Guidance for Industry

Guidance for Premarket Submissions for Kits for Screening Drugs of Abuse to Be Used By The Consumer

Draft Guidance – Not for Implementation

This guidance document replaces Points to Consider for Approval of Home Drugs of Abuse Test Kits-draft September 17, 1997

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Clinical Chemistry Branch
Division of Clinical Laboratory Devices
Office of Device Evaluation

Preface

Public Comment:

Comments and suggestions regarding this draft document should be submitted by [90 days after FR] to Docket No. [insert number], Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 12420 Parklawn Drive (HFA-305), Room 1-23, Rockville, MD 20857

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Guidance For Premarket Submissions For Kits For Screening Drugs Of Abuse To Be Used By The Consumer

This guidance document represents the Food and Drug Administration's (FDAs) current thinking on Premarket Submissions for Drugs of Abuse Screening Kits sold over the counter (OTC). It does not create any rights for any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulation, or both.

INTRODUCTION:

FDA has developed a proposal for regulating OTC test sample collection systems for drugs of abuse. That proposal is outlined in a Federal Register Notice [Docket No. 97N-0135]. The systems addressed are those where a urine sample is collected at home, mailed to certified laboratories, and tested and interpreted by professional laboratory personnel using FDA cleared products.

This document addresses drugs of abuse screening devices where the screening test is performed by the lay user and results are obtained and interpreted by them. It incorporates much of the Review Criteria for Assessment of *In Vitro* Diagnostic Devices for Drugs of Abuse Assays Using Various Methodologies. **Testing of body fluids or other sample types other than urine may introduce additional issues which are beyond the scope of this document.**

Premarket review of any OTC *in vitro* diagnostic (IVD) kit where testing is performed at home requires consideration of two key issues:

1. Can the lay user perform the test and obtain acceptable initial screening results?

2. Can the product be labeled in a manner to assure that use of the kit in the home setting provides beneficial information that can be used by the tester?

PURPOSE:

This document is an adjunct to the Code of Federal Regulations (21 CFR 807) and to FDA Publication Number 97-4224, the manual entitled: *In Vitro* Diagnostic Devices: Guidance For The Preparation of 510(k) Submissions. It is not to supersede those publications but is to provide additional guidance and clarification for this type of device. The FDA will make informed

decisions based on adequate valid scientific evidence submitted by the manufacturer of the product.

DESCRIPTION OF DEVICE:

This type of device is one intended for use in the home setting as an IVD screening test for any single one or combination of the following five substances in urine: amphetamine/methamphetamine, cocaine, cannabinoids, opiates, and phencyclidine. Although barbiturates, benzodiazepines, ethanol, inhalants, and other drugs are widely abused, the focus of this document is on the five drugs previously mentioned, because there is adequate experience with these substances to support the development of this guidance.

These products are screening or initial testing devices. These devices are typically designed to be simple, rapid, and reasonably sensitive. The results provided by these devices indicate whether the drug or drug metabolite **may** be present or not. A positive result from a screening device is considered to be a **screened "presumptive" or "indeterminate" result** and should **never** be interpreted as final without **laboratory confirmation**.

Products **may** be appropriate for marketing via premarket notification [510k] if: 1) adequate directions for use for the lay person to perform the drug screen at home are provided in the labeling, 2) a positive result is reported as "**preliminary", "indeterminate", "inconclusive" or "uncertain"**, 3) either follow-up with a health care provider, confirmation testing, or both, is recommended, and 4) access to confirmation testing in a laboratory setting is provided as part of the test.

Home screening tests for drugs of abuse where no access to confirmatory testing is included, are expected to require premarket approval applications (PMAs), or Product Development Protocols (PDPs). This is because there are likely to be new types of questions of safety and effectiveness for screening products without available confirmatory testing.

ANALYTICAL PERFORMANCE CHARACTERISTICS:

The performance of a new device may be demonstrated by using a valid evaluation protocol. The NCCLS [NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, Tel (610) 688-0100, Fax (610) 688-0700, e-mail exoffice@nccls.org, Home Page http://www.nccls.org] is a good source for evaluation methods.

The premarket notification submission needs to contain evidence that the device, when available OTC and used in the home, is as safe, effective, reliable, and otherwise substantially equivalent

to another device (often termed the “predicate” device) that is legally marketed in the United States, for example, screening devices currently available for professional use.

