NIDA Development of a Standardized E-Cigarette to Support Clinical Research

Kevin Walton, PhD
Chief, Clinical Research Grants Branch
Division of Therapeutics and Medical Consequences
National Institute on Drug Abuse, NIH
NIDA and NIH Interest in E-Cigarettes

How safe are they? Are they addictive? Are they a gateway to smoking? Do they have a role for harm reduction and cessation? What are the issues for vulnerable populations: youth, mentally ill, pregnancy?

How to answer these questions?

• Some can only be answered in preclinical and clinical studies.
• These studies may need devices with known aerosol / delivery characteristics.
• Clinical studies often need FDA review, requiring a detailed data package describing the device components and operation.
• Availability of a commercial device throughout a study can be uncertain.
How is NIDA facilitating e-cigarette research?

• In 2014, NIDA issued a contract solicitation (SBIR) to develop a Standardized Research E-Cigarette (SREC) with an associated data package.

• Four companies received Phase 1 contracts, NJOY LLC will be the first to complete Phase 2.

• Devices and refills will be available by 4Q 2017.

• NJOY will sell the SREC directly to researchers together with permission to reference the data package for FDA submissions.
Key features of the SREC

• E-liquids made under GMP-like conditions (to allow use in clinical studies).
• Fully characterized e-liquid and aerosol.
• Tobacco flavor, nicotine-containing and placebo e-liquids.
• Unique battery connector and sealed cartridges limit use to the characterized e-liquid.
• Reproducible aerosol delivery from start to end of cartridge & battery charge.
• Demonstrated nicotine delivery (pharmacokinetics).
# Technical Characteristics

<table>
<thead>
<tr>
<th>E-LIQUID</th>
<th>SREC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>COMMERCIAL&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puffs (3 s) per Cartridge</td>
<td>&gt; 350</td>
<td>Variable</td>
</tr>
<tr>
<td>Nicotine Concentration</td>
<td>15 mg/mL</td>
<td>7-21 mg/mL</td>
</tr>
</tbody>
</table>

### AEROSOL CHARACTERISTICS (per 10 puffs)

<table>
<thead>
<tr>
<th></th>
<th>SREC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>COMMERCIAL&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>1 mg</td>
<td>0.3 – 3 mg</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>1 μg</td>
<td>0.6 - 5 μg</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>0.9 μg</td>
<td>0.4 – 21 μg</td>
</tr>
<tr>
<td>Acrolein</td>
<td>0.2 μg</td>
<td>? – 1.4 μg</td>
</tr>
</tbody>
</table>

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Pharmacokinetic nicotine delivery: SREC vs User’s own device

Evening before study, subjects arrive at residential facility to ensure abstinence

**Day 1: Nicotine delivery by “own device”**

1. 10-inhalations over 4.5 minutes, followed by 2h abstinence with regular blood draws.
2. Over the next 6h, *ad lib* use with regular blood draws.
3. After *ad lib* session, subjects return home with SREC to gain familiarity.

**Day 2, Evening: Subjects return to facility for overnight abstinence**

**Day 3: SREC is evaluated using procedure above**
Mean Pharmacokinetic Profiles (± SD)

**Cmax (ng/mL)**

<table>
<thead>
<tr>
<th></th>
<th>Own</th>
<th>SREC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>11.08</td>
<td>17.68</td>
</tr>
<tr>
<td>Variance</td>
<td>71.31</td>
<td>306.69</td>
</tr>
<tr>
<td>Observations</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.21</td>
<td></td>
</tr>
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</table>

**Tmax (min)**

<table>
<thead>
<tr>
<th></th>
<th>Own</th>
<th>SREC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>9.07</td>
<td>5.71</td>
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<tr>
<td>Variance</td>
<td>42.69</td>
<td>0.99</td>
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<tr>
<td>Observations</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.06</td>
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Funding Announcement PAR-17-156
Evaluating the NIDA Standardized Research
E-Cigarette in Risk Reduction and Related Studies

The SREC is not restricted to NIDA research

- Characteristics influencing e-cigarette use relative to other tobacco products
- Characteristics affecting e-cigarette addictive potential
- Factors influencing dual use or switching between combusted tobacco and e-cigarettes
- Factors influencing e-cigarette appeal to smokers in vulnerable populations
- Health effects of e-cigarette aerosol – directly and second-hand
Overall Research Direction

Harm Reduction is the current focus
(Smoking/Nicotine Cessation considered for the future)

• Harm Reduction studies reviewed by FDA Center for Tobacco Products (CTP).
  - We expect the SREC Product Master File will support the device’s use as an Investigational Tobacco Product.

• Smoking/Nicotine Cessation is a therapeutic indication, regulated by FDA Center for Drug Evaluation and Research (CDER).
  - Investigational New Drugs require evidence of safety in animals prior to “First in Human” studies.