

# Oral Fluid Drug Tests: FDA Perspective

DTAB Meeting

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# FDA

- Center for Devices and Radiological Health
- Office of Regulatory Affairs
- Center for Food Safety and Applied Nutrition
- Center for Biologic Evaluation and Research
- Center for Drug Evaluation and Research
- Center for Veterinary Medicine
- Center for Tobacco

# Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

- One Stop Shopping
  - Premarket *and* Postmarket Regulation of IVDs
- ~150 scientists, managers & support staff
- >1000 Premarket Applications /yr
- ~150 Compliance Actions /yr
- ~10,000 Adverse Event reports /yr
- Outreach/Education

# What is an IVD?

- In Vitro Diagnostic Tests are for:
  - Diagnosis
  - Screening
  - Prevention
  - Risk Assessment
  - Surveillance
  - First Response
  - Etc.
- Used in clinical laboratories
- Other settings (e.g., Point-of-Care/Over-the-Counter)

# Division of Chemistry and Toxicology Devices

- General Clinical Chemistry tests (Na<sup>+</sup>, K<sup>+</sup>, bilirubin, etc.)
- Cardiac Markers (i.e., Lipids/Cholesterol, CRP)
- Pregnancy tests
- Osteoporosis Markers
- Glucose tests (diabetes)
- Therapeutic Drug Monitoring
- Drugs of Abuse tests
- Etc.

# DOA Test Regulation

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

<b>Drugs</b>	<b>Drugs</b>
Acetaminophen	Methadone
Alcohol (serum and breath tests)	Morphine
Amphetamines	Opiates (including Oxycodone)
Barbiturates	Phencyclidine (PCP)
Benzodiazepines	Propoxyphene
Cocaine	Cannabinoids (marijuana)
Methamphetamines	Tricyclic Antidepressants
Etc.	

# Premarket Review

- All tests must establish adequate:
  - Analytical performance
    - How accurately does the test measure the drug?
    - How reliably?
  - Clinical performance
    - 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, performance summary

# Standards for Clearance

- 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

# Standards for Clearance

- 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)
    - Blood, mouthwash, etc. (oral fluids)

# Standards for Clearance

- Accuracy
  - Is the system accurate compared to a gold standard reference 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

# Standards for Clearance

- 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 must demonstrate that they are 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<sup>th</sup> grade)\
  - Human factors are considered in the review

# Standards for Clearance

- Observed Performance Issues:
  - Positive results when no drug present
  - Cutoff set incorrectly (e.g., positive results at -80% of claimed cutoff value)
  - Poor recovery of drug following pre-analytical steps
  - Too many false negative results at very high drug concentration

# Effective Design/Performance

- Established cutoffs:
  - Analytical studies only
- New cutoffs:
  - Sponsor provides data to establish that the cutoff is effective (safe and effective balance of FP and FN results)

# 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 DOA Tests

- Example: Impact of collection kit
  - Rapid Oral Fluid THC test submitted
  - After sample collection, drug recovery >10%
  - 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)

# Oral Fluid DOA Tests

- Example: Self-contained collection
  - Device contains swab and test in one piece
  - No sample reservoir
  - No way to collect confirmation sample

# Oral Fluid DOA Tests

- Example: 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

- Example: 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

# 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”
- Guidance Documents
  - Premarket Submissions and Labeling Recommendations for Drugs of Abuse Screening Tests - Draft Guidance for Industry and FDA Staff
    - (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071040.pdf>)
  - Guidance for Labeling for Over-the-Counter Sample Collection Systems for Drugs of Abuse Testing
    - (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM092793.pdf>)

# How can the FDA regulatory process for tests be facilitated?

- Communication!
  - Sponsors should discuss their device with FDA as early as possible
- A “Pre-IDE” should be used to discuss new tests prior to starting studies.  
Interactive process to discuss:
  - Regulatory path (classification, etc.)
  - 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**

# Resources: 510k Review Summaries

- Decision Summary contains the information used to support clearance

# Summary

- Rapid oral fluid tests for drugs of abuse should provide convenient testing technology
- FDA is committed to helping companies who wish to develop and market these types of products
- These devices are challenging to develop, and should demonstrate safety and effectiveness (including the ability to confirm results), and be labeled truthfully, prior to market