Status of Availability of FDA 510(k) Cleared Assays

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Laboratory Decisions for Oral Fluid Testing

- Type of collection device
  - Neat
  - Buffered
- Screening technology
  - Immunoassay
  - Alternate technology
- Confirmation technology
  - GC-MS(/MS)
  - LC-MS(/MS)

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Agenda

- Collection Devices
- ‘Oral Fluid Math’
- Commercial Immunoassays
- Q&A

Collection Devices

Options for Oral Fluid Sample Collection

Expectorated oral fluid (drooling, spitting)

- Potential issues with hygiene, frothing, speed and drug stability

Collection devices with pad only

- May not have volume indicator
- Additional laboratory sample preparation to remove drug from pad

Collection devices with pad and buffer

- Some devices indicate when adequate volume has been collected
- Stabilizes drugs during transportation
- Removes drug from the collection pad
- Prevents bacterial growth in biological specimens

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Devices Marketed to Collect Oral Fluid

- Finger Collector
- Oral Diffusion Sink
- Oral-Eze®
- ORALscreen™
- OraSure® / Intercept® / i2HE®
- Proflow Sialometer
- Salivette
- Quantisal™ / Quantisal™ II
- Versi·SAL™

Oral Fluid Specimen Collection Devices

- Types of oral fluid collections
  - "Neat" – i.e., undiluted/no buffer preservative solution
  - "Buffered" – i.e., device incorporates a buffer preservative solution (BPS)
- Oral Fluid collection device must meet FDA, HHS, and DOT specifications
  - Generally, "neat" devices are Class-1 (like urine kits) and "buffered" devices are Class-II Medical Devices (FDA)
  - HHS does not require FDA 510(k) Clearance (but….)
- For Regulated testing, a "Split" collection is required
  - HHS: "Split"→ Bilateral/simultaneous or Sequential (<2 min interval) collection
    - Buffered - Single (simultaneous or sequential) pads or dual ***(joined)*** pads placed in same region of oral cavity, then subdivided into two separate containers
    - Neat - – oral fluid is collected and split
      - May be a device that directs OF into two separate containers
  - DOT: Specimen must be "subdivided"
    - Buffered – Two different swabs that are adjacent to one another in oral cavity
    - Neat – oral fluid is collected and split
      - May be a device that directs OF into two separate containers

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Oral Fluid Collection Device Requirements (Regulated)

- Minimum 1 mL undiluted ("Neat") each, or other volume acceptable to NLCP required, for each "A" & "B" specimen
  - Specimen adequacy (volume) indicator required
  - If "Buffered", accuracy within +/-10%
- Specimen tube sufficiently transparent to assess volume and contents
- Tamper-evident seal must not obscure expiration date
- Components that ensure pre-analytical drug and drug metabolite stability
  - Stability (≥80%) of the drugs and/or drug metabolites for at least five days at room temperature (18-25 °C)
- Components that do not substantially affect the composition of drugs and/or drug metabolites in the oral fluid specimen
  - Recover ≥80% (but no more than 120%) of drug and/or drug metabolite in the undiluted ("neat") oral fluid at (or near) the initial test cutoff listed in the drug testing panel.
- Must be approved by HHS/NLCP for use by specified laboratory
  - NLCP requires laboratories to also verify: collection volume, diluent fill volume (if buffered), drug recovery and stability and cannot rely on manufacturer's FDA-clearance

Oral Fluid ‘Math’

Buffered Collection Systems
Cutoffs / Dilution Factors

- Two way to express cutoffs
  - "Diluted" – *i.e.*, without correction for dilution factor with BPS
    - *e.g.*, Intercept® (no sample adequacy indicator)
    - Listed as concentration in the ***specimen tube*** after dilution with BPS
  - "Neat" – *i.e.*, with correction for dilution factor with BPS
    - *e.g.*, Intercept ® i2HE™, Oral-Eze®, Quantisal™, Quantisal™ II (all have 1 mL indicator)
    - Listed as concentration in oral fluid in the ***oral cavity*** prior to dilution with BPS
      - Concentration in the specimen tube is lower, by the dilution factor, than that in the oral cavity
        - Assay requirements are driven by the concentration in specimen tube
    - HHS/DOT cutoffs listed as "neat"
    - Enables consistent cutoff and comparability irrespective of device/system used
- Dilution factors
  - 3x - Intercept® i2HE™, Oral-Eze® (1 mL oral fluid + 2 mL BPS)
  - 4x – Quantisal™, Quantisal™ II (1 mL oral fluid + 3 mL BPS)

Buffered Collection Systems
Immunoassay Labelling

- "Neat" testing systems
  - Assay labelling expressed in "***neat***" concentrations
  - Calibrator (and control) may be labelled at "***neat***" equivalent concentration or at ***"diluted"*** (*i.e.*, 'weighed-in' amount) concentration
  - *e.g.,* for an opiate assay with a 30 ng/mL cutoff labelling calibrators at a "***diluted***" concentration
    - Assay package insert (IFU) is 30 ng/mL
    - Listed calibrator concentration for a 3x dilution system is 10 ng/mL
    - Listed calibrator concentration for a 4x dilution system is 7.5 ng/mL
- "Diluted" testing systems
  - Assay and calibrator (and control) labelling expressed as "***diluted"*** concentrations
  - Not directly comparable with "Neat" systems!

