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Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane
Room 1061
(HFA-305)
Rockville, MD 20852

Enclosed is MEDTOX Diagnostics response to the draft version of, "*Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications*".

Sincerely,

Alan Morris

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Manager, Research and Development

00D-1587 C1

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Response to the Draft Version of
Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications

This response is organized into two sections. First, an introduction that gives an overview of our response. Second, detailed responses to individual issues organized by page number and paragraph heading.

INTRODUCTION

We appreciate the FDA's effort to develop guidance documents for the difficult issue of drugs of abuse tests. However, we believe that the FDA focus on test performance for positive urine samples below the cutoff is misguided because the results are not clinically significant. The purpose of screening assays is to eliminate negative samples from needing additional testing, not to differentiate samples that differ in concentration by 25%. For example, according to the FDA guidelines a perfect cocaine test would give a positive result for both a 300 ng/mL urine sample and a 10,000 ng/mL urine sample however a 225 ng/mL urine sample would give a negative result. We are unaware of any studies indicating there is a significant clinical difference between 225ng/mL and 300 ng/mL urine sample. However, a 10,000 ng/mL result may be clinically significant. However, the FDA recognized the limitation of screening test and requires clear labeling multiple times in the insert and on the box label that the tests are screening assays only and all positive results should be confirmed. The confirmation testing of positive samples will eliminate the false positives and give users the ability to eliminate samples that are negative. While we agree with the FDA that OTC tests should be used for home use only. The FDA should clarify that prescription use one-step tests are applicable in professional settings such as workplace, sports and insurance testing. Prescription one-step tests should be allowed in professional settings since:

- No special skills, training, education or licensure are required to transfer drops of urine to a device.
- One-step tests have an excellent track record of use by consumers initially as pregnancy tests, currently as drug tests.
- Test results do not detect either disease state or impairment.
- Tests are clearly labeled that all presumptive positive tests should be confirmed.

COMMENTS ABOUT INDIVIDUAL ISSUES IN THE GUIDANCE DOCUMENT BY PAGE NUMBER AND PARAGRAPH HEADING

Page 2 B. DEVICE FUNCTION

COMMENT: The FDA should clarify that prescription use one-step tests are applicable in professional settings such as workplace, sports and insurance testing while over-the-counter tests are for home use only. Prescription one-step tests should be allowed in professional settings since:

- No special skills, training, education or licensure are required to transfer drops of urine to a device.
- One-step tests have an excellent track record of use by consumers initially as pregnancy tests, currently as drug tests.
- Test results do not detect either disease state or impairment.
- Tests are clearly labeled that all presumptive positive tests should be confirmed.

Page 5 A. SCREENING AND CONFIRMATION TESTING

COMMENT: EMIT should be deleted from the list of screening assays since it is a trademarked name and covered under the EIA screening tests. The agency should consider adding an immunochromatographic test designation since many new tests are now in the popular one-step format.

Page 6 Confirmation testing

COMMENT: The wording in the final sentence should be changed to, *"Methods used in the confirmation of presumptive positive results include but are not limited to: "*, so new techniques can be used in confirmation testing as they become available.
Confirmation testing should also include LC/MS and LC/MS/MS.

Page 6 SPECIMEN COLLECTION DEVICES

COMMENT: In our experience, the usual range of specific gravity in human urine is 1.002 to 1.030 instead of 1.002 to 1.040 and the usual range of pH in human urine is 4.5 to 9.0 instead of 4.5 to 8.5.

Page 6 SPECIMEN COLLECTION DEVICES

COMMENT: We agree that collection devices with drug tests incorporated into the collection cup should undergo rigorous testing to demonstrate that the drug tests do not interfere with the confirmatory assays. However, the proposed guidelines for a sample collection cup is unduly burdensome given the large historical data base of knowledge for successfully using collection cups for drugs of abuse assays.

Page 8 1. Analytical Sensitivity or Minimum Detection Limit

COMMENT: The FDA should clarify the language on the definition of detection limit in a qualitative assay.

COMMENTS ABOUT INDIVIDUAL ISSUES IN THE GUIDANCE DOCUMENT BY PAGE NUMBER AND PARAGRAPH HEADING

Page 9 2. Cutoff Concentration

COMMENT: We agree that the current definition of cutoff concentration is appropriate for a quantitative instrumented assay. Instruments measure drug concentrations very precisely by comparing the response generated by a standard with a known concentration of drug to a clinical sample with an unknown drug concentration. However it has been suggested that the proposed definition of cutoff concentration is not appropriate for a qualitative screening assay such as one-step tests for both logical and related technical reasons.

