FDA Regulation of Drugs of Abuse Tests

SAMHSA DTAB Meeting
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Center for Devices and Radiological Health
Food and Drug Administration
Drugs of Abuse (DOA) Tests

• Tests used to screen for the potential presence of abused drugs in a specimen obtained from a subject in clinic, home, workplace, sports, or insurance settings.

• May test in blood, urine, sweat, saliva, hair, or other specimen matrices.

• Positive screening results should be tested by a more specific confirmation method.
DOA Test Regulation

Most DOA tests are Class II and require clearance [510(k)] prior to marketing, including tests for:

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>Methadone</th>
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</thead>
<tbody>
<tr>
<td>Alcohol (serum and breath tests)</td>
<td>Morphine</td>
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<tr>
<td>Amphetamines</td>
<td>Opiates (including Oxycodone)</td>
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<tr>
<td>Barbiturates</td>
<td>Phencyclidine (PCP)</td>
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<tr>
<td>Benzodiazepines</td>
<td>Propoxyphene</td>
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<tr>
<td>Cocaine</td>
<td>Cannabinoids (marijuana)</td>
</tr>
<tr>
<td>Methamphetamines</td>
<td>Tricyclic Antidepressants</td>
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</tbody>
</table>

etc…
DOA Test Regulation

DOA tests may be for:

- Prescription use - in a central clinical chemistry laboratory
- Point of Care Use – prescription use at doctor’s office labs, in the ER, or at the patient bedside
- Over-the-Counter use
- Workplace use – may be prescription or OTC
- Forensic use only – currently the FDA does not actively regulate (via enforcement discretion) devices labeled to be used only by law enforcement
What is FDA looking for?

Performance as designed

• Does it do what it says it does?
• How well does it do that?
• Is that function valid?

THINGS GOT REALLY INTERESTING WHEN THE STATISTICIAN STARTED DOING WARD ROUNDS
Premarket Review

All tests should establish adequate:

Analytical validity
  • How accurately does the test measure the drug?
  • How reliably?

Clinical validity
  • How reliably does the test reflect the person’s status?
    (cutoff effectiveness, etc.)

Labeling (21 CFR 809.10)
  • Adequate instructions for use
  • Intended use, directions for use, warnings, limitations, interpretation of results, cross-reactivity/interferences, performance summary
To obtain clearance, sponsors must establish adequate analytical performance.

• **Precision**
  - Will I get the same result in repeated tests over time?
  - Will I get the same result as someone else testing the same sample?
  - Performance around cutoff
    - Tests performance on repeated tests in samples spiked with zero drug, and to -75%, +/-50%, +/-25%, and +100% of the cutoff

• **Recovery (Semi-quantitative only)**
  - Evaluates how well the test system measures drug across the calibration range
Analytical Validity

• **Cross-reactivity**
  Evaluates how much the antibody cross-reacts with similar drugs/metabolites/compounds

• **Interferences**
  Evaluates whether the system provides accurate results even in the presence of potential interferents
  • Endogenous substances (bilirubin, uric acid, etc.)
  • Drugs (e.g., common OTC drugs)
  • pH, specific gravity (urine)
Analytical Validity

• Accuracy

Is the system accurate compared to a gold standard comparator method?

• Gold standard usually GC/MS, LC-MS/MS, etc.

• Study performed on real samples.
  • Generally at least 40 positive and 40 negative samples
  • Unaltered clinical samples (spiked and diluted samples only accepted for PCP)
  • Near cutoff samples needed (~10% of positives and 10% of negatives)

• Evaluate positive and negative percent agreement
  • Any false positive and negative samples should be near cutoff
Clinical Validity

Established cutoff concentrations:
• May reference existing experience with marketed devices, SAMHSA guidelines, etc.
• Analytical studies only

New cutoff concentrations:
• Sponsor provides data to establish that the cutoff is effective, for example:
  – safe and effective balance of false positive and false negative results
  – Information to provide adequate instructions for use (detection window, population differences, etc.)
Setting of Use

• **Point of Care (POC)**
  - Precision and Accuracy studies performed in the hands of the intended user (e.g., nurse)
  - Generally performed at 3 POC sites

• **Over the Counter (OTC)**
  - Sponsors demonstrate that the test is accurate in the hands of lay users
  - Studies are performed to evaluate how well lay users can understand the instructions without prompting, perform a test, and obtain an accurate result
  - Labeling is evaluated for reading level (7th grade)
  - Human factors are considered in the review
Oral Fluid DOA Tests

• First cleared in 2000

• Many drugs:
  – Amphetamines, barbiturates, benzodiazepines, THC, cocaine, cotinine, methadone, methamphetamine, opiates, PCP
  – Dozens cleared

• Most are central lab tests, few point of care oral fluid drug tests cleared yet
Oral Fluid DOA Tests