A. The following characteristics of performance are of importance in evaluating these products for equivalent safety and effectiveness:

1. Analytical Sensitivity - Minimum Detection Limit

a. Definition.
Analytical sensitivity may be defined as the smallest concentration of a drug or drug metabolite that produces a response distinguishable from the background or blank value. Alternatively, this may be the minimum detection limit. Minimum detection limit is the minimum concentration of a drug or drug metabolite that has a high probability of being detected.

b. Content.
The submission should contain information and data that describes the method that was used to determine either analytical sensitivity and/or minimum detection limit, as well as this value.

2. Cut-off Concentration

a. Definition.
The cutoff concentration is the specific concentration of drug or drug metabolite in the sample that is chosen as a limit to distinguish a positive from a negative test result. Results with concentrations above the cutoff level are considered positive, e.g. “preliminary,” and results below the cutoff are considered negative.

b. Content.
1) The submission should contain information that describes the concentration or level that has been selected to be the cutoff. The Substance Abuse and Mental Health Services Administration(SAMHSA) has recommended threshold cut-off concentrations for 5 classes of drugs of abuse: amphetamine/methamphetamine, cocaine, opiates, cannabinoids, and phencyclidine. In order to be consistent, FDA supports the uniform use of SAMHSA cutoff levels. These current cutoff concentrations are shown in Table 1.

Table 1.

SAMHSA Initial Screen Drug Cutoffs (ng/mL) In Urine	
Drug/Substance	**Screen Test**
Canabinnoids metabolites	50
Cocaine metabolites	300
Opiates	2,000
morphine	
codeine	
Amphetamines	1,000
amphetamine	
methamphetamine	
Phencyclidine	25

2) The submission should contain an estimate of the precision of the device at the cutoff level. It is important to validate the test performance of new assays near the chosen cut-off concentration. A new assay may be validated by testing urine samples obtained from drug users that have known concentrations of drugs distributed around the cut-off as established in a toxicology lab. (The College of American Pathologists recommends the concentrations of such specimens be at 25% above and 25% below the cut-off). This should include a statistically valid number of samples with known concentrations on both the “positive” and “negative” sides of the cutoff concentration. Results of testing are then compared to the known concentrations of the samples. The cut-off concentration is often set higher than the device sensitivity level or minimum detection limit.*

* FDA does not suggesst that individuals be deliberately exposed to drugs of abuse to obtain samples for these studies. Samples can be obtained from laboratories that perform this testing.

3. Recovery

a. Definition.
Recovery may be defined as the ability of a test method to measure a drug and/or drug metabolite when a known amount of it is added to the test matrix (in this case urine). An assessment of

recovery is a method of obtaining accuracy information because it tests whether the assay can detect the drug and/or drug metabolite in the presence of other substances that may be contained within a sample of urine.

b. Content.
It is recommended that analytical recovery studies of drug and drug metabolites be conducted by adding known amounts of drug and drug metabolites to urine samples (often termed “spiking” the sample) and then testing them. This testing should include samples at or close to the cutoff concentration (90%-110%) of the device.

These “spiked” (90%-110%) samples are used to determine the specificity of the procedure or the ability of the procedure to only detect the drug or drug metabolite of interest. These values are in contrast to those generated using spiked samples in the range of 25% above and below the cutoff value to assess performance of the test in the measurement zone within 25% of the cutoff.

4. Analytical Specificity

a. Definition.
Analytical specificity is a measure of the ability of the method to determine exclusively the drug and/or drug metabolites that are claimed to be detected without cross-reacting with other related substances that are not intended to be detected.

b. Content.
It is recommended that analytical specificity studies of drug and drug metabolites be conducted. If a test is specific for multiple molecular entities within a class of drugs or drug metabolites, the submission should demonstrate reactivity with each claimed molecular entity and metabolite. Results of specificity testing should distinguish specimens that do not contain drugs or metabolites from those that do contain drugs. See Appendix A for an example of what is useful to submit.

