



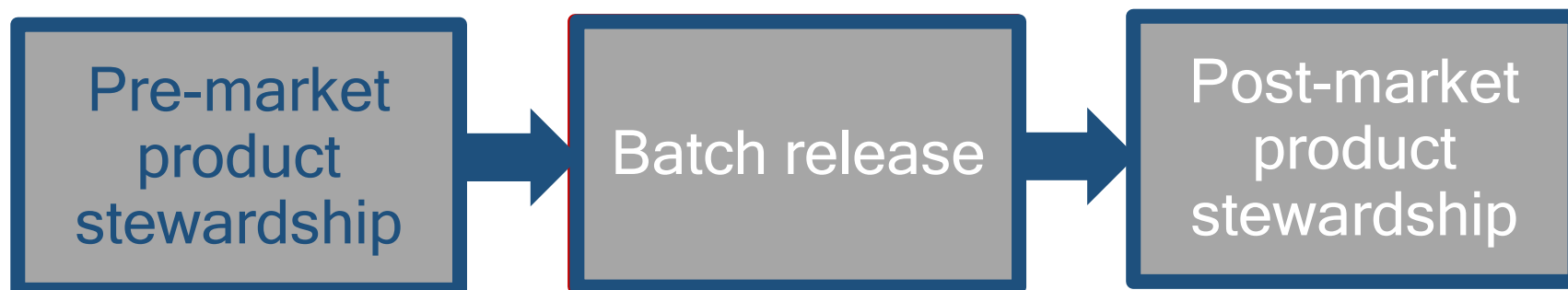
Responsible Practice in E-Vapour Products (EVP) Product Stewardship

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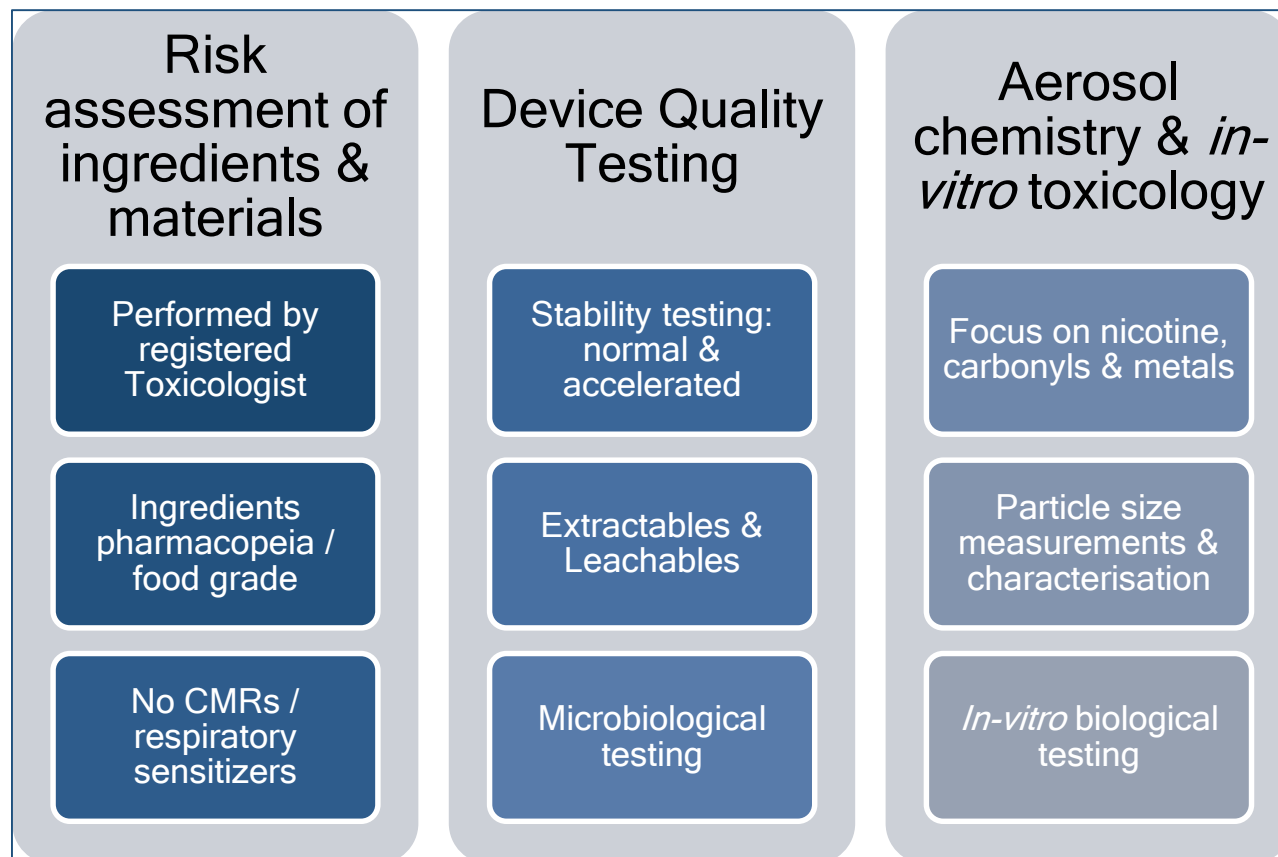
11 October 2016