Buffered Collection Systems
Confirmatory/Alternate Technology Testing

- Laboratories using buffered devices ***without*** a sample adequacy indicator generally use diluted concentrations and don't correct for dilution factor based on nominal volume collected
- Laboratories using buffered devices ***with*** a sample adequacy indicator may:
  - Utilize a "dilution factor" (corresponding to device used) for both calibrators and unknowns
    - Complicates the dilution factor math with high concentration samples requiring dilution
  - Prepare calibrators and controls at diluted concentrations and label it at "neat" equivalent concentrations
    - Similar approach as immunoassay test systems
    - Eliminates need for dilution factor on all samples
      - Only diluted high concentration samples have a dilution factor
    - Complicates using the same assay/calibration scheme if laboratory processes devices with different inherent dilution factors with BPS!

Commercially Available Oral Fluid Immunoassays

FDA Requirements

- FDA clears immunoassay test systems with a specified collection device
  - Cannot "mix and match" collection devices with different reagent systems
- Mandatory Guidelines do not require FDA clearance for initial (urine or oral fluid) testing reagents (10/2017) or oral fluid collection devices (10/2023)
- Non-Regulated testing ("E&I" labelling, **82 FR 31976**, 7/11/2017)
  - Does not require 510(k) clearance for all ***current*** analytes other than PCP when used for employment and insurance testing purposes
    - Limited to specified 'Product Codes'
- Regulated testing requires 510(k)
  - E&I limitation:

    Exemption is limited to test systems intended for employment and insurance testing that include a statement in their labeling that the device is intended solely for use in employment and insurance testing, and ***does not include test systems intended for Federal drug testing programs (e.g., programs run by the Substance Abuse and Mental Health Services Administration (SAMHSA), the Department of Transportation (DOT)****, and the U.S. military.)*
- Forensic Use Only (FUO)
  - Devices designed to be used ***only*** for criminal justice (*e.g.*, probation/parole, court-ordered) testing
- Timeline for assay development
  - 510(k) cleared: 2-4 years, depending on antibody availability
  - E&I labelled, 1-1.5 years faster

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IA Testing Systems

Collector	OFMG	Intercept ®	Intercept ®	*i2he* ™ (FUO)	Oral-Eze ®	Quantisal ™	Quantisal ™ / Quantisal ™ II
Adequacy Indicator		**No**	**No**	**Yes**	**Yes**	**Yes**	**Yes**
Assay Manufacturer		**OraSure**	**OraSure**	**Thermo Fisher**	**Thermo Fisher**	**Immunalysis**	**Immunalysis**
Technology		**ELISA**	**ELISA**	**CEDIA ™ (FUO)**	**CEDIA ™**	**HEIA FUO**	**SEFRIA ™**
Cutoff Listed as Neat/Diluted (Factor)	Neat	Diluted (X3)	Nominal Neat Equivalent (X3)	Neat (X3)	Neat (X3)	Neat (X4)	Neat (X4)
Marijuana	4	1*	3*	3*	3*	8* [1]	4† (HEIA)
Cocaine / Benzoylecgonine	15	5*	15*	15◊	15‡	20*	15†
Opiates (Codeine / Morphine)	30	10*	30*	30◊	30‡	40*	30†
Opiates (Hydrocodone / Hydromorphone)	30	△	△	△	△	△	30†
Opiates (Oxycodone / Oxymorphone)	30	△	△	30◊	30◊ FUO	△	30‡
6-AM	4	△	△	△	△	△	4†
Phencyclidine (PCP)	10	1*	3*	3*	3*	10◊	10‡
Amphetamine	50	100*	300*	150*	150*	50◊	50†
Methamphetamine	50	40*	120*	120*	120*	50◊	50‡
MDMA/MDA	50	△	△	△	△	△	50†

*	**Not Compliant with HHS &/or FDA Requirements**
◊	**Not Compliant with FDA Requirements - Correct Cutoff**
†	**E&I Listed - Correct Cutoff**
‡	**FDA Cleared - Correct Cutoff**
△	**Not Available**

[1] Cutoff and color corrected June 6, 2024

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Current Status of Ferally-Mandated Immunoassay Screening

- While there is likely one FDA-cleared, buffered collection system that meets HHS/DOT requirements, it is not yet commercially available
- Not all HHS analytes have FDA-clearance for the paired immunoassay test system
  - Currently, only three 510(k) cleared OF assays at SAMHSA cutoffs
  - The other seven (7) assays are E&I labelled and have been commercialized for non-regulated testing
  - Some labs may opt for neat/unbuffered systems (using Alternate Technology for Initial Testing) which still require extensive validation

Q&A

Thank You!

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