Responsible Practice in E-Vapour Products (EVP) Product Stewardship

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Responsible practice can be divided into 3 areas:

1. Pre-market product stewardship
2. Batch release
3. Post-market product stewardship
Pre-market product stewardship

<table>
<thead>
<tr>
<th>Risk assessment of ingredients &amp; materials</th>
<th>Device Quality Testing</th>
<th>Aerosol chemistry &amp; <em>in-vitro</em> toxicology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performed by registered Toxicologist</td>
<td>Stability testing: normal &amp; accelerated</td>
<td>Focus on nicotine, carbonyls &amp; metals</td>
</tr>
<tr>
<td>Ingredients pharmacopeia / food grade</td>
<td>Extractables &amp; Leachables</td>
<td>Particle size measurements &amp; characterisation</td>
</tr>
<tr>
<td>No CMRs / respiratory sensitizers</td>
<td>Microbiological testing</td>
<td><em>In-vitro</em> biological testing</td>
</tr>
</tbody>
</table>

Please note that the views and arguments presented in this paper have been designed to encourage and stimulate debate and do not necessarily reflect Fontem Ventures' position.
Focus today on batch release and post-market product stewardship

- Emphasis on testing approaches and strategies
Batch Release
Manufacturing Quality - Process Control


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Batch release
Traceability

- Device and packaging authenticity
- Corrective actions

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Batch release

Testing

Solid investment in quality and testing provides reassurance to consumers and regulators and contributes to development of the e-vapour sector.

- DFMEA
- PFMEA
- CoA & CoC batch reconciliation
- Puff count verification
- Liquid batch nicotine assay
- Bioburden testing
- Final device nicotine assay
Post-Marketing Surveillance

Why is it important?

"In a nutshell, best estimates show e-cigarettes are 95% less harmful to your health than normal cigarettes"

All of the evidence suggests that the health risks posed by e-cigarettes are relatively small by comparison but we must continue to study the long term effects.

“ENDS use poses serious threats to adolescents and foetuses”
## Regulatory Frameworks

### What is pre-market & what is post-market?

<table>
<thead>
<tr>
<th>EUTPD2 (Article 20)</th>
<th>UK MHRA (Medicinal License)</th>
<th>US ENDS PMTA</th>
</tr>
</thead>
</table>
| Notification to contain:  
- List of ingredients  
- Toxicological data  
- Nicotine dosage  
- Production process description | Meet the essential requirements of Medical Device Directive 93/42/EEC (Class Iia)  
ISO 13485 Quality Management System | Detailed descriptive information  
- Production process description  
- Product formulation & design  
- Conditions for using the product and instructions for use  
- Discussion demonstrating how the data contained in the PMTA is appropriate for the protection of public health |
| Nicotine containing liquid to be placed in dedicated containers with volume <10ml | Dossier to include relevant information on:  
- Development  
- Manufacturing process  
- Characterisation & properties  
- Quality control operation & requirement  
- Stability  
- Emission testing: Nicotine, Carbonyls & Metals | Environmental assessment |
| Nicotine containing liquid to be placed in dedicated containers with volume <10ml | Manufactured at sites which operate with principles of GMP  
Extensive safety literature review | Scientific studies to include  
- Ingredient assessment  
- Aerosol chemistry (HPHCs & particle size)  
- Stability, E&L  
- In-vitro toxicology studies  
- Bridging studies  
- Pharmacokinetics  
- Exposure response  
- Likelihood of initiation/cessation  
- Abuse liability assessment  
- Impact to both user & bystander |
| Liquid in tanks and cartridges is <2ml | ‘Abridged application - PK study with PD assessment (VAS for nicotine) | |
| Only ingredients of high purity to be used | | |
| Doses delivered at consistent levels | | |
| Emission testing: Nicotine, Carbonyls & Metals | | |

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Increasing pre-market requirements depending on regulatory framework

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Post-marketing surveillance
The ‘4 Big’ Questions

1 What impact do EVPs have on consumers?
2 What impact do EVPs have on bystanders?
3 Do EVPs renormalise or act as a gateway to tobacco?
4 What is the addictiveness and health impact of nicotine?
### Post-marketing surveillance

#### Q1 Impact of EVP on Consumers

<table>
<thead>
<tr>
<th>Clinical Studies Registered</th>
<th>Clinical Studies published since 2011</th>
<th>Outcomes investigated in these studies</th>
</tr>
</thead>
</table>
| >100 studies registered on ClinicalTrials.gov | >30 scientific publications for Randomised Clinical Trials identified | - Safety and Tolerability  
- Nicotine PK  
- Smoking reduction  
- Subjective effects  
- EVP vs Nicotine Inhalator  
- EVP awareness, use and harm perceptions  
- Cardiovascular function  
- Evaluation of weight gain  
- Use amongst smokers with mental illness  
- Consumer behaviour & Topography  
- Biomarkers of Exposure & Biomarkers of Biological Effect |

