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

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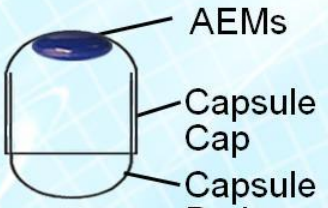
SMART® Adherence System

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)



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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

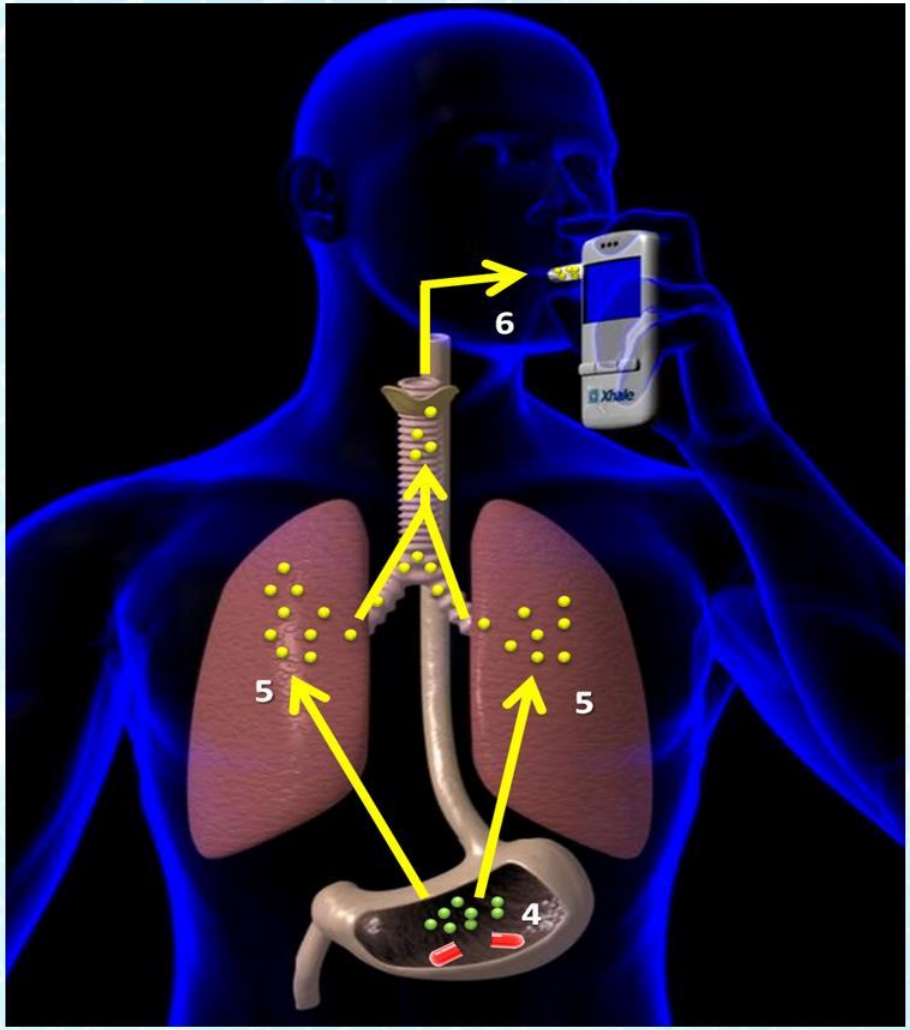
Better Outcomes

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*

Confidential

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

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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

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2-Butanol: An Ideal AEM

2-butanol

= AEM

$C_4H_{10}O$
MW=74.12
BP=99 °C
$K_H=C_L/C_G=2699$
LD_{50} PO rat = 6.48 g/kg
PDE = 300 mg/day (Q3C Guidance)
FDA Direct Food Additive (GRAS)