Responsible practice can be divided in to 3 areas:



Pre-market product stewardship



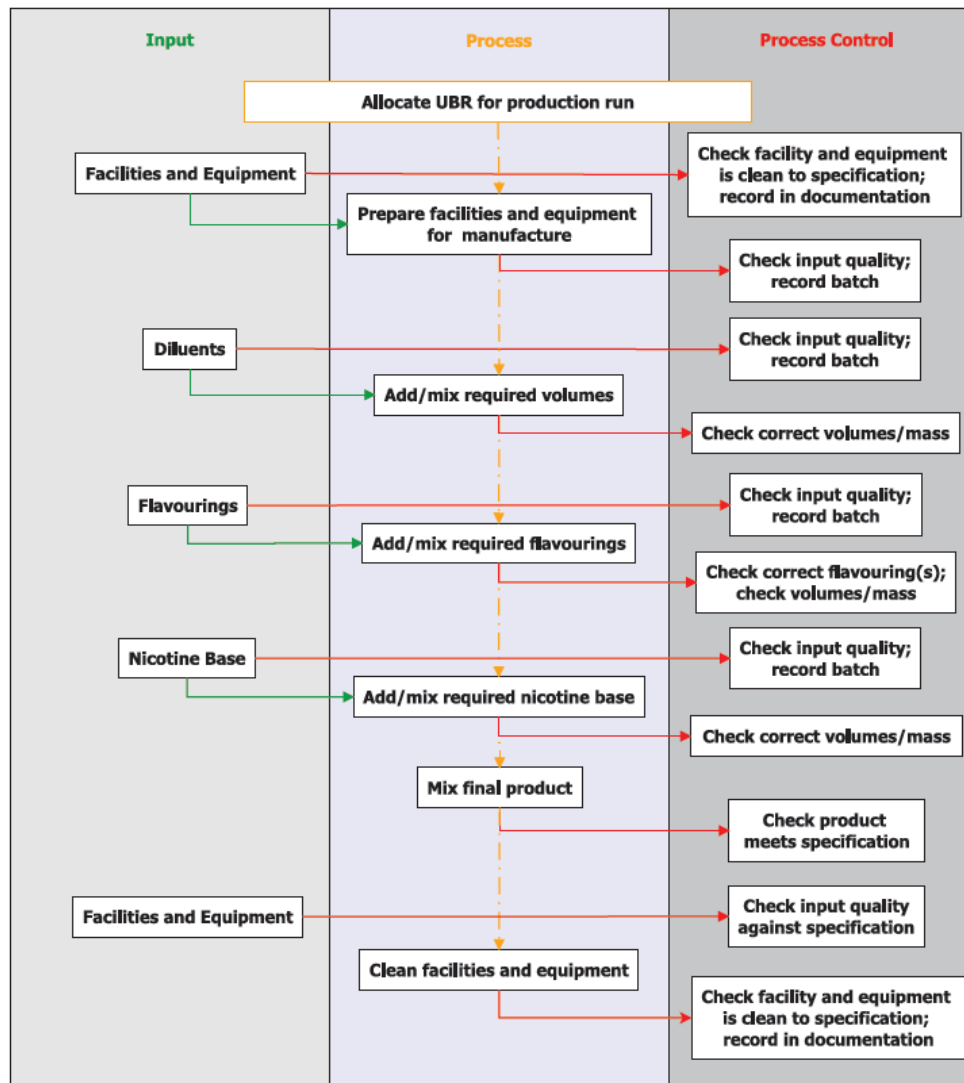


Focus today on batch release and post-market product stewardship

- Emphasis on testing approaches and strategies

Batch Release

Manufacturing Quality - Process Control



Source: BSI PAS 54115:2015 Vaping products, including electronic cigarettes, e-liquids, e-shisha and directly related products - Manufacture, importation, testing and labelling - Guide

