FDA Regulation of Drugs of Abuse Tests

SAMHSA DTAB Meeting

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Courtney H. Lias, Ph.D.
Office of In Vitro Diagnostic Device Evaluation and Safety
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:

Acetaminophen	Methadone
Alcohol (serum and breath tests)	Morphine
Amphetamines	Opiates (including Oxycodone)
Barbiturates	Phencyclidine (PCP)
Benzodiazepines	Propoxyphene
Cocaine	Cannabinoids (marijuana)
Methamphetamines	Tricyclic Antidepressants

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?

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

Analytical Validity

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 (7^{th} 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 -
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm
- 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

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

Resources: 510k Review Summaries

New Search | Back To Search Results

Device Classification Name	Enzyme Immunoassay, Cocaine And Cocaine Metabolites
510(K) Number	K062929
Device Name	QUEST DIAGNOSTICS URINE COCAINE METABOLITE EIA
Applicant	QUEST DIAGNOSTICS, INC. 10101 Renner Blvd. Lenexa, KS 66219 975
Contact	Liuming Yu
Regulation Number	862.3250
Classification Product Code	DIO
Date Received	09/28/2006
Decision Date	12/18/2006
Decision	Substantially Equivalent - CLIA Submission (CS)
Classification Advisory Committee	Toxicology
Review Advisory Committee	Toxicology
Summary	Summary
FDA Review	Decision Summary
Type	Traditional
Reviewed By Third Party	No
Expedited Review	No

Resources: 510k Review Summaries

Decision Summary contains the information used to support clearance:

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k062929

B. Purpose for Submission:

New Device

C. Measurand:

Cocaine

D. Type of Test:

Qualitative

E. Applicant:

Quest Diagnostics Incorporated

F. Proprietary and Established Names:

Quest Diagnostics Urine Cocaine Metabolite EIA

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.3250

2. Classification:

   II

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!