Roche

Diagnostics

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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

February 1, 2001

To whom it may concern,

Two documents are attached to this letter. They contain comments from Roche Diagnostics Corporation on two of FDA's draft guidance documents:

1) Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications

2) Over the Counter (OTC) Screening Tests for Drugs of Abuse: Guidance for Premarket Notifications

Please log our comments into your system.

Sincerely,

Luann Ochs

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Guidance for Prescription Use Drugs of Abuse Premarket Notifications – Comments from Roche Diagnostics

Purpose

The purpose of this document is to provide comments to FDA regarding the draft "Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications". The sections below include general and specific comments and issues provided by the scientists from Roche Diagnostics Corporation.

General Comments

Roche Diagnostics would like to thank FDA for developing this guidance document. Documents such as this one help us to understand FDA's criteria for clearance for our products. The clearance process can proceed smoothly and efficiently when the criteria are well understood. Also, we are hopeful that this guidance will allow us to utilize the Abbreviated 510(k) approach for bringing products to market. We are always appreciative of FDA's efforts to streamline regulatory processes.

In regard to this specific guidance, we appreciate the opportunity to offer comments. This guidance is specifically for prescription use screening tests for drugs of abuse. We ask FDA to ensure that this guidance includes all drugs of abuse tests, not just the NIDA 5 tests.

Screening tests are useful because they clearly identify true negative samples. When zero drug is present, the result is clearly negative. Those samples don't need to have confirmation testing, thereby saving much time, cost, and worry. Results on other samples may not be so clear. Those samples are assayed by more definitive methods. The resources of the definitive method are appropriately utilized to test only the samples that need it.

The technology used in the screening devices available today is simple to use and gives quick results. It appropriately identifies true negative samples. It appropriately identifies those samples that need additional testing. However, today's technology does not provide very sharp color changes exactly at the desired cutoff. Color changes are more gradual, and are somewhat subject to individual reader interpretation. This means that the precision around the cutoff is more variable than the precision seen with laboratory analyzer tests. We believe that the precision of these devices today is adequate for their intended screening use. More specific comments are included below.

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Specific Comments

Section II. Background

FDA states "The prevalence and use of many drugs of abuse in the general population continue to increase." This statement is contradictory to the Drug Testing Index©, published annually by Quest Diagnostics since 1988. Recent data indicates that drug screening tests may be acting as deterrents to drug use:

Drug Testing Positive Rate (3 year trends)
For federally mandated, safety-sensitive workforce

Drug Category	Jan-Jun 1999	1998	1997
Amphetamines	0.24%	0.25%	0.30%
Cocaine	0.68%	0.78%	0.73%
Marijuana	1.88%	1.87%	2.00%
Opiates	0.29%	0.49%	0.53%
PCP	0.05%	0.05%	0.04%

Section III. Device Description

Section A: Please add "lateral flow immunoassays" to the list of the most common methods used for screening.

Section B: Sample acceptance criteria. FDA suggests that data supporting acceptance/rejection of samples be included in each premarket submission. Roche does not agree that this data is necessary. Literature clearly supports rejecting samples based upon the criteria listed for urine (pH, specific gravity, odor, color, and temperature). Validation of this criteria need not be repeated for each new submission. Often, adulteration checking devices, that check for specific compounds present in the urine, are used to check sample integrity. These must be continually updated to ensure that they are picking up today's popular adulterants. Any data included in a 510(k) to support such a checking device would be soon out of date.

FDA has repeatedly determined that adulteration checking devices are not subject to DCLD review. This data does not need to be included in each 510(k) submission.

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Specific Comments, Continued

Section IV Performance Characteristics – Point A	FDA states "Performance for devices intended to be used outside central testing laboratories (point of care settings) should be established at multiple representative sites by individuals who are not medical technologists or technicians." Roche agrees with this statement in concept. Our TesTcup and TesTstik devices are all very similar to each other. The physical characteristics and instructions for use are exactly the same for all of the devices in each family. Only the reagent membrane inside the device is different for each specific analyte. We believe that one study, for any analyte, proving equivalency between laboratory professionals and non-laboratorians should be sufficient. We should not have to repeat this study for each analyte, since all are handled in exactly the same manner. After submission of a representative point of care study, future submissions may include in-house generated data only.

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Specific Comments, Continued

Section IV Performance Characteristics – Point B

Part 1. Detection limit for a qualitative visually read assay. FDA states "The lowest concentration of drug detected above the detection cutoff would be the detection limit." Actually, the detection limit could be above or below the cutoff. Remove the words "above the detection cutoff".

At concentrations around the cutoff, both positive and negative results will appear for the same sample. Please define the percentage of positive readings that render the result "detectable".

Part 2. Table 1. Cutoff concentrations listed in the table are not the new SAMHSA limits, and are not consistent with the table on page 21. Since SAMHSA frequently changes their limits, this table is likely to outdate. We recommend that the guidance refer the manufacturers to SAMHSA documentation regarding cutoffs, rather than listing them.

The state of technology for screening devices is such that these devices are not consistently 100% accurate at ± 25% of the cutoff. Extending the levels to show 100% agreement with GCMS will also give variable data, as GC/MS can have an imprecision of ± 20%. Certified GC/MS labs get perfect scores for proficiency when the tested values of their PT samples are within ±20%. Any study for accuracy around the cutoff should include reporting of results with 95% confidence.