- Screening assays eliminate samples that do not contain drugs from needing additional testing. Samples that test positive are tested further by confirmatory assays. Therefore, false positive results will be detected by the confirmatory assay. The need for confirmatory testing is clearly labeled in the insert and box labels. However, more importantly screening assays only indicate the presence of drugs in the urine. Insert labeling clearly states that the screening assays do not detect impairment.
- More importantly, there is no clinical significance if urine samples with concentration at 50% below the cutoff or the cutoff give a positive result. Drug concentrations in urine vary widely from person to person because of many different factors, such as urine output. Therefore, the drug concentration in urine, between individuals that received the same amount of drug can vary by 100% to 500%. Even if a screening test gives no false positive results, the end user does not know if a positive sample has drug at the cutoff concentration or 1000 times the cutoff concentration.

There are three major technical reasons why the proposed protocols are not appropriate. The precision of competitive one-step tests is significantly different from instrumented tests at the cutoff concentration and therefore:

1. Near the cutoff concentration, the precision of one-step tests is less then the precision of instrumented tests because of where the cut off concentration is on the standard curve. Test users expect all urine samples with drug concentrations at the cutoff concentration to yield a positive assay result. When competitive immunoassay one-step tests are positive the test line is generating no visible response. As shown in Figure 1, as the drug concentration increases, the line intensity decreases logarithmically. Therefore, the cutoff concentration is at the end of the standard curve, near the limit of signal detection (LOD). Therefore, the precision and accuracy exhibit a large variation. Conversely, as shown in Figure 2, instrumented tests generate a response in the middle of the standard curve at the cutoff concentration. Therefore, the precision and accuracy exhibit a small variation. Therefore it is not scientifically valid to expect a one-step test that is performing at the LOD to have the same precision as an instrumented assay that is performing in the middle of the standard curve.

COMMENTS ABOUT INDIVIDUAL ISSUES IN THE GUIDANCE DOCUMENT BY PAGE NUMBER AND PARAGRAPH HEADING

2. Instrumented tests generate a signal in the middle of the standard curve when assaying urine samples with drug concentrations at the cutoff because they compare the signal of clinical samples to the signal of standard samples with known concentrations. However, one-step tests must be clearly positive (no line) when assaying urine samples with drug concentrations at the cut off because the user does not compare the line intensity of a clinical sample to the line intensity of a standard. Each one-step test device is self-contained. Therefore, while instrumented tests generate an easily measurable difference in response with a 25% increase or decrease in drug concentration, one-step tests cannot. Using the example in Figure 2, an instrumented assay with a cutoff of 100 ng/mL and a response of 1.5 would generate a response of 1.71 an increase of 0.21 or 14%. An instrument would have no trouble measuring such a 14% increase in response. Using the example in Figure 1, a one-step test with a cutoff of 100 ng/mL and a response of .27 would generate a response of 0.35 an increase of 0.14. Few individuals would able to see such a small increase in line intensity. Indeed, depending where the cutoff was set in the standard curve, very few people would even be able to see a line. Although individuals do not have any problem detecting negative samples, they do not see very light lines. Therefore, even small concentrations of drugs cause a line to lighten to where many individuals do not see them. Since one-step tests have the cutoff concentration set at the end of the standard curve a 25% decrease in drug concentration does not produce an increase in line intensity the same way an instrumented assay can detect with the cutoff set in the middle of the standard curve. Given the logarithmic nature of immunological assay standard curves and having the cutoff concentration give no visible line, there must be a significant decrease in drug concentration to generate a line most users can see. Therefore, decreasing the drug concentration 25% below the cutoff does not generate a 25% increase in line intensity and is not sufficient to generate a line that every one can see. A 25% increase in drug concentration only slightly affects the test since the one-step tests are usually positive at the cutoff concentration. Instrumented tests usually formulate the standard curve so that the cutoff concentration is in the middle of the standard curve. Additionally, instrumented tests do not require a linear standard curve response to work properly, because they compare the response of unknown samples to the result of standard samples with known concentrations. Therefore if the instrument response is less then the standard the sample is positive and if the response is greater then the standard the sample is negative. Instruments can also store and use nonlinear standard curves to calculate concentrations.

- Samples containing drug concentrations below the cutoff value are <u>not negative</u>, but should be considered as samples containing less then cutoff drug concentrations after confirmatory testing. Currently there are individuals that want to know if there is any drug concentration present and there are analytical services that are providing them with the answers.

Performing the described studies is acceptable since it will allow the users to decide which tests are appropriate for their application. However, we believe it is inappropriate to impose the classical definition of cutoff concentration proposed in this guidance document, for one-step immunoassay tests.