5. Interference

a. Definition.
The term interference describes the effect that a compound or a group of compounds, other than the

drugs or drug metabolites selected for testing, has on the accuracy of measurement of the test.

b. Content.
The submission should contain studies that evaluate possible interference with the test by related compounds or a group of compounds such as: 1) other drugs or drug metabolites not intended to be detected, e.g., those drugs with similar chemical structures or epitopes, and 2) substances that are commonly found in the urine which may interfere with test results.

Testing should include commonly prescribed therapeutic drugs, antimicrobials, and common OTC remedies, e.g., acetaminophen, acetylsalicylic acid, caffeine, ibuprofen, etc. Additionally, experiments should be conducted that evaluate the effect of substances commonly found in urine, e.g., urine pH, presence of hemoglobin, protein, ascorbic acid, urates, glucose, etc., for their potential to interfere. To assist in this process, the NCCLS has published a document that describes how to conduct interference testing. In addition, a listing of drugs and how they interfere with many tests is also available (Young, D.S. Effects of drugs on clinical laboratory tests. 3rd ed. Washington DC, AACC Press, 1990).

6. Precision

a. Definition.
Precision may be defined as the ability of a test to produce the same value for repeated measurements of the same sample. For initial screening tests, positive and negative samples are usually assessed.

b. Content.
The submission should contain a study that evaluates precision or random error associated with a device. These studies may entail: 1) testing a negative and a positive sample daily for a total 20 for each sample, or 2) testing a negative and positive control in replicates of 10 for each of 2 days. Testing should include samples with concentrations at 25% above and 25% below the cut-off concentration because these provide the most meaningful information on the precision of the test.

7. Comparison Studies

a. Definition.
A comparison of the new device to a legally marketed test for drugs of abuse (the predicate device)provides information in support of the accuracy of the assay and evaluates comparability of performance between two devices.

b. Content.
The submission should contain information and data regarding the comparison between two devices. For the comparison, clinical samples should be used having values that span the entire range of testing. After comparison with another screening method, confirmation of all positive results and some portion of negative results should be conducted using Gas Chromatography/Mass Spectrometry (GC/MS) techniques. GC/MS is considered to be an accepted standard method in drugs of abuse confirmation programs.

The new and the predicate device should be compared using at least 40 positive and 40 negative clinical specimens. It is advisable to acquire adequate positive specimens to cover the entire testing range with particular emphasis near the stated cut-off concentration. The results of testing of each sample once with each test should be presented in the form of 2 x 2 contingency tables (new device versus comparative device). Table 2 gives an example of a 2 x 2 contingency table:

Table 2.

		Comparative Screening Method	
		+	-
New Screening Test Method	+		
	-		

c. Comparison discrepancies

The submission should contain information regarding any discrepancies that may have occurred during the device comparison. All differing results occurring between the new device and the

comparative device should be investigated. GC/MS should be used as a reference method in resolving any discrepant results. In addition, any range of concentration in which the comparison between devices is borderline (sometimes termed the "equivocal zone") should be defined. The results of the resolution should be presented in the form of a 2 x 2 table (new test versus GC/MS).

8. Stability

Definition.
Stability refers to the ability of a product to resist conditions that may affect its stated performance, for example, the effects of time, temperature, and humidity.

Content.
Files should be maintained in accordance with Good Manufacturing Practices (GMPs) and with Quality Systems Regulations (QSRs) covering the stability of all device components. The submission should contain a summary that includes details of the stability testing protocol, and the concentration(s)of drug(s)and drug metabolite(s) tested in the samples. Storage stability tests should be conducted under conditions that would make product deterioration likely.

B. The following performance characteristics are of importance in evaluating initial screening products for safety and effectiveness in the home-use setting:

1. Consumer Accuracy

a. Definition.
For initial screening devices intended for marketing directly to the consumer (OTC), a consumer field study conducted at three independent locations provides information to demonstrate that the lay users can correctly follow the labeling instructions, obtain acceptable initial screening results, and can understand and interpret the meaning of the results.

b. Content.
A statistically adequate number of consumers who represent the population expected to use the home drug screen is recommended. A demographically diverse group including a range of ages, education, races, and regional variation should be

included so that observations from the sampled group permit reasonable extrapolation of performance to the general public.

