SMART®: A Breath-Based Technology to Definitively Document Adherence to HIV Medications (Oral and Microbicide Gels)

Novel Technologies and Assays for Adherence Assessment and Support

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Conflict of Interest Disclosure

- Professor, University of Florida
- Chief Science Officer, Xhale, Inc. and Co-founder
- Stock Ownership in Xhale

Xhale is developing patient centric technologies and has licensed > 70 patents from the University of Florida. I may benefit financially if these products are commercially successful.
The SMART® Adherence System
(Self Monitoring and Reporting Therapeutics)

- Breath-based system that accurately verifies that the right **person** took the right **dose** of the right **medication** via the right **route** at the right **time**
- Enables improvement in medication adherence and persistence
- By providing a definitive measure of adherence, SMART® can help identify and correct behavioral factors associated with poor medication adherence and clinical outcomes
SMART® Adherence System

**SMART® Medication**
FDA food (GRAS) additives incorporated into a capsule, as adherence-enabling markers (AEMs), with a medication to generate exhaled drug ingestion markers (EDIMs)

**Patient / Study Participant**
Trial participant at home exhales into SMART® device; biometric facial ID used to identify

**SMART® Device**
Definitive breath analysis proves ingestion; wirelessly reports adherence in real-time

**Better Outcomes**
Monitored call-back within minutes to participants who miss doses = adherence increase and higher success

- Increase in adherence
- Enhanced data quality & integrity
- Successful trial outcome

8th International Conference on HIV Treatment and Prevention Adherence
SMART® Adherence: How Does It Work?

1. Patient reminded by SMART® device and swallows SMART® medication
2. Medication transits esophagus to stomach
3. Adherence-enabling marker (AEM) released in stomach
4. AEM absorbed in stomach and small intestines
5. AEM or metabolite of AEM transported via blood to the lungs and exhaled
6. Breath sample blown directly into SMART® device
7. SMART® device analyzes breath sample for presence of an exhaled drug ingestion marker (EDIM), which could be the AEM and/or a metabolite of AEM
8. If the EDIM is detected, definitive confirmation that medication was ingested
9. Data stored and transmitted

Route: Oral vs Transdermal (e.g., Vaginal, Rectal) – same principle
Any Medication Can be Made “SMART”

SMART® Medications

- FDA designated food additives (GRAS) can be packaged with any CTM or marketed drug to create a SMART® drug
- Any route of administration: oral, transdermal (skin, vaginal), inhalation, etc.
- Any solid oral dosage form (SODF): tablets, capsules, liquid formulations, ODTs
2-Butanol: An Ideal AEM

2-butanol (methyl ethyl ketone, MEK)

- Simple aliphatic alcohols are significantly absorbed in stomach
- 22 secondary alcohols are in the GRAS flavorant database \( \Rightarrow \) 22 unique ketones
Incorporation of AEMs into SODFs

1. FDA (October 2011) advocates the incorporation of food additives (GRAS flavorants) as physical-chemical identifiers (PCIDs) into solid oral dosage forms (SODFs) to ensure drug authenticity.

2. SMART® is identical but medical application is medication adherence
   • the AEMs are PCIDs
SMART® Adherence Device
SMART® miniature gas chromatograph (mGC) device assigned to each study participant or patient

Typical EDIM Breath PK

Concentration of Adherence Marker in Human Breath (ppb)

- 2-butanone (n = 30)
- 2-pentanone (n = 30)

Time (min)

LOD
Capabilities of SMART® Device

- Easy to use (1st grade level) – “1 button”
- Patterns of EDIMs - verify adherence with excellent sensitivity/specificity
- Biometric authentication (i.e., facial recognition) for definitive adherence
- Acetone and isoprene confirm breath matrix
- Ethanol detection in blood
- Remotely monitors mGC function

- Instructions: visual and verbal (any language)
- Orchestrates info exchange among subject, monitoring personnel, and database
- Adherence data (e.g., raw chromatograms with facial recognition, signal processing, peak detection, mGC operating parameters, yes/no adherence status) automatically uploaded (WiFi and/or cell phone) to central data repository and stored locally on device
### SmartGC Device Output

**Available Devices**

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SMART® Performance in Clinical Studies

- 29 human studies (oral, SL, and vaginal microbicide)
- 821 experiments in 176 subjects with 6,010 breath analyses
- Key outcomes:
  - POC demonstrated for oral, SL, and vaginal drug administration routes
  - Optimized SMART® mGC devices with IT developed
  - AEM packaging achieved (i.e., long term stability in small hard gel capsules using std accelerated and real time capsule testing techniques)
  - 100% accuracy across all routes of administration
  - $\approx 90\%$ and $\approx 100\%$ of subjects had detectable breath markers (EDIMs) at 5 and 10 min, respectively, post-ingestion of capsules containing AEMs
  - Acceptable variability in human biology (inter $>>$ intra)
  - Acceptable usability in HIV/AIDS patients with oral therapy
  - No interference from food or large volumes of liquid
  - No effect of AEMs on API dissolution w different BCS drug classes
Use of SMART® with Microbicide Gels

