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

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Responsible practice can be divided into 3 areas:
Pre-market product stewardship

Risk assessment of ingredients & materials
- Performed by registered Toxicologist
- Ingredients pharmacopeia / food grade
- No CMRs / respiratory sensitizers

Device Quality Testing
- Stability testing: normal & accelerated
- Extractables & Leachables
- Microbiological testing

Aerosol chemistry & *in-vitro* toxicology
- Focus on nicotine, carbonyls & metals
- Particle size measurements & characterisation
- *In-vitro* biological testing
Focus today on batch release and post-market product stewardship
- Emphasis on testing approaches and strategies
Batch Release
Manufacturing Quality – Process Control

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

#### EUTPD2 (Article 20)
- Notification to contain:
  - List of ingredients
  - Toxicological data
  - Nicotine dosage
  - Production process description
- Nicotine containing liquid to be placed in dedicated containers with volume <10ml
- Liquid in tanks and cartridges is <2ml
- Only ingredients of high purity to be used
- Doses delivered at consistent levels
- Emission testing: Nicotine, Carboxyls & Metals

#### UK MHRA (Medicinal License)
- Meet the essential requirements of Medical Device Directive 93/42/EEC (Class Iia)
- ISO 13485 Quality Management System
- Manufactured at sites which operate with principles of GMP
- Extensive safety literature review
- "Abridged application – PK study with PD assessment (VAS for nicotine)"

#### US ENDS PMTA
- 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
  - Environmental assessment
  - Scientific studies to include
    - Ingredient assessment
    - Aerosol chemistry (HPHCs & particle size)
    - In-vitro toxicology studies
    - Bridging studies
    - Pharmacokinetics
    - Exposure response
    - Likelihood of initiation/cessation
    - Abuse liability assessment
    - Impact to both user & bystander

**Increasing pre-market requirements depending on regulatory framework**
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 |
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
Post-marketing surveillance
Q1 Impact of EVP on Consumers

- Pharmacokinetic
- Biomarkers of Exposure
- Exposure response studies
- Registries

Increased duration of use; ‘artificial’ to ‘real life-settings’
Exhaled breath analysis shows far fewer peaks compared to conventional cigarette.

Retention [%] = \frac{[\text{inhaled}] - [\text{exhaled}]}{[\text{inhaled}]} \times 100%
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

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

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  \( P3 + P4 - (P1 - P2) \)
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
Post-marketing surveillance
Answers to 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?
## 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
Thank you for your attention!

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