Advantages:
• Easy to collect sample
• Easily observable testing

Challenges:
• Collection method may impact results
• Sample collection for confirmation
• Sample collection adds variability (volume, etc.)
• What cutoff to use? – different than urine
Oral Fluid Collection Devices

• Oral fluid collection devices are class II and require 510(k) clearance (product code PJD)

• Oral Fluid collection devices can have a great impact on test performance

• Collection device must be specified with oral fluid tests and is cleared with the test when named as part of the test system
  – Drug recovery
  – Volume recovery
  – Use in test’s performance validation studies
Analytical Validity – Oral Fluid

Interference studies based on substances that may be present/interfere:

• Blood
• mouthwash
• Food
• Salt
• whitening strips
• Gum
• cigarette smoke
• etc…
Oral Fluid DOA Tests

Observed Performance Issue: Impact of collection kit

- Rapid Oral Fluid THC test submitted
- After sample collection, poor drug recovery
- THC in oral fluid sticks to collection container
- Inaccurate screening results
- No sample left for confirmation (and if collected using this device, would be incorrect as well)

**Example:**
- Marijuana:
  - Test designed to detect drug at or above 4 ng/mL
  - Data demonstrated that the test could not detect drug until there was > 255 ng/mL
- Cocaine:
  - Test designed to detect drug at or above 25 ng/mL
  - Data demonstrated that the test could not detect drug until there was > 63 ng/mL
Oral Fluid DOA Tests

Observed Performance Issue: Self-contained collection

- Device contains swab and test in one piece
- No sample reservoir
- No way to collect confirmation sample – parallel collection?
Oral Fluid DOA Tests

Observed Performance Issue: Dilution imprecision

• Oral fluid collection device uses a diluent/preservative
• Method of collection (e.g., swab) introduces variability
• Impacts screening results around the cutoff
• Poor correlation with sample reference value
Oral Fluid DOA Tests

Observed Performance Issue: Inappropriate cutoff

• New type of oral fluid test submitted
• No information in literature/precedents to support drug cutoff in oral fluid
• Clinical data collected to support chosen cutoff
• Device detected only prescribed (chronic, low dose) use, but did not detect abuse patterns
Oral Fluid DOA Tests

Observed Performance Issue: Cutoff set incorrectly

- Device designed inappropriately for intended use
- Example
  - claimed cutoff of 50 ng/mL
  - Detected positive results as low as 18 ng/mL
Hair DOA Tests

• First cleared in 2000

• All laboratory-based
Hair Collection Devices

• Hair drug test collection devices are class I and exempt from 510(k) clearance requirements, but are restricted devices

• If the collection device is offered over-the-counter (OTC), the screening test must be FDA-cleared

• This is the reason hair tests, even if they are laboratory-developed tests (LDTs), require FDA clearance
Analytical Validity – Hair

Studies based on substances that may be present/interfere, or may impact results:

• Hair treatments
  – Dyes
  – Permanents/straighteners
  – Shampoo
• Hair color/texture
• Wash buffers/wash steps
Hair DOA Tests

Observed Performance Issues:

• False negative results
• False positive results
• Variability in performance
• False results due to hair treatments
Resources: FDA website

• Device Classification Database -

• Device Advice
  http://www.fda.gov/cdrh/devadvice

• 510(k) Releasable Database -
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

• Register for “What’s New”
How can the FDA regulatory process for tests be facilitated?

**Communication!**

Sponsors should discuss their device with FDA as early as possible

A Pre-Submission should be used to discuss new tests prior to starting studies. Interactive process to discuss:

- Analytical and Clinical Data requirements
- Test-specific challenges can be discussed prior to the start of validation studies
Resources: 510k Review Summaries

## Resources: 510k Review Summaries

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<td><strong>Applicant</strong></td>
<td>QUEST DIAGNOSTICS, INC.</td>
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<tr>
<td><strong>Address</strong></td>
<td>10101 Renner Blvd. Lenexa, KS 66219 975</td>
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Resources: 510k Review Summaries

Decision Summary contains the information used to support clearance:

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<td>New Device</td>
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<th>C. Measurand:</th>
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<tr>
<td>Cocaine</td>
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<th>D. Type of Test:</th>
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<th>E. Applicant:</th>
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<td>Quest Diagnostics Incorporated</td>
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<table>
<thead>
<tr>
<th>F. Proprietary and Established Names:</th>
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<tbody>
<tr>
<td>Quest Diagnostics Urine Cocaine Metabolite EIA</td>
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<th>G. Regulatory Information:</th>
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<tr>
<td>21 CFR 862.3250</td>
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<tr>
<td>2. Classification:</td>
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<td>II</td>
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Summary

• Drugs of abuse screening tests provide convenient testing technology

• Screening tests should perform as intended and have adequate instructions for use

• FDA is committed to helping companies who wish to develop and market these types of products
Thank you!