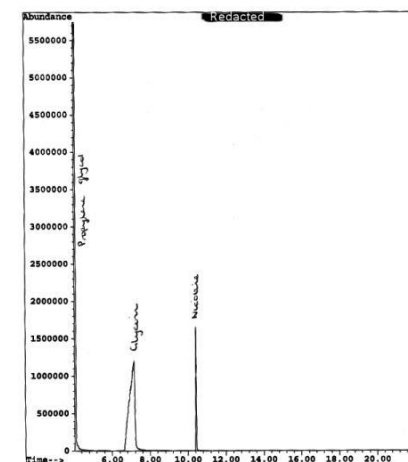
Batch release

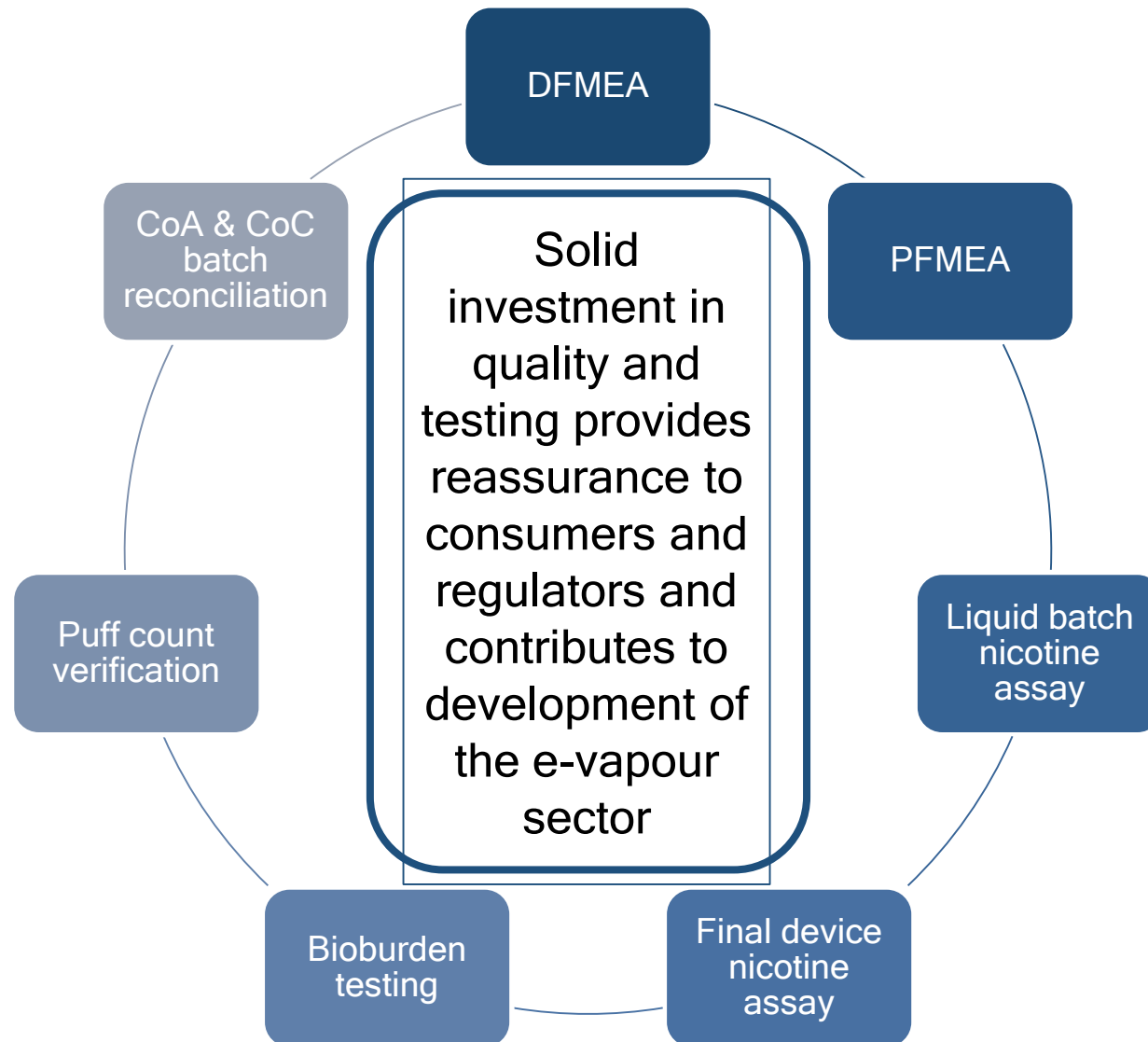
Traceability

Traceability

Device and
packaging
authenticity

Corrective
actions





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?

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
- 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, Carbonyls & Metals

UK MHRA (Medicinal License)

- Meet the essential requirements of Medical Device Directive 93/42/EEC (Class Iia)
- ISO 13485 Quality Management System
- Dossier to include relevant information on:
 - Development
 - Manufacturing process
 - Characterisation & properties
 - Quality control operation & requirement
 - Stability
 - Emission testing: Nicotine, Carbonyls & Metals
- Manufactured at sites which operate with principles of GMP
- Extensive safety literature review
- 'Abridged application - PK study with PD assessment (VAS for nicotine)