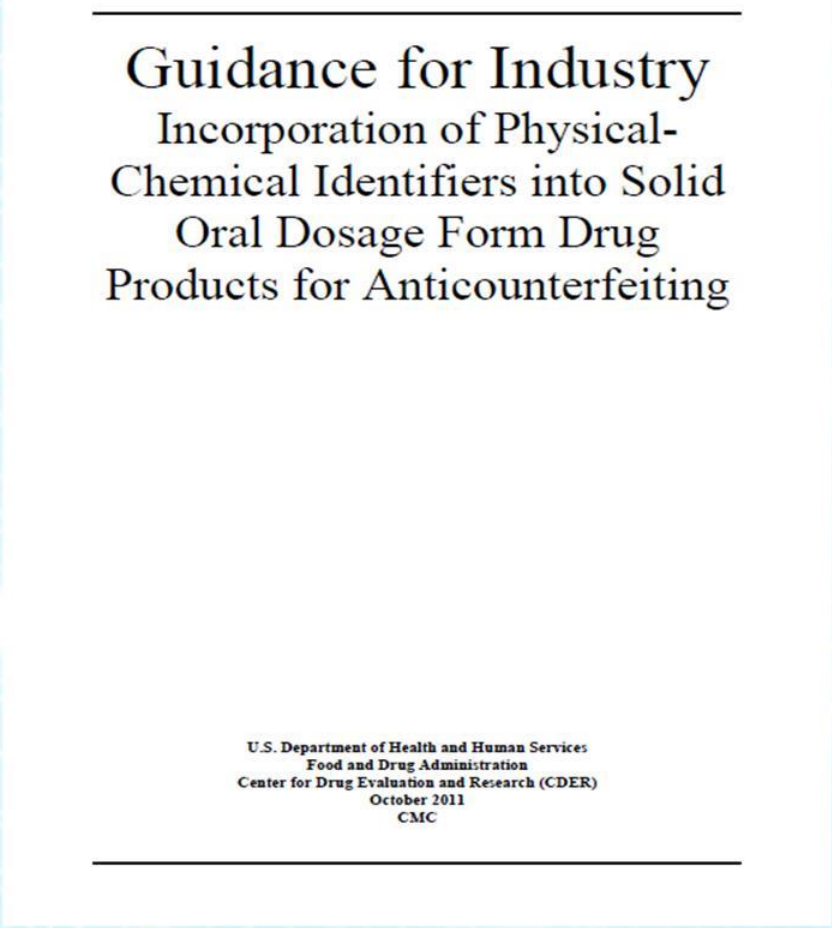
2-butanone (methyl ethyl ketone, MEK)

= EDIM = metabolite of AEM

C_4H_8O
MW=72.10
BP=80 °C
$K_H=350$
LD_{50} PO rat = 2.737 g/kg
PDE = 104 mg/day (Q3C Guidance)
FDA Direct Food Additive (GRAS)

- Simple aliphatic alcohols are significantly absorbed in stomach
- 22 secondary alcohols are in the GRAS flavorant database ⇒ 22 unique ketones

Incorporation of AEMs into SODFs



Guidance for Industry

Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting

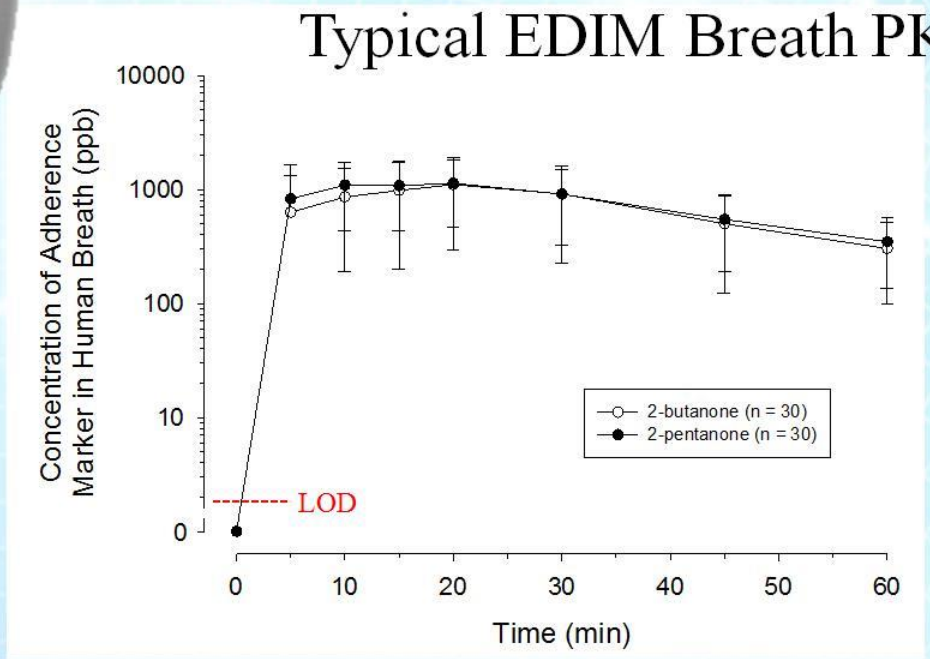
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2011
CMC