Studies consistent with guidance in the Analytical Performance Characteristics Section A.7 of this document should be conducted. For example, include selected clinical samples (n = 180) and control samples (n = 20) for each drug that is intended for detection. An aliquot of each specimen should be tested by 200 consumers and a second aliquot should be assessed by GC/MS. The specimens to be evaluated should include: negatives at 25% below the cutoff concentration, negatives greater than 25% below the cutoff concentration, positives at 25% above the cutoff concentration, and positives greater than 25% above the cutoff concentration. An example of specimen selection and distribution would be n = 30 negatives, n = 60 at 25% below cutoff concentration, n = 60 at 25% above cutoff concentration, and n = 30 positives. The remaining 20 samples could be spiked control samples, for example n = 5 negatives, n = 5 at 25% below cutoff concentration, n = 5 at 25% above cutoff concentration, and n = 5 positives.

Lay users should test all specimens used in the consumer study in a masked manner. The consumer study should be designed in such a way as to test all of the procedures associated with the product to be marketed, i.e. mixing, timing, result interpretation, etc., under observation but without direct assistance other than the labeling instructions.

The results of consumer testing of each sample once with each test, should be presented as follows: each sample, once with each test, in the form of 2 x 2 tables (consumer result versus GC/MS result). The results of the consumer testing should demonstrate that when used by a consumer, the home screening device is able to discriminate results that are positive or negative based on the GC/MS result. This association may be evaluated by using statistical techniques such as Fisher’s Exact Test or Chi-Square Test.

c. Consumer discrepancies

The submission should also contain information

regarding the investigation of possible discrepancies that may have occurred between 1) the result that the consumer obtained and the GC/MS confirmed result, and 2) when a consumer could not read or determine the result. In addition, any range of concentrations that the consumer may have evaluated as borderline (sometimes termed the “equivocal zone”) should be defined. This may be achieved by having an unbiased surveyor observe the test result after the consumer has performed the testing.

All observations and results should be collated and recorded in a masked fashion. The results of the resolution should be presented in the form of a 2 x 2 table (consumer versus surveyor).

2. Consumer precision

a. Definition.
For initial screening devices intended for marketing directly to the consumer (OTC), a consumer field study conducted at three independent locations is needed to assess whether the lay user can follow the labeling instructions and can produce precise and reproducible results on the same sample.

b. Content.
Studies consistent with guidance in Analytical Performance Characteristics Section A.6 of this guidance should be conducted. The experiment may be performed in a single day to evaluate reproducibility among and within individuals. However, it is advisable to also include a study to determine day to day precision.

3. Consumer survey

A most important aspect of the consumer trial is a post-testing questionnaire designed to assess ease of use, comprehension of test results, and broader interpretation of positive and negative results. The questionnaire should be designed with both open ended questions to permit analysis of understanding as well as direct questions which address ease of use and correctness of test interpretation. This feed-back information will be beneficial to validate the test design and labeling adequacy.

Labeling

The information in the labeling should be organized and presented from a user's perspective and sequenced in a way logical to the intended user. Testing instructions for use by consumers should be directed at a reading comprehension level no higher than 8th grade.

There are several publications that may be used as references for writing consumer labeling. FDA's publication, FDA 93-4258, Write it Right, available through the Division of Small Manufacturers Assistance (DSMA) (301-443-6597), 21 CFR § 809.10 Labeling for *In Vitro* Diagnostic Products, and Labeling of Home-Use In Vitro Testing Products, document number GP14-A, available through NCCLS, are sources for clear and concise instructions. Both manual and software programs are available to predict readability. Methods for enhancing the understanding of the text, e.g., consistent terms, active verbs, personal pronouns, lay language, examples to explain concepts, etc. may be found in the publications cited above.

FDA recommends using pre-testing methodology (e.g., focus group interviews, individual in-depth interviews, etc.) in the design of the labeling. This methodology gathers typical potential users' perceptions, opinions, beliefs, attitudes, and comprehension of the potential labeling. Pre-testing can uncover problems with user-friendliness of the labeling and can help produce labeling that is understood by potential users.

Example of a Home Package Insert for Screening:

1. State the Name of the Device

2. For Intended Use:

    a. Provide a description of the essential information about the product, including the following information:

        1) State that the device is for home drugs of abuse screening or initial screening, e.g., "a first step test, etc."