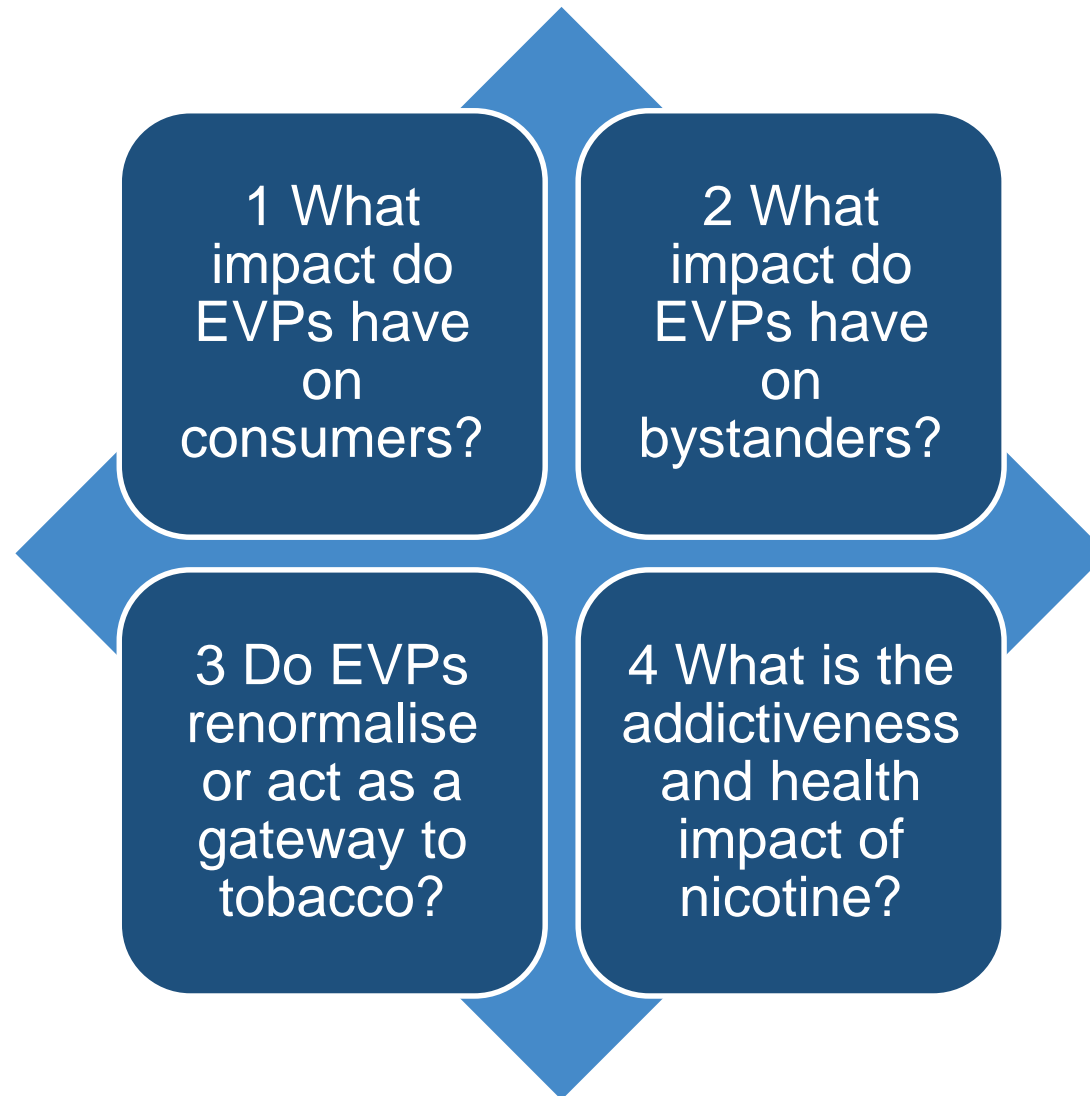
US ENDS PMTA

- 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)
 - Stability, E&L
 - 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



Post-marketing surveillance

Q1 Impact of EVP on Consumers

Clinical Studies Registered	Clinical Studies published since 2011	Outcomes investigated in these studies
>100 studies registered on ClinicalTrials.gov	>30 scientific publications for Randomised Clinical Trials identified	<ul style="list-style-type: none"> - 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	

Registry

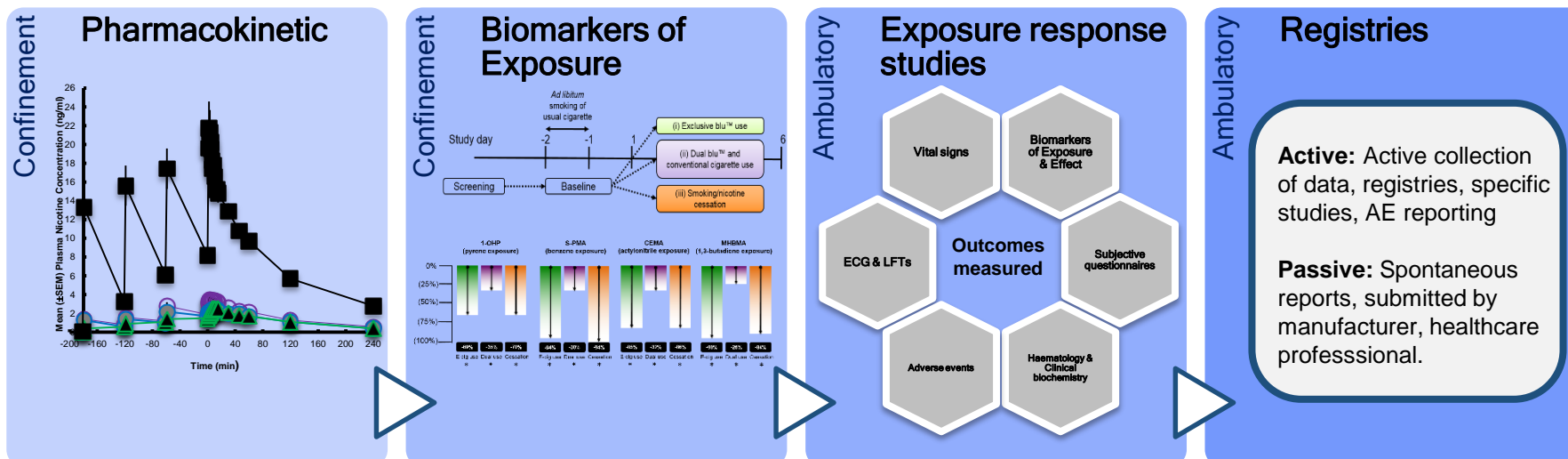
- “Real world” data
- Large “N”
- Observational
- Hypothesis generating
- Effectiveness
- Flexible, sub-studies
- Opportunistic or mandatory