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



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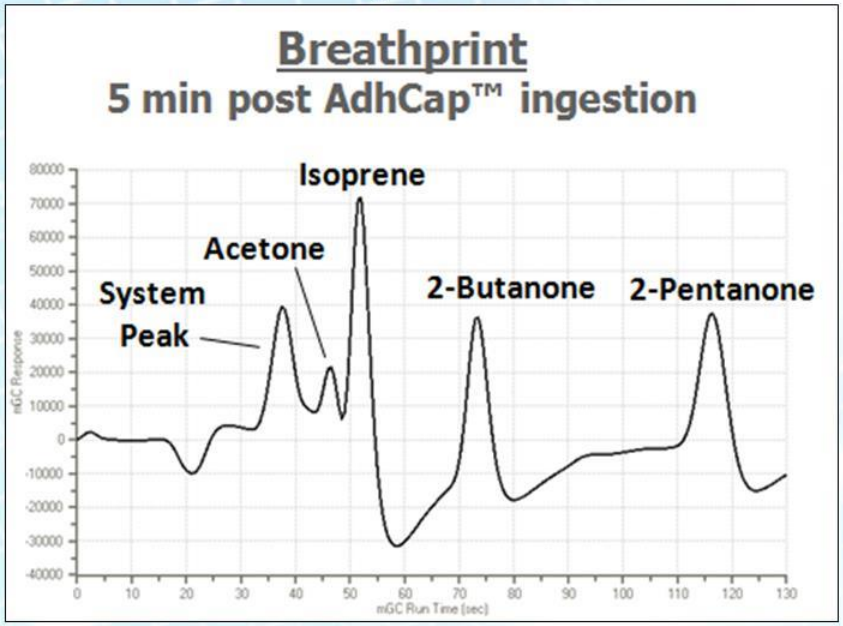
Capabilities of SMART® Device



- 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

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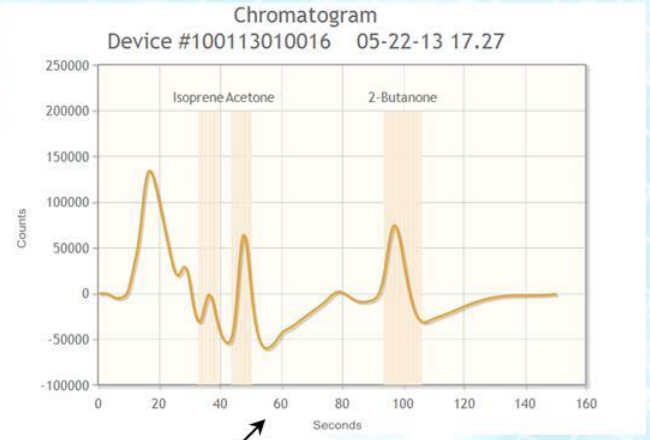
Real time Internet Logging of SMART® Adherence Data via Wireless Communication



SmartGC
Device Output

Available Devices

Device ID: 100113010016

Create Peaks CSV

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000000000000
100112070007
100112070013
100112080002
100112120001
100112120002
100112120003
100112120004
100113010001
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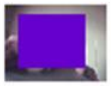
05-22-13 17.27		Log	Status	Raw Data	D1 Data	Peaks (2Hz) (Seconds)	Chromatogram
05-22-13 17.12		Log	Status	Raw Data	D1 Data	Peaks (2Hz) (Seconds)	Chromatogram
05-22-13 17.03		Log	Status	Raw Data	D1 Data	Peaks (2Hz) (Seconds)	Chromatogram
05-22-13 16.52		Log	Status	Raw Data	D1 Data	Peaks (2Hz) (Seconds)	Chromatogram
05-22-13 16.42		Log	Status	Raw Data	D1 Data	Peaks (2Hz) (Seconds)	Chromatogram
05-22-13 16.22		Log	Status	Raw Data	D1 Data	Peaks (2Hz) (Seconds)	Chromatogram