- We hypothesized that 2° alcohol-based ester taggants added to vaginal gels would generate exhaled alcohol and ketone metabolites and provide a “breath test” for vaginal gel use
  - 2 gels: TFV placebo (4 ml) and HEC (1 ml)
  - 4 esters (30 mg): 2-butyl acetate: $\Rightarrow$ 2-butanol $\Rightarrow$ 2-butanone
    - 2-pentyl-acetate: $\Rightarrow$ 2-pentanol $\Rightarrow$ 2-pentanone
    - isopropyl butyrate: $\Rightarrow$ isopropanol $\Rightarrow$ acetone
    - 2-pentyl butyrate: $\Rightarrow$ 2-pentanol $\Rightarrow$ 2-pentanone

- Same formulations administered dermally (forearm) to determine if skin administration might confound the system
- 8 women crossed over to the various formulations on separate visits
- Breath measurements made with SMART® mGC sensor at various times pre- and post-application of the gel formulations
SMART® with Microbicide Gels – Results

- Acetate-based esters in TFV gel and HEC (and related metabolites) rapidly appeared in breath: ester > ketone > alcohol levels
- Breath markers persisted at least 60 min
- Butyrate-based esters did not generate any breath markers
- No ester given dermally generated breath markers
- Mild (self resolving) AEs with vaginal application
  - mild burning (37.5%)
  - “bubble gum” taste (11%)
- Conclusion: SMART® appears feasible with microbicides; dose of ester can be reduced

Data shown is mean ± SD LOD, limit of detection

Use of SMART® with Microbicide Gel

- Determine the presence/absence of taggants and their metabolites in the breath, and measure their breath kinetics over 75 min, following gel and condom used at ≥ 1 day interval:
  - 4 ml TFV placebo gel ± 15 mg 2-pentyl-acetate = tagged and untagged gel
  - 1 ml HEC as condom lubricant ± 15 mg 2-butyl acetate = tagged and untagged condoms

- Assessments made when gel and condom used alone and together
- Assess the accuracy of the breath test to detect tagged vs. untagged vaginal products (gel or condom), applied under direct observation.

Conclusion:
SMART was 100% accurate in identifying placement of tagged (or untagged) gel and condom, confirmed by the presence (or absence) of taggants (and metabolites) in breath.

Current Status of SMART®

**Completed**
- Design lockdown, mass manufacturable
  - Sub-ppb sensitivity and excellent specificity to relevant EDIMs
  - Cost effective, 5 yr life span; Q 6 month refurbishing
  - 10-15 breath samples on single battery charge
  - 510(k) clearance Q1 2013
  - Developing World (dW): SMART® mGC battery recharge via small 12V solar panel; Usability and effect of environmental temperatures

**Ongoing**
- AEM packaging: Type IV Drug Master File (DMF) as excipients
- Aiming for 2 year AEM formulation stability with soft and hard gel caps (no migration)
- dW: Needs for oral HIV meds unchanged but unique for Microbicide Gels
Next Steps: Incorporating AEMs into SODFs

API Source
1. Tablet
2. Powder
3. Capsule

+ SMART® SODF Meds

Adherence-Enabling Marker (AEM) Solutions for Incorporation in SODF
Developed through Partnerships with Leaders in Formulation Sciences and Dosage Form Delivery

R&D Endpoints:
1. Mass CTM filling processes available
2. Minimal-to-no effect on API CMC or BA
3. No extra CTM steps
4. Long term stability of AEM formulation within smart SODF
5. Excellent AEM formulation performance (breath PK of EDIMs)
Next Steps: Incorporating AEMs into Microbicide Gels

**API Source**
Microbicide Gels (e.g., Tenofovir) located in syringe applicator

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**AEM Location in Syringe**
1. Double barrel syringe: a) 4 ml Tenofovir gel, b) 0.2 ml Tenofovir placebo gel containing $\approx 10-30 \mu L$ AEM formulation; or One barrel syringe with AEMs at syringe tip
2. Alter Microbicide Gel CMC: place AEMs directly in Gel (e.g., partially substitute glycerin with 2-butanol)

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**SMART®**

- Microbicide Gels

**Design Requirements**
1. EDIM half life in breath? 1-2 hr versus longer
2. Definitive adherence
3. No effect on gel viricidal activity or HIV transmission
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SMART® References