        2) State that urine is the type specimen to be screened.

    b. A typical Intended Use statement might be stated as follows: "(This device) is a home screening kit for drugs of abuse. It is the first step in a two-step process to screen urine for the presence of marijuana (cannabinoids), crack (cocaine), heroin (opiates), speed/uppers (amphetamines), and angel dust/PCP

(phencyclidine).”

3. Limitations of Screening:

A statement should be included in the package insert, immediately following the Intended Use statement that identifies the testing limitations. This statement should appear in bold lettering. The limitation statements below are suggestions or examples of language that could be used:

(This device) is only the first step in a two step process to look for the presence of drugs of abuse. In order to be sure that the result of your screening test is correct, you must send the rest of the urine sample that you have tested to the laboratory for a final result which is more accurate.
Or:

(This device) is only the first step in a two step process for in-home testing for drugs of abuse. The home test is not as accurate as the laboratory test. Before you take any action, send the rest of the sample to the laboratory for further testing.

Or:

(This device) is only the first step of a two step process to look for the presence of drugs of abuse. The first step is not always accurate. If the UNCERTAIN, you should send the remainder of the sample that you tested to the laboratory. If the initial screen is negative, you DO NOT NEED to send a sample to the laboratory. Step two, called the confirmatory test, is done in a laboratory using a method that is highly accurate. Only the laboratory test can confirm the presence of drugs or drug metabolite. There is NO ADDITIONAL COST for the confirmation testing.

4. Specific or Detailed Explanation of the Test: This section of the labeling could alternatively be placed in a Question & Answer format, e.g., “Which drugs of abuse does this screening kit detect (include street names for each drug)?” “Drugs this kit can check for are:

- Pot/Grass/Marijuana/THC (Cannabinoids),
- Crack/Rock/Coke (Cocaine),
- Heroin/Smack (Opiates),
- Speed/Uppers (Amphetamine/Methamphetamine), and
- Angel Dust/PCP (Phencyclidine).”

5. Test Principle: Describe the chemical or physical process that occurs in order to detect a drug or drug metabolite. This section of the labeling contains a description or explanation of how the drug(s) is detected. The section could alternatively be placed in a Question & Answer format, e.g., “How does this drugs of abuse screening kit work?”

6. Contents of the Screening Kit: The contents of the test kit should be listed, e.g., “This test kit contains a:

- Specimen container,
- Confirmation mailer,
- Screening device,
- Absorbent material,
- Instructions for performing the test, and
- Pipette or specimen transfer device.”

7. For Specimen Collection and Handling: Describe how and when a specimen is to be collected, e.g., “When should I test the urine? How much sample do I need?”

Provide information concerning the length of time following drug use for which a positive result may occur. Providing examples and explanations that discuss a description of clearance rates for the drug-of-abuse in question is helpful. Table 3 may be used as a guide.

Table 3.

Drug	**How Soon Drug Can Be Found In Urine**	**How Long Drug Can Be Found In Urine**
Pot/Marijuana (Cannabinoids)	Within 1 to 3 hours after use	For 1 to 7 days after use
Crack (Cocaine)	Within 2 to 6 hours after use	For 48 to 72 hours after use
Heroin (Opiates)	Within 2 to 6 hours after use	For 24 to 72 hours after use
Speed/Uppers (Amphet/meth)	Within 4 to 6 hours after use	For 48 to 72 hours after use
Angel Dust/PCP (Phencyclidine)	Within 4 to 6 hours after use	For 7 to 14 days after use

The length of time following drug use for which a positive result may occur is dependent on several factors: frequency and amount of drug, metabolic rate, excretion rate, drug half-life, and the drug user's age, weight, activity, and diet.

The following information should be provided:

a. Type of specimen to be collected, e.g., urine.

b. Amount of specimen required, both optimum and minimum, e.g., as a mark or line on the side of the collection container.

c. Statement of appropriate collection procedures including special precautions regarding the specimen (e.g., collection, transportation, adulteration, non-absorbable plastic containers) as they bear on the validity and integrity of the test.

d. Description of any additives, preservatives, etc. necessary to maintain the integrity and quality of the specimen, e.g., “The blue tablet that you added to the urine will help preserve it in case more testing (step 2) is needed, etc.”

e. List of known interfering substances or conditions, e.g., nasal inhalants, diet pills, poppy seed ingestion, etc.

f. Statement of storage, handling, or shipping instructions for the protection and maintenance of the specimen and comments concerning the stability of the specimen, e.g., “do not leave sample in direct sunlight or avoid exposure to high temperatures, etc.”

