

The Food and Drug Administration Predictive Toxicology Roadmap and its Implementation

Public Hearing Request for
Comments

Gary Phillips PhD | Principal
Scientist



Limited Guidance

Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

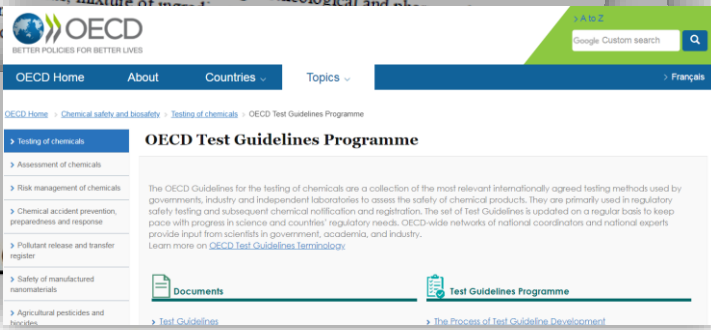
Guidance for Industry

DRAFT GUIDANCE

Comments should be submitted within 60 days of publication in the Federal Register of the notice of the draft guidance. Electronic comments may be submitted to the Division of Dockets, U.S. Food and Drug Administration, 1650 Fishers Lane, Room 1051, Rockville, MD 20852. Comments should be identified with Docket No. FDA-2013-D-2496.

Contains Nonbinding Recommendations
Draft – Not for Implementation

1281 Nonclinical health risk information should provide a thorough toxicological and
1282 evaluation of each of the ingredients, mixture of ingredients, and the
1283 tobacco product. FDA records the information in the tobacco product
1284 with the new tobacco product.
1285
1286
1287



Bacterial Reverse Mutation Test

INTRODUCTION

1. The bacterial reverse mutation test uses amino-acid requiring strains of *Salmonella typhimurium* and *Escherichia coli* to detect point mutations, which involve substitution, addition or deletion of one or a few DNA base pairs (1)(2)(3). The principle of this bacterial reverse mutation test is that it detects mutations which revert mutations present in the test strains and restore the

toxicants under both intense and non-intense use conditions as described in section VI.H.1.a;'

- ▶ In vitro Toxicology studies (e.g., genotoxicity studies, cytotoxicity studies);
- ▶ In vivo toxicology studies (to address unique toxicology issues that cannot be addressed by alternative approaches, and;
- ▶ Computational modelling of the toxicants in the

In vitro Pre-clinical Assessment- Novel Techniques



The use of human 3D reconstructed bronchial tissue to study the effects of cigarette smoke and e-cigarette aerosol on a wide range of cellular endpoints

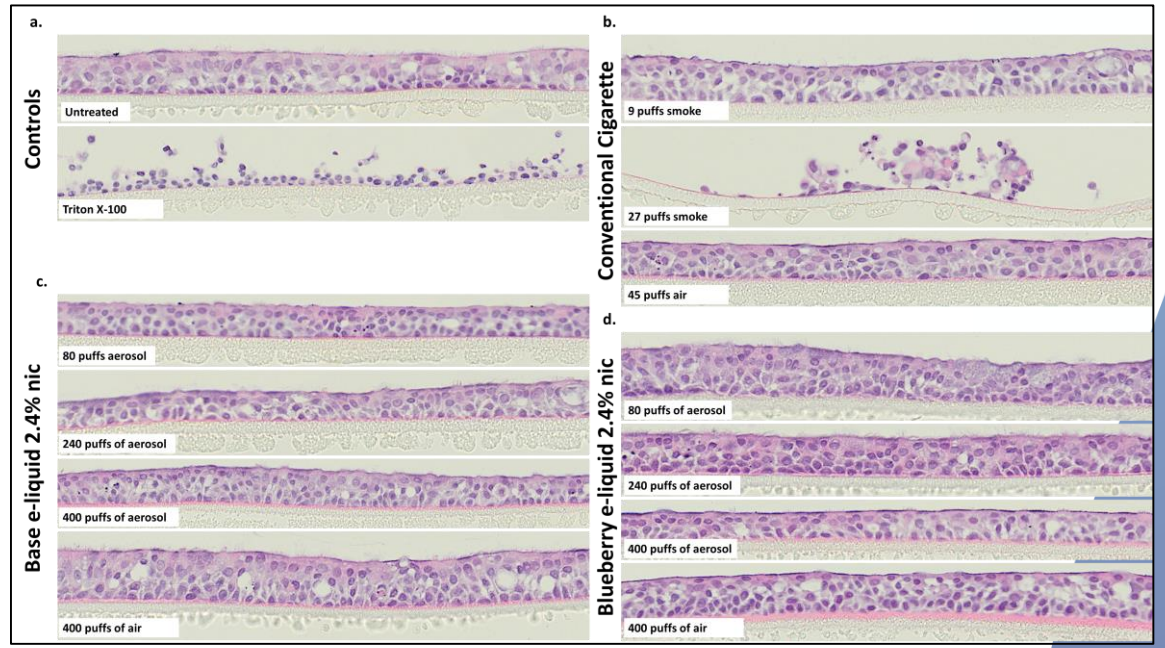
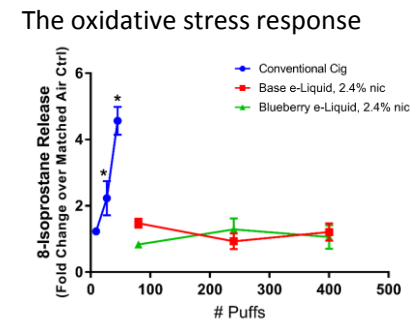
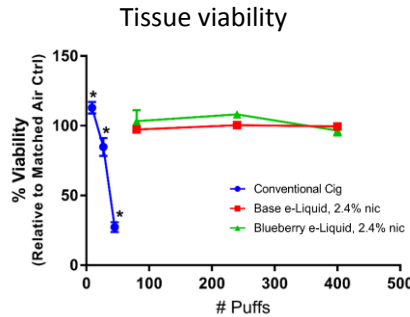
Lukas Czakala¹, Matthew Stevenson¹, Liam Simms¹, Nicole Tschierske¹, Anna G. Maione¹, Tanvir Walele¹