Clinical Trial

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

Post-marketing surveillance

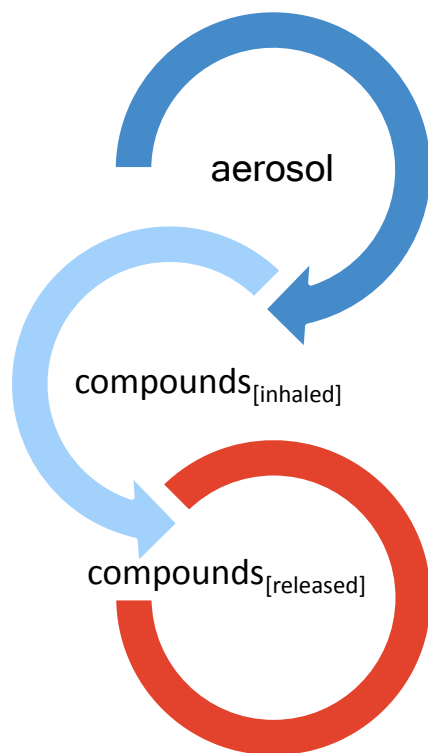
Q1 Impact of EVP on Consumers



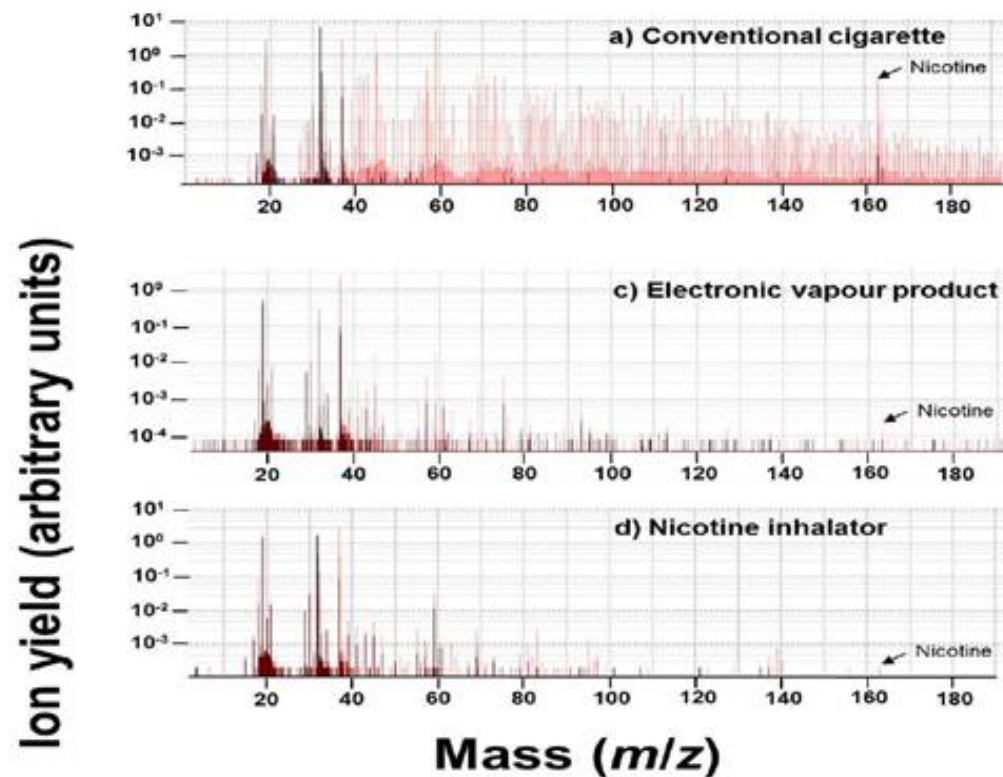
Increased duration of use; 'artificial' to 'real life-settings'

Post-marketing surveillance

Q2 Impact of EVP on bystanders



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



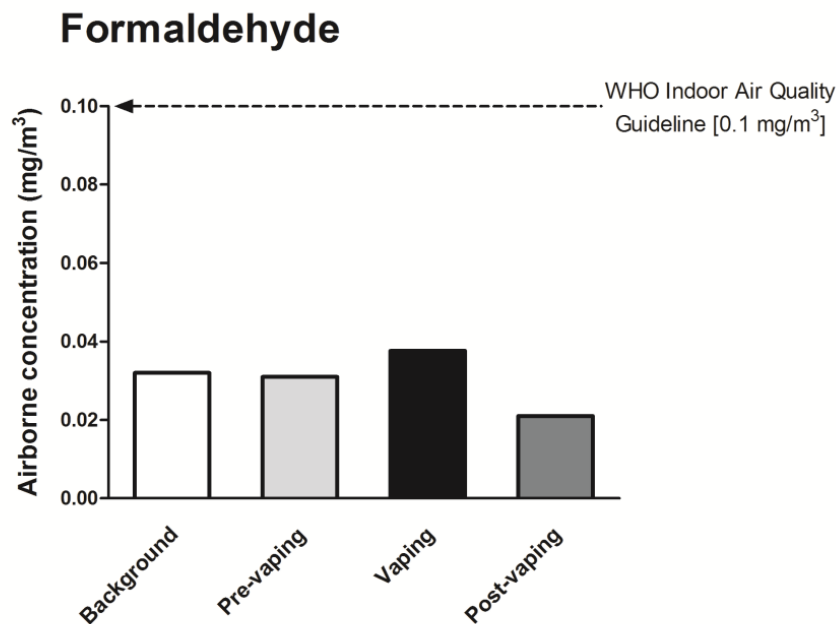
Exhaled breath analysis shows far fewer peaks compared to conventional cigarette