Huge investment and research invested in clinical studies

>10 scientific publications for Non-Randomised Clinical Trials identified
Post-marketing surveillance
Q1 Impact of EVP on Consumers

Registry
- “Real world” data
- Large “N”
- Observational
- Hypothesis generating
- Effectiveness
- Flexible, sub-studies
- Opportunistic or mandatory

Clinical Trial
- Formatted data (selection criteria)
- Small “N”
- Usually randomized
- Hypothesis driven
- Efficacy
- Powered
- Usually mandatory

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Post-marketing surveillance
Q1 Impact of EVP on Consumers

Pharmacokinetic: Mean (-SEM) Plasma Nicotine Concentration (ng/ml) vs Time (min)

Biomarkers of Exposure: Study day, All subjects starting study on day 1 of smoking cessation program

Exposure response studies:
- Vital signs
- ECG & LFTs
- Biomarkers of Exposure & Effect
- Subjective questionnaires
- Adverse events
- Haematology & Clinical biochemistry

Registries:
- Active: Active collection of data, registries, specific studies, AE reporting
- Passive: Spontaneous reports, submitted by manufacturer, healthcare professional.

Increased duration of use; ‘artificial’ to ‘real life-settings’
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Post-marketing surveillance
Q2 Impact of EVP on bystanders

Detected at low levels at all sampling times and substantially below respective WHO or Indoor Air Quality Guideline levels

**Formaldehyde**

<table>
<thead>
<tr>
<th></th>
<th>Background</th>
<th>Pre-vaping</th>
<th>Vaping</th>
<th>Post-vaping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airborne concentration (mg/m²)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.04</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Acrolein**

- UK WEL (8 hrs) [0.23 mg/m²]
- LOD [0.002 mg/m²]

**Acetaldehyde**

- EU Indoor Air Quality Guideline [0.2 mg/m³]

Room temperature: 22°C 25°C 28°C 27°C
Relative humidity: 44% 56% 57% 50%

Source: O’Connell *et al.* An Assessment of Indoor Air Quality before, during and after Unrestricted Use of E-Cigarettes in a Small Room. *Int. J. Environ. Res. Public Health* 2015, 12, 4889-4907.

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Post-marketing surveillance
Q2 Impact of EVP on bystanders

No difference in the levels of nicotine detected on the surfaces before, during or after use of both the closed and open system e-cigarettes

Source: O’Connell et al. An assessment of nicotine levels on office surfaces before, during and after use of electronic cigarettes. In preparation for poster presentation at Society for Research on Nicotine and Tobacco (SRNT), Italy, 2017

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Post-marketing surveillance
Q3 Does EVP act as a gateway to tobacco

Two behavioural studies conducted by the UK Centre for Substance Use Research (funded by Fontem Ventures)

- Investigating EVPs and smoking initiation, relapse and dependency on nicotine
  
  - 24,000 vapers enrolled

- EVPs are a roadblock to smoking initiation not a gateway
  
  - EVPs de-normalise smoking, rather than re-normalise it
Dynamic Population Modelling

Probability that never-user will come to smoking via EVPs whereas if EVPs does not exist they would still never-smoker

Gateway effect \( P3 + P4 - (P1 - P2) \)

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### Post-marketing surveillance

#### Q4 Addictiveness & Health Impact of Nicotine

| Nicotine is regarded as addictive | • Nicotine is regarded as addictive  
|                                  | • EVPs meet consumers smoking-ritual needs  
|                                  | • Growing evidence that EVPs support smoking cessation |
| No toxicity concern             | • No toxicity concern with nicotine in the small doses in an EVP |
| Long term health risks?         | • USSG: Science is inadequate to conclude either way on nicotine and cancer  
|                                  | • Any long term risks are unknown  
|                                  | • Further long term research is required |
1 What impact do EVPs have on consumers?
2 What impact do EVPs have on bystanders?
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Consumer perception and behaviour assessment
Post-market surveillance

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Summary
Responsible Practice in EVP Product Stewardship

Pre-market product stewardship
- Risk assessment of ingredients & materials
- Device quality testing
- Aerosol chemistry & in-vitro toxicology

Batch release
- Process Control
- Batch traceability
- Specification testing

Post-market product stewardship
- Long-term health effects
- Impact to bystanders
- Abuse liability

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