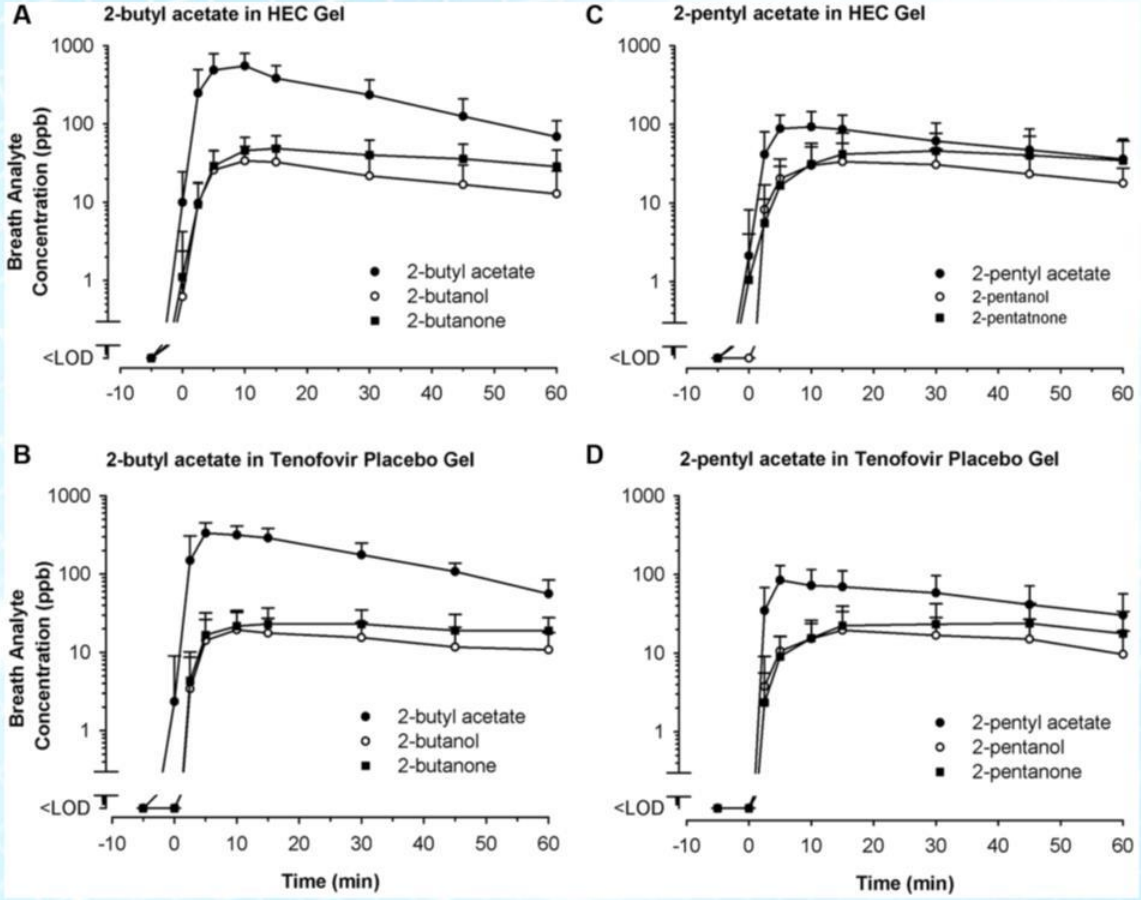
SMART® Performance in Clinical Studies

- 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
  - ≈90% and ≈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 2º 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: ⇒ 2-butanol ⇒ 2-butanone
    2-pentyl-acetate: ⇒ 2-pentanol ⇒ 2-pentanone
    isopropyl butyrate: ⇒ isopropanol ⇒ acetone
    2-pentyl butyrate: ⇒ 2-pentanol ⇒ 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

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Ref: Morey-TE et al: *J Clin Pharmacol*, 53(1):103, 2013

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:

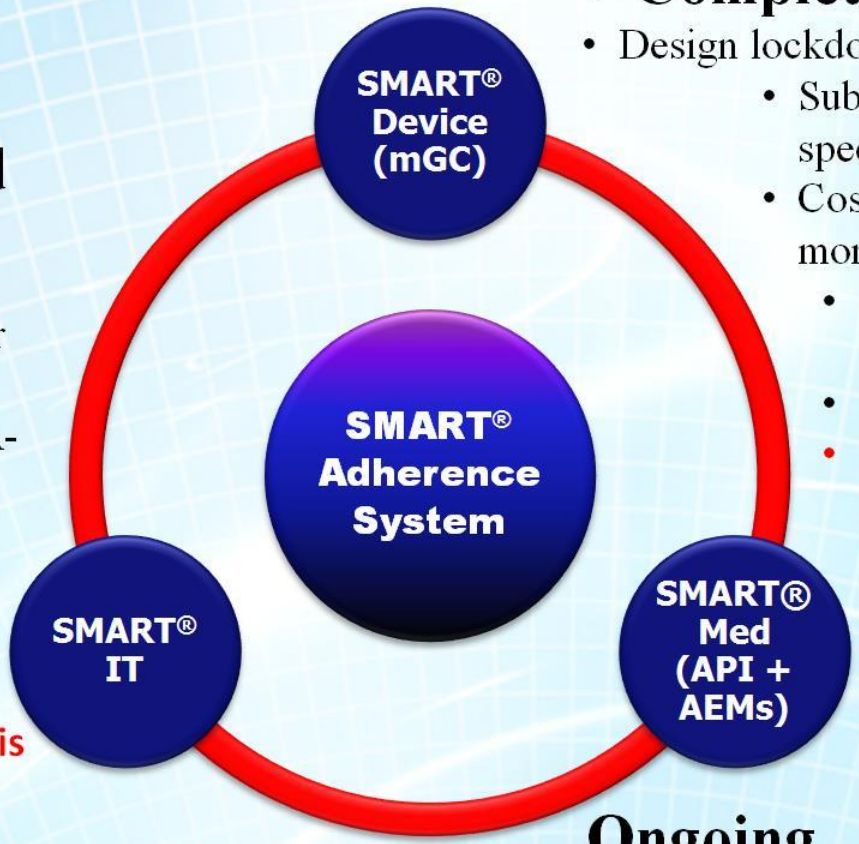
SMART was 100% accurate in identifying placement of tagged (or untagged) gel and condom, confirmed by the presence (or absence) of taggants (and metabolites) in breath.