Source; O'Connell *et al.* Indoor Air Quality and Exhaled Breath Composition After Use of Nicotine Delivery Products. Poster presented at Society for Research on Nicotine and Tobacco (SRNT), USA, 2015. Available at www.imperialtobaccoscience.com

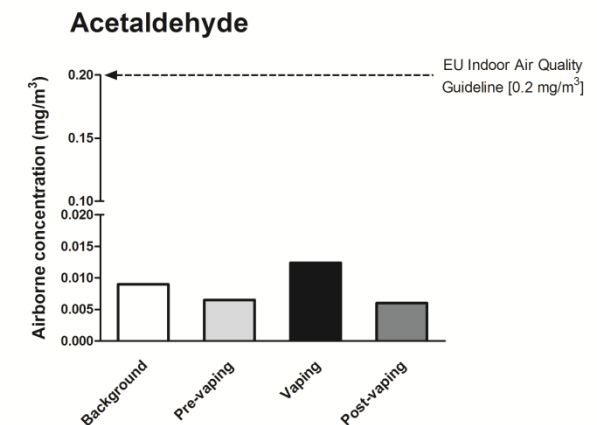
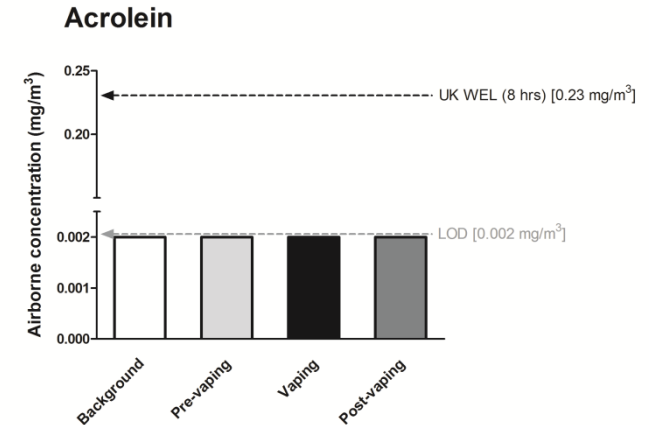
Post-marketing surveillance

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



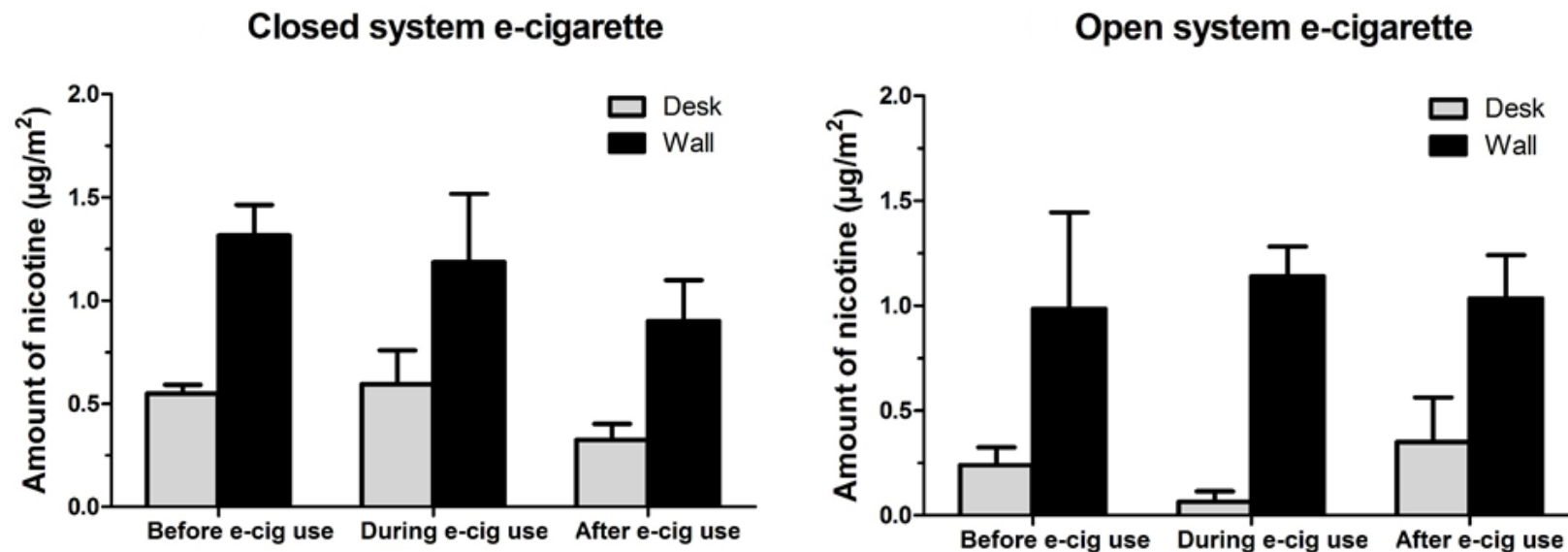
Room temperature:	22°C	25°C	28°C	27°C
Relative humidity:	44%	56%	57%	50%



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.