FDA states "Cutoff levels should be far enough away from the detection limit of the test to permit accurate and reproducible results." We do not understand this statement in regards to qualitative tests. Our prior communication with FDA has indicated that they would like for the detection limit and the cutoff concentration to be the same, so as to render fewer false presumptive positive results. In practice, the detection limits are lower than the cutoffs. This is to ensure that the rate of false negative results is very low. When a result is negative, no further action is taken. When a result is positive, the sample is sent for additional screening and confirmation. It is more important to eliminate false negative results, so the detection limit is usually somewhat below the cutoff.

Part 5. For qualitative tests, precision should be defined by the confidence limit of producing a given result at a particular level. For example, 95% of results (confidence interval) are positive at 150% of cutoff value.

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Specific Comments, Continued

Section IV Performance Characteristics – Point B (continued)

Roche believes that it is not necessary for external sites to perform precision studies on multiple lots of reagents. Good Manufacturing Practices require us to manufacture reagent lots within our specifications and tolerances. Lot to lot variability can be determined with internal testing. External precision testing can then be performed on one lot, at three sites, for example. The external precision can be compared to the internally achieved precision, if desired.

Part 6. The method comparison studies as outlined by FDA are difficult to perform. It is very difficult to obtain 20% of the samples to be within ±25% of the cutoff value. These samples are very rare in actual practice. It is also not practical to dilute higher level samples, because they don't dilute linearly due to the presence of many metabolites with varying cross-reactivities. Allow manufacturers to characterize cutoffs using artificial matrices, e.g., controls or calibrators, rather than native samples. The over-emphasis on cutoff does not reflect the actual use of these screening devices. FDA is failing to take into account the fact that actual positive rate is low, and the actual near-cutoff samples are even lower. Please refer back to the table that is included in this document on page 2. Actual negative rates are generally >99% of all samples. The purpose of these devices is to clearly separate the true negative samples from the questionable samples. This purpose is achieved even without exceptionally good performance right at the cutoff.

A study published by SAMHSA clearly showed what can be expected from both instrument-based and visually read drug screening assays if the samples were deliberately selected to emphasize near cutoff performance. Out of the 16 products evaluated, TesTstik was the best with r=0.778 and SYVA Emit d.a.u. on the ETS instrument was the second best with r=0.757 accuracy for all drugs. This data appears different from package insert data, and is sited to illustrate one point: imposing these studies and labeling requirements at this point puts new products at a competitive disadvantage over products already on the market, that were not required to perform such studies. FDA needs to establish and maintain consistent requirements for all manufacturers of drugs of abuse tests. Older products in the market need to also be brought to these standards.

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Specific Comments, Continued

Section IV Performance Characteristics – Point B (continued)

Point 6, continued. Correlations must be performed against the GC/MS value, not the GC/MS determined positive or negative result. GC/MS is allowed an imprecision of ±20%. At concentrations near cutoff, this variability can change the positive or negative determination. Also, the GC/MS cutoff and the screening cutoff are not always the same value. Because of its better specificity, GC/MS results may be determined to be positive at a lower concentration than the screening test. To do the correlation studies, the same cutoff value must be used for both methods. For a device with a cutoff of 300 ng/mL, for example, the table would look like this:

New device	GC/MS <225	GC/MS 225 – 300	GC/MS 301-375	GC/MS >300	% Agreement with GC/MS
Positive					
Negative					

What is to be done with discrepant points that are investigated by a reference method? We understand that it may be desirable to determine which result is the correct answer, but what then should go into the labeling? It is statistically incorrect to resolve only discrepant samples, and then include the resolved result in the original data set. Manufacturers may prefer to just include the discrepant results in the data tables in the labeling, if there are few.

Questions to November 13, 2000 Panel – Roche Response

Question 1

The study designs in the guidance are appropriate, except as noted in the comments above. We believe there is too much emphasis on the results around the cutoff.

Once a device has been shown to be successfully usable by non-laboratorians, that testing should not need to be repeated for each new similar member of the device family.

Testing of three lots of reagent at the external sites is overly burdensome, and is not necessary to characterize lot to lot variability. Testing externally provides information regarding the usability of the device, and operator to operator variability. Lot to lot variability can best be assessed by internal bench testing at the manufacturer. To assess operator to operator or site to site variability, only one lot is necessary.

Question 2

Roche would like for this guidance to apply to drugs other than the NIDA 5 drugs. Cutoffs for those other drugs are requested by the clinical community, not selected by the manufacturer. Cutoff selection will, most likely, be validated from literature articles, not clinical utility studies. Manufacturers are not prepared to conduct arduous long term clinical studies to determine the clinical effectiveness of cutoff levels. FDA needs to recognize that customer demand creates cutoff requirements.

Validation of detection of multiple metabolites can be done with laboratory studies of cross reactivities. Method comparison studies will be comparison to the major metabolites, assayed on GC/MS or other reference method.

Question 3

No. Any device that is shown to have acceptable performance in the hands of lay users should be allowable for OTC use. Acceptable performance is defined as performance not significantly different from that obtainable by trained laboratorians.

Question 4

Our customers want sensitive tests. They do not want to have false positive results. They want true negatives (zero drug) to give negative results. This is achievable with a performance requirement that 95% of results (confidence interval) read correctly at ±50% of the cutoff, and a zero drug sample gives no positive results.

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