8. For Test Procedure or Directions for Use provide:

a. Step-by-step instructions. Instructions should be adequate and tested for home use of the device. FDA suggests the use of pictures, drawings, and illustrations.

b. A description of the stability of the final reaction.

9. For Quality Control: FDA urges manufacturers of drugs of abuse screening kits for home use to design their devices in order to address quality control (both internal and external quality checks) and adulteration issues. This section could alternatively be placed in a Question & Answer format.

a. Internal Quality Control Check

1) The format of the home screening device may be such that "built-in" internal or reference control checks may be included. These reference controls may indicate that the sample has migrated properly, the antigen-antibody reaction has

occurred properly, or that a sequence of reagents have been added in a proper manner. The labeling should explain the purpose and function of the internal or reference quality control check, e.g., "A line will appear in the control window on the test strip if the proper amount of urine is added, etc."

2) The labeling should indicate a recommendation for the proper interpretation of internal quality control checks, e.g., "If a line does not appear in the control window of the test strip then…, etc."

b. Adulteration Check(s)

1) FDA urges manufacturers of drugs of abuse screening kits for home use to design their devices in order to address possible sample adulteration issues. Optimally the design of the screening kits would incorporate built-in mechanisms, e.g., for monitoring pH, or for monitoring sample dilution (either external or internal sample dilution).

Example: "The temperature strip on the collection bottle should be between 90˚F and 100˚F. If not in this range, the sample may be altered and another sample should be collected."

2) The issue of sample adulteration may also be addressed in labeling, through a clear explanation of possible sources of adulteration and/or pre-analytical error, e.g., "drinking large amounts of liquids may dilute the urine so that drugs cannot be detected."

10. For Results: FDA suggests the use of pictures, drawings, and illustrations to explain how to interpret the initial screening result. In addition, this section should include a discussion of what the result(s) mean. Information about the following should be included, when appropriate:

a. "Uncertain" result. When an "uncertain" result is obtained, describe what the consumer should do next, e.g., step-two or confirmation is needed, etc.

b. "Negative" result. When a negative result is obtained, describe what this means. One suggestion is: "if no drug was found in the urine, the person probably has not used drugs within the last few days; a person can

use drugs, but not have drugs found in the urine; other reasons could be that only a small amount of drug was used; the urine sample was collected either too soon after drug use, or too late after drug use; the urine sample was diluted with water; the person drank a lot of liquids within a few hours before giving the sample, etc."

c. "Invalid" or "No" Result. When the results of the initial screen cannot be interpreted, describe what this means, e.g., the reference or "built-in" control check (line) did not function or did not appear; therefore, you must repeat the test using a new device, etc.

d. Repeat screening. Advise the consumer when and if repeat screening should be conducted.

e. Referral. FDA encourages manufacturers of home screening kits to provide professional counseling and referral services though a 1-800 telephone service, e.g., "Call our toll free number, 1-800-_____, between 8:00a.m. and 8:00p.m. Eastern Time, to discuss the results of your test and what they mean, etc."

11. Limitations:

a. Provide an explanation of the limitations of the test including a list of substances known to interfere. A list of substances known to interfere with the home screening kit should be presented under the Limitations section of the package insert.

This section of the labeling could alternatively be placed in a Question & Answer format, e.g., "What if I am taking an Over-The-Counter Drug? Could I have eaten something that could cause a false result?"

b. Need for confirmation testing. The labeling should provide information concerning the need for confirmation testing for all preliminary "uncertain" screening results.

12. Name and Place of Manufacturer, Packer, or Distributor.

13. Date of last labeling revision.

Outside Box Labeling:

In addition to the package insert described above, the following

labeling statement should be included on the outside box labeling for drugs of abuse screening devices:

> **(This device) is only the first-step in a two-step process for determining the presence of drugs of abuse. You must consult your health care provider or refer all "uncertain" results to the laboratory in order to obtain step-two: a confirmed result (see package insert).**