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

February 4, 2004

Re: Vol. 68 (December 2, 2003): Docket No. 2003D-0522, CDRH 200383

*Draft Guidance for Industry and Food and Drug Administration Staff; Premarket Submissions and Labeling Recommendations for Drugs of Abuse Screening Tests*

We are hereby submitting comments on the FDA Guidance Docket No. 2003D-0522, CDRH 200383, *Draft Guidance for Industry and Food and Drug Administration Staff; Premarket Submissions and Labeling Recommendations for Drugs of Abuse Screening Tests* (Dec. 2, 2003)

In referencing the "previous guidance" we are specifically addressing the document *Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications*, released for comment on Nov. 14, 2000. Our comments will be directed at drugs of abuse (DAU) qualitative or semi-quantitative assays for automated clinical analyzers in a professional laboratory setting.

**Comment 1: DAU Product Codes**

DAU product codes in 21CFR862 do not adequately reflect current technologies. We suggest an additional code for immunoassays in general, or additional codes specifically for FPIA and specifically for Latex Agglutination Inhibition.

**Comment 2: Analytical Sensitivity**

Table 1 on page 6 of the new guidance does not recommend any testing for *analytical sensitivity*, although it is mentioned in the Labeling Considerations, Performance Characteristics section (p. 20) along with cutoff characterization. The new guidance recommends on page 8, Special Notes: "For semi-quantitative tests, you should establish cutoff levels far enough above the background noise of the test to permit accurate and reproducible results."

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The *previous guidance* document specifically describes an Analytical Sensitivity or Minimum Detection Limit study design on pages 8-9. We recommend that this same MDL study design description be included in the new guidance document.

**Comment 3: Cutoff Characterization**

Page 9 of the guidance states “For semi-quantitative tests, we recommend that you also characterize the linear range of the assay...” and recommend following NCCLS Document EP6-P. EP6-P is specifically for linearity of a quantitative analytical method. The FDA has consistently emphasized the *semi-quantitative* or *qualitative* nature of DAU tests, and has not allowed *quantitative* claims for immunoassay screening tests. We recommend that FDA clarify the guidance document’s requested characterization of linearity for our semi-quantitative and qualitative assays.

**Comment 4: Method Comparison**

Roche believes our current practices for Method Comparison testing are consistent with the new guidance. However, we would like to comment on several statements in this section.

Page 12:

*“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.”* It is very difficult to find clinical samples like this for many assays. For example, Barbiturate assays are typically calibrated using secobarbital, but clinical samples containing secobarbital are difficult to find.

Page 12:

*“As some drugs deteriorate in specimens over time (especially benzoyllecgonine), we suggest that you minimize the time between the reference (e.g., GC/MS) measurement and analysis on the new device.”* Note that it is difficult to obtain fresh samples with minimal time between reference and immunoassay testing, based on some lab requirements for retention of positive samples for approximately 1 year. Also, the volume of sample available for purchase is limited and often may not be sufficient for further GC/MS analysis.

Given the statements above, Roche recommends the new guidance specifically allow the use of spiked samples in drug free human urine in Method Comparison studies when native clinical samples are not available. Spiking should be done with the drug used to calibrate the assay. The spiked samples would be analyzed by a reference method, as well as the positive clinical samples and a portion of the negative clinical samples.

## Labeling Considerations

### Comment 5: Intended Use

Page 16:

The sample Intended Use statement describes a qualitative, prescription use DAU assay in a clinic or physician's office setting. The second paragraph of the sample intended use statement ("*Minimum training for operators is defined as...*") is specific to the type of settings described above and not applicable to professional clinical laboratory settings. The new guidance should specifically characterize the sample intended use statement included as *an example, where appropriate*.

### Comment 6: Summary and Explanation of the Test

Page 17:

Roche questions the value of adding a Clearance Rate table to professional use or OTC labeling. Depending on what source is being quoted, these values can vary widely. Further, this type of information is readily available to the laboratory clinician / toxicologist. For the OTC market, we believe that including this information in the labeling could aid a home user taking illegal drugs in how to "beat the test."

### Comment 7: Understanding the Test Result

Pages 17-18: "For Preliminary Positive Tests"

The "SAMHSA report" quoted (actual report should be referenced) appears that it was designed to "challenge the cutoff" for these assays rather than show performance in actual practice. We do not believe these "accuracy of drug tests" results are at all representative of the true incidence of false positives for our prescription use drugs of abuse assays in a clinical laboratory setting. A vast majority of positive drug tests contain large amounts of drug / drug metabolites well above testing cutoffs. The true rate of false positives (or negatives) relative to GC/MS is dependent on the quality of the technology used and the type of assay, i.e., visually read vs. qualitative or semi-quantitative. It is also affected by different cutoffs used for confirmation by GC/MS and the ability of immunoassays to intentionally pick up multiple drug metabolites that may not be tested for by GC/MS.

The recommendation on page 18 "*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)*" would require the screening of thousands of samples to obtain statistically significant amounts of positive samples for GC/MS confirmation to ultimately determine false positive rates. This type of testing would be very expensive and impractical for manufacturers to perform.

Further, Roche already shows extensive characterization of the accuracy of each of our assays in our labeling. Roche provides control precision and recoveries, cut-off validation with near cut-off concentration studies, and method comparison studies with all positive clinical samples and a portion of the negative clinical samples referenced to GC/MS. We believe this gives the laboratorian / clinician a more accurate picture of how our assays will perform than the statements of false preliminary positive results included in the new guidance document. The recommended statements from the SAMHSA study do not represent the performance of our products. Inclusion of this information in our labeling would be confusing to the laboratorians / clinicians using our products.

Page 18: "For Negative Tests"

Roche already includes the statement requested on page 19 under *Limitations* in our labeling, that is, "There is a possibility that other substances and / or factors may interfere with the test and cause erroneous results (e.g., technical or procedural errors)." We believe the language requested on page 18 under "For Negative Tests," while perhaps appropriate for OTC or Workplace testing assays, is not appropriate and would not add value for laboratorians / clinicians using DAU assays in a professional setting.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Kerwin Kaufman". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

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