of the study design and results, such as:

- the concentration of the study samples
- the number of runs per day
- the number of days of the study
- the means of measured values
- standard deviations
- coefficients of variation.

Visually-read Tests: Refer to the Cutoff Characterization and Analytical Sensitivity section above.

Comparison to predicate or reference method

We suggest that you provide a summary of the study design including:

- a description of the samples (for example, clinical or diluted clinical samples)
- a description of any pre-screening conducted or selection criteria applied
- the instrument used, if applicable
- the number of runs or number of testing days
- training of user and description of setting

We suggest that you display your data in a table, such as:

New device	Low Negative by GC/MS (less than -50%) or negative by Predicate	Near Cutoff Negative (between –50% and cutoff)	Near Cutoff Positive (between cutoff and +50%)	High Positive (greater than +50%)	Percent Agreement with GC/MS
Positive					
Negative					

If you performed your studies at more than one location and there are no significant differences between the data sets, then you may pool the results. If a significant difference exists, we suggest that you present each data set separately.

NOTE: Information on performance characteristics described above may not be appropriate for home use tests. See the following section for labeling recommendations for devices designed for home use.

B. SPECIAL CONSIDERATIONS FOR LABELING FOR HOME USE DEVICES

1. Overview

We encourage the use of diagrams and illustrations in labeling for home use tests. A question and answer format has been shown to be an effective tool for presenting information to untrained users. In addition, you may find it helpful to obtain labeling of previously cleared home use tests as examples.

We recommend that you caution users to read all instructions first, and to check for and familiarize themselves with the materials before performing a test. We suggest that you provide a telephone number that a user can call if the kit is missing any of its contents.

We suggest that you present a comprehensive discussion concerning the potential for false positive results and false negative results. Your labeling should describe the procedures for obtaining confirmation testing of presumptive positive results. In addition, you may consider using additional methods to encourage confirmation testing. These may include providing a prepaid mailer or providing access to a customer advice number. Some companies have provided the confirmation tests at no additional charge. Our previous draft guidance recommended bundling the cost of screening with the cost of confirmatory testing. We are now clarifying that bundling was not and is not required. We recognize that measures other than bundling these costs, such as clear and accurate labeling, may help mitigate the risk of inaccurate test results.

We recommend that you include a prominent statement in appropriate language in the complete set of labeling, including all box labels, the package insert, and the labels on the device itself informing the user what to do if a test produces a preliminary positive result. For example:

> *The XYZ test is only the first-step in a two-step process for determining the presence of drugs of abuse. If you get a "preliminary positive" test result when you use this product, we recommend that you send the urine to a certified laboratory, which can test the urine again with a more accurate and reliable test. The second test is called confirmation testing, which is most often done using a test called gas chromatography/mass spectrometry. We recommend that you consult with your doctor or another qualified*

professional to help you understand test results and to address problems such as drug use.

2. Overview of steps

It may be helpful to include an overview of the procedural steps before explaining each step in detail. These steps might include reading the instructions, checking contents, collecting a sample, running the test, reading the results, and considering the need for confirmation testing. We recommend that you be consistent throughout the package insert when using words or phrases. For example, if in the overview section you refer to sending the sample for "laboratory testing," it may be confusing if you later start referring to "confirmation testing."

3. Sample collection and handling instructions

We recommend that you provide instructions for collection and handling of the sample. It may be helpful to present information in question and answer format, for example: "When should I collect the sample?" or "How much sample do I need?" We recommend that you provide instructions for maintaining integrity of the sample during shipping, such as: "cap the vial tightly," "avoid high temperatures and sunlight," "do not freeze the sample," or "mail the sample immediately."

You may elect to provide examples of ways that samples can be adulterated, and to provide recommendations for minimizing tampering.

4. Reading test results

We recommend that you describe and illustrate all possible test results, including what actions users should take when they observe certain results. It may be helpful to include a toll-free number that users can call for help. The following are suggestions for describing results:

"Uncertain," "Preliminary," "Preliminary Positive," or "Non-negative" Result We recommend that you clarify that an uncertain result means that something in the sample has reacted with the test and the sample can be sent to the laboratory for further testing to find out if a particular drug is in the sample. For example, you may say "Sometimes this test gives an uncertain result when drugs have not been taken. Laboratory testing is the most reliable way to know if drugs are present in the sample."