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

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



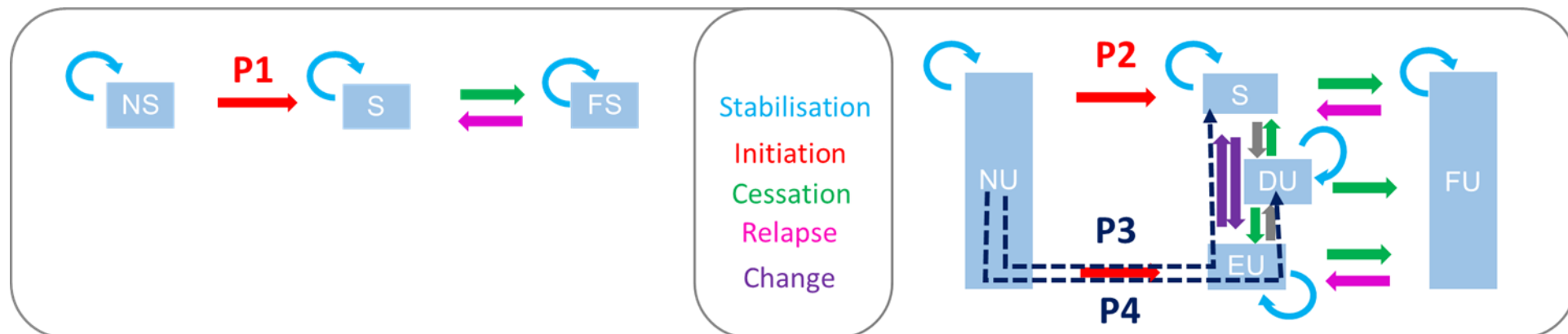
- EVPs are a roadblock to smoking initiation not a gateway
- EVPs de-normalise smoking, rather than re-normalise it

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



$$\text{Gateway effect } P3 + P4 - (P1 - P2)$$

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

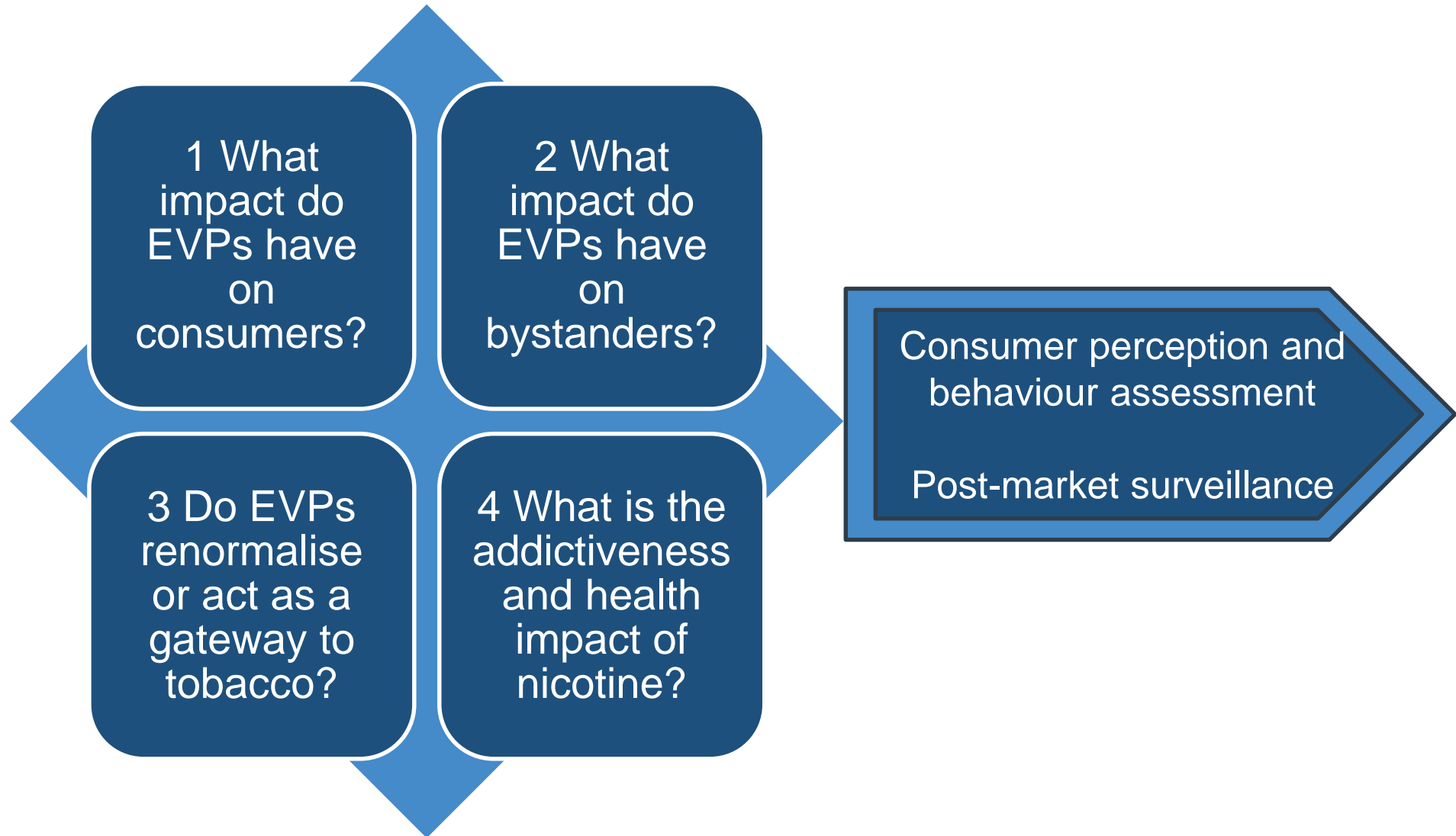
- No toxicity concern with nicotine in the small doses in an EVP