COMMENTS ABOUT INDIVIDUAL ISSUES IN THE GUIDANCE DOCUMENT BY PAGE NUMBER AND PARAGRAPH HEADING

Page 11 4. Interference

COMMENT: The false negative portion of the interference study design, fortifying urine samples that contain a minimum concentration of the test drug able to generate a positive result, with hundreds of different OTC, prescription and unrelated compounds is not appropriate for one-step colloidal gold tests because:

- A false negative result could only occur if an interfering compound caused the colloidal gold in a one-step test to bind to the conjugate line in a nonspecific manner. Chemically, there is no basis to believe that OTC, prescription and unrelated compounds, at physiologically relevant concentrations, cause false negatives with the colloidal gold one-step tests. The false negative portion of the interference study design is appropriate with ELISA tests, since yield false negative results can be obtained when assaying urine samples that contain drugs that interfered with enzyme activity.

Some have suggested that both the positive and negative interference test study designs are flawed. Although we agree that the interference study will determine if OTC, prescription and unrelated compounds will effect test sensitivity, it is not clear how this information will be useful to the end-user. The interference studies conducted on the majority of existing tests only examined the effect of the OTC, prescription and unrelated compounds on negative control urine. Therefore, users will not be able to accurately compare the cross reactivity results of current versus future tests by looking at the results reported in the insert. Retaining the current cross reactivity protocols, fortifying negative control urine, will reduce end-user confusion, since the test inserts will have the studies done in a consistent manner.

Perhaps more importantly, the information provided by the proposed interference study is of limited value to end user for several reasons:

- The tests are screening assays and are clearly labeled that all positive results should be confirmed. Therefore false positives caused by interfering compounds will be detected.
- Although end-users may know the OTC, prescription and unrelated compounds a patient is taking, they do not know the drug concentration in the urine they are testing. Therefore, they will not be able to evaluate the cross reactivity effect any better with a classical study then with the proposed one.
- Although the parent compound of many OTC, prescription and unrelated compounds can be tested, many drugs have metabolites that are not commercially available or unknown. Thus cross reactivity studies with parent compounds are not clinically relevant for many drugs.
- Even if a drug is excreted mainly as parent compound it is difficult to determine what is a clinically relevant concentration.

Page 18 A. INTENDED USE

COMMENT: Workplace testing should be added to the intended use list for prescription tests for reasons outlined in "Page 2 B. DEVICE FUNCTION".

COMMENTS ABOUT INDIVIDUAL ISSUES IN THE GUIDANCE DOCUMENT BY PAGE NUMBER AND PARAGRAPH HEADING

Page 18 A. INTENDED USE

COMMENT: We disagree with the FDA definition of false positives and incorrect result. When one-step tests detect drug in urine below the cutoff concentration the results are neither false nor incorrect since the samples contain a confirmable concentration of drug. The purpose of screening assays is to eliminate samples that do not contain drugs from needing additional testing. We believe that the users can judge if the precision of the test around the cutoff concentration is suitable for their application. Stating, *"at concentrations 50% above the or below the cutoff concentration, provides more incorrect results then correct results."*, is unnecessary. A more accurate statement would be, "*in fortified samples with drug concentrations 50% below the cutoff, XX% of the samples were positive and YY% of the samples were negative.*" Additionally, the FDA proposed language could confuse users who compare recently approved test inserts to previously approved test inserts. Users could easily infer recently approved tests with warnings in the inserts are inferior to current tests with no warning in the insert. The user can determine if the test meets their needs by reading the data in the precision and accuracy section of the insert.

Page 20 G. QUALITY CONTROL

COMMENT: The statement, "*Users should follow the appropriate federal, state and local guidelines concerning the running of external quality controls"*, should be modified to, "*Users should contact the appropriate federal, state and local agencies for guidelines concerning the running of external quality controls"* so users do not expect the manufacturer to have the required quality control information. Users would benefit if the FDA/CDRH would set up a web page or 800-information hotline to address the external quality control issues that will be raised due to the new labeling statement in the insert. Currently this information is not available at one central location.