Negative Result We recommend that you explain that if the test is negative, it might mean the donor has not taken the drug, has not taken the drug being tested for several days, or might have taken a drug that is not detected by the test. You may provide examples of when it may be appropriate to re-test.

"Invalid" or "Error" Result We recommend that you describe what untrained users should do if the control or check line did not appear.

5. Instructions for obtaining professional counseling

We recommend that your labeling suggest that the user contact a doctor or health care professional to discuss options for treating substance abuse if positive results are confirmed. We encourage you to provide access to professional counseling and referral services through an 800 number. It may also be helpful to include web sites or telephone numbers for organizations which may provide assistance, such as the National Clearinghouse for Drug and Alcohol Information.

C. SPECIAL CONSIDERATIONS FOR LABELING OF WORKPLACE AND OTHER REPETITIVE SITE TESTING

Note: If you intend to sell a product for workplace testing that has not been evaluated in that type of setting, your labeling should clearly convey that the performance has been evaluated only in a professional laboratory and, as a result, workplace performance may be inferior to the labeled performance.

Because the number of subjects and available oversight will vary among workplace settings, it is important that the labeling accurately and fully explain how you evaluated the performance of your test.

If you demonstrated test performance with untrained users, then we recommend that the labeling follow selected parts of General Use Labeling as described in IV. A. (see table below) and closely follow Home Use Labeling Section as described in IV. B of this document. If you demonstrated performance with trained users (i.e., laboratory users, health care professionals without laboratory experience, and/or trained lay users), then we recommend that the labeling follow to the labeling recommendations in IV.A. above.

If your performance testing was based on a particular training program or level of competency, the labeling should explain the level of training or experience necessary to obtain that level of performance. The label should also caution that performance may be inferior if the end user doing the testing does not have that level of training and experience.

We recommend that you cite information on SAMHSA guidelines, standards, and quality control practices, since these may be valuable sources of information on how to ensure quality results. We also recommend that you provide information on the value of having access to a medical review officer to ensure reliable interpretation of results.

The following table summarizes our recommendations for information to be included in the labeling for drugs of abuse screening tests.

	Laboratory Use	**Home Use**	**Workplace Use**
Instructions on how confirmatory testing can be obtained	No	Yes	Yes
Summary and explanation of clinical performance characteristics (Section IV.A.3.)	Yes	Yes	Yes
Information on understanding the test result	Yes	Yes	Yes
Information on analytical performance in the user population studied	Yes	No	Yes
Specificity and cross–reactivity	Yes	No	Yes
Interference	Yes	No	Yes
Cutoff validation/Precision	Yes	No	Yes
Method comparison	Yes	No	Yes
Test principle	Yes	Yes	Yes
Reagents	Yes	Yes	Yes
Specimen collection and handling	Yes	Yes	Yes
Instructions for use	Yes	Yes	Yes
Quality control	Yes	Depends on claims made and design	Yes
Limitations	Yes	Yes	Yes
Home use labeling	No	Yes	Depends on claims made
Seventh grade reading level	No	Yes	Depends on claims made
Clearance rates	Yes	Yes	Yes
Recommendations for use of professional counseling	No	Yes	Depends on claims made
Workplace labeling	No	No	Yes

D. OUTER BOX LABELING

1. For Devices Intended for Laboratories and Workplace Settings

In addition to *in vitro* labeling requirements for package inserts, we suggest that you include a statement on the outside box labeling and in all promotional material, such as:

This assay provides only a preliminary result. A more specific alternate chemical method is needed to obtain a confirmed result (see package insert).

2. Labeling for Home Use Devices

We recommend that the outside box labeling include a statement such as:

The XYZ test is only the first-step in a two-step process for determining the presence of drugs of abuse. To complete the second step, you should send your sample to the laboratory to be tested if you get an "uncertain" test result. Laboratory testing is the only way to get a reliable test result.