Reference: van der Straten-A et al: *AIDS Behav*, Epub ahead of print, Jan 13, 2013

Current Status of SMART®

✓Completed

- Communication stakeholders via WiFi and cellular routers with complete HIPAA-compliant datasets
- **dW: GSM frequency band for cellular communication is viable**



✓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**

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Next Steps: Incorporating AEMs into SODFs

API Source

1. Tablet
2. Powder
3. Capsule

+

Adherence-Enabling Marker (AEM) Solutions for Incorporation in SODF

Developed through Partnerships with Leaders in Formulation Sciences and Dosage Form Delivery

→ **SMART® SODF Meds**

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)

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Next Steps: Incorporating AEMs into Microbicide Gels

API Source

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

+

AEM Location in Syringe

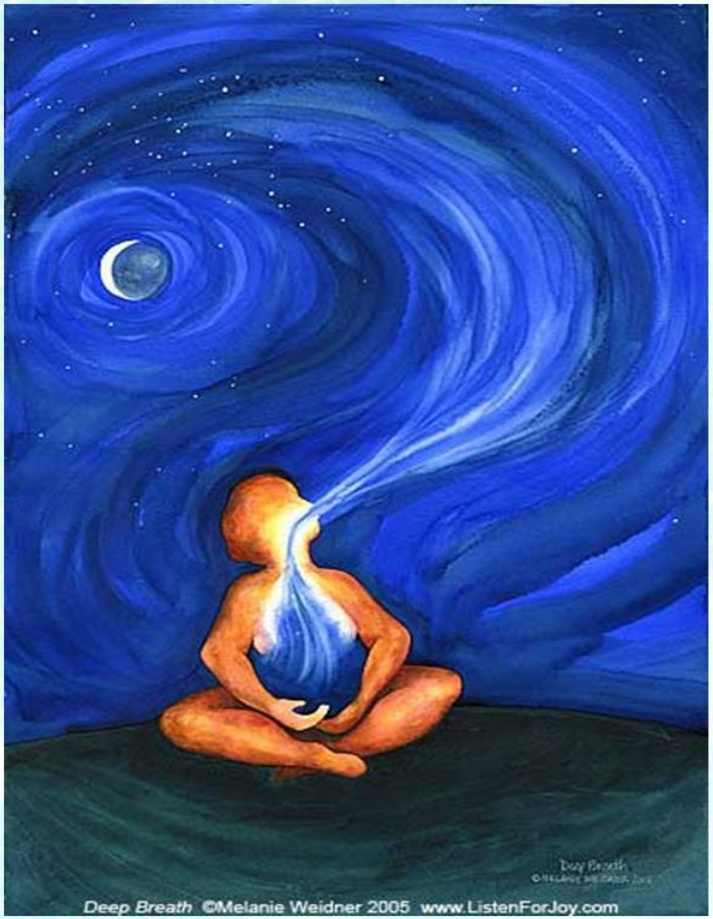
1. **Double barrel syringe: a) 4 ml Tenofovir gel, b) 0.2 ml Tenofovir placebo gel containing ≈10-30 µL AEM formulation; or One barrel syringe with AEMs at syringe tip**

2. **Alter Microbicide Gel CMC: place AEMs directly in Gel (e.g., partially substitute glycerin with 2-butanol)**

→ **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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Xhale
RTI
University of California – San Francisco
University of Washington

SMART® References

1. van der Straten-A et al: *AIDS Behav*, Epub ahead of print, Jan 13, 2013
2. Morey-TE et al: *J Clin Pharmacol*, 53(1):103, 2013
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