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

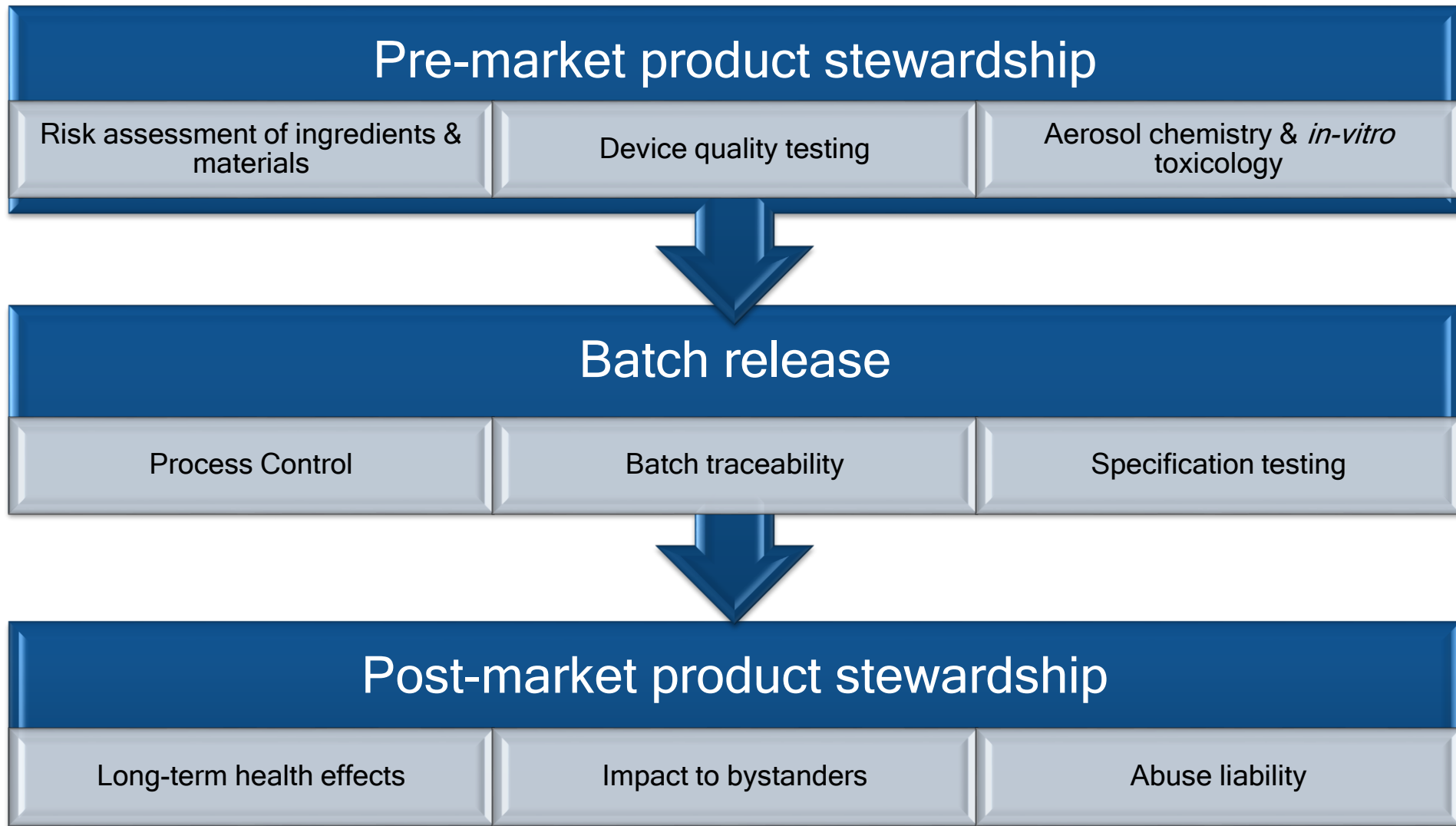
Post-marketing surveillance

Answers to the '4 Big' Questions



Summary

Responsible Practice in EVP Product Stewardship



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