Figure 1
ONE-STEP Immunoassay
Cut off = 100 ng/mL

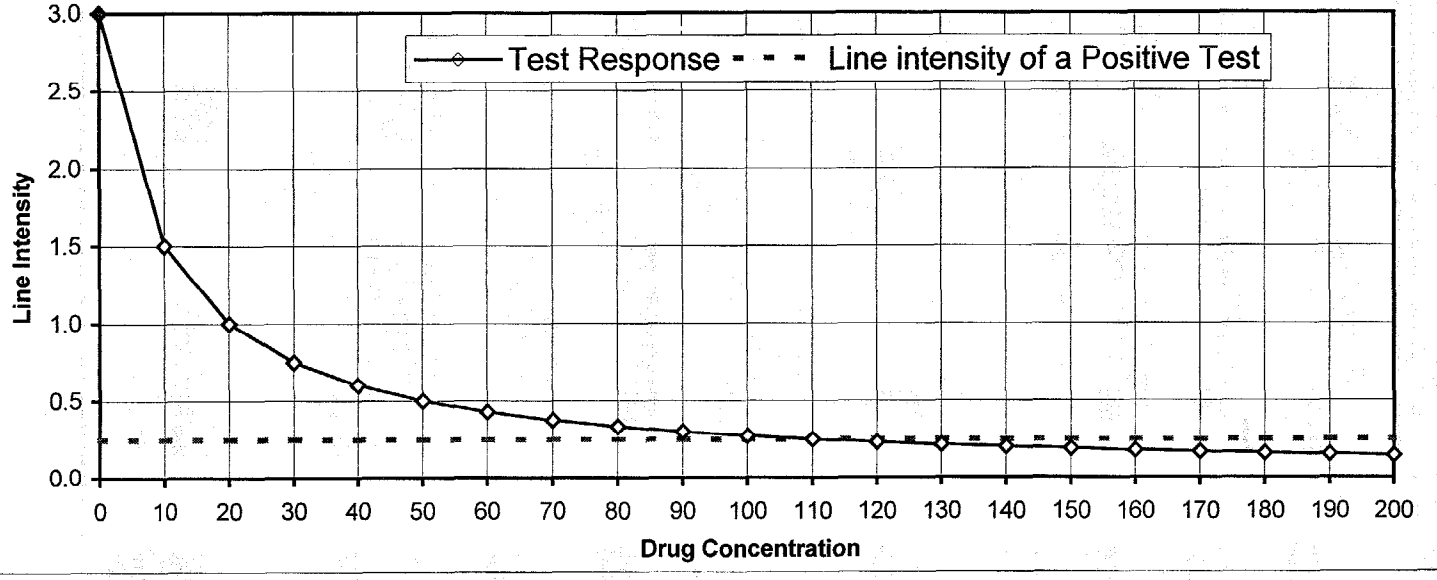
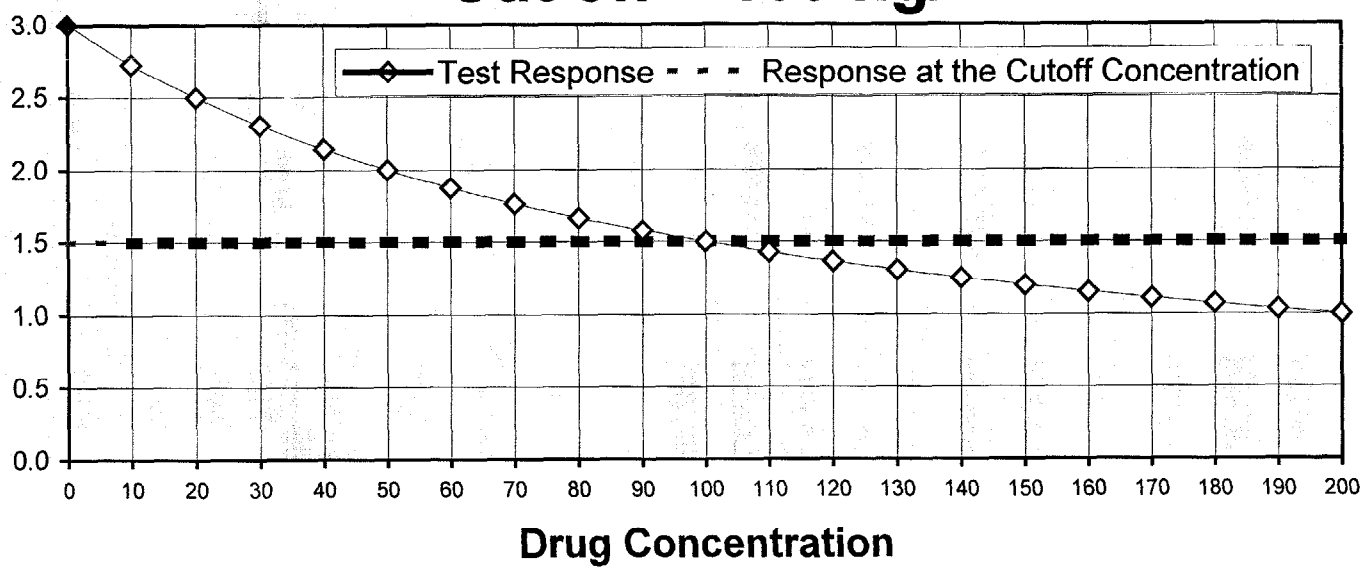


Figure 2
Instrumented Immunoassay
Cut off = 100 ng/mL



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