Imperial Tobacco Ltd, 121 Waterlooburg Road, Bristol, BS3 2JL, UK; MarlTel, 200 Homer Ave., Ashland, MA, USA; Fontem Ventures B.V., an Imperial Brands PLC Company, Aegweg 60, 3943 NT Arnhem

1. Introduction
2. Materials and Methods
3. Results
4. Summary/Future work

SCOT 57th Annual Meeting
11-15 March 2018
Abstract Number 2023
Session 02.02.23

2018 San Antonio
March 11-15



- ▶ This preclinical approach adds weight and mechanistic understanding of specific endpoints.
- ▶ Such techniques can also be conducted rapidly and be repeated and reproduced by other qualified laboratories.

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

In vitro Pre-clinical Assessment

TT21C



Novel human relevant *in vitro* assays

In silico modelling

Clinical samples

In vitro regulatory toxicology

Ames

IVM

NRU

CVD endpoints

Cancer endpoints

COPD endpoints

Organ interactions

AOP Development

Pre-clinical and clinical bridging studies

Scratch wound

CTA

3D lung models

2 compartment models

Regional lung deposition

Monocyte adhesion/migration

Mechanistic Reporter Assay

Organ-on-a-chip

In silico modelling QVIVE

Systems Toxicology approach

Current Challenges

- ▼ Limited Industry-FDA communication and collaboration
- ▼ Limited guidance on types and number of assays or tools required to complete an in vitro assessment
 - ▼ Inhibits uptake of assays
- ▼ No template process map for product assessment

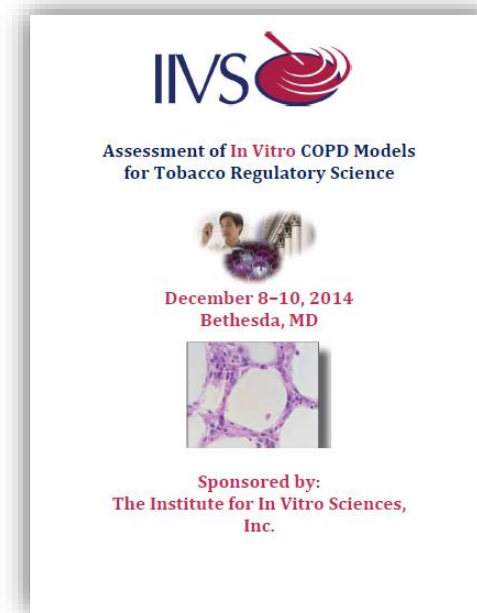


1. Collaboration

- ▼ Increased FDA and Industry collaborations (e.g. FDA input into the IIVS COPD Ring trial)
- ▼ Collaboration with CORESTA and relevant working groups
- ▼ Improve regular dialogue with industry. The journey must be taken together!



CORESTA - Cooperation Centre for Scientific Research Relative to Tobacco



2. Research

Guidance required to build a testing framework centred on the use of new and emerging technologies

Use of reference compounds or product as an example which has been through this process

Fast track qualification process for New Assessment Methodology (NAMs)

Use of appropriate standards and positive and negative controls

Improve and support the qualification process

Lack of qualified / validated methods for NAMs

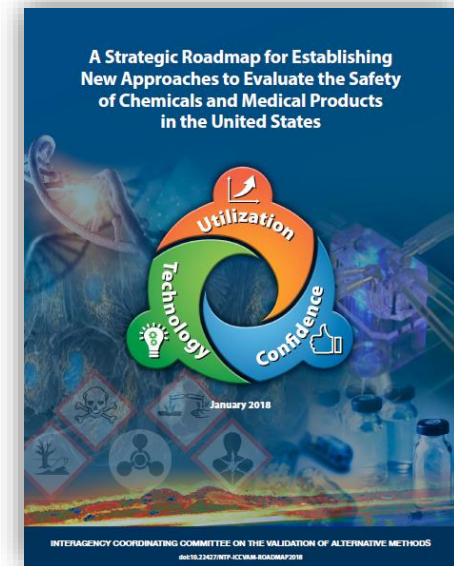
Acceptability of NAMs by FDA e.g. Tox21 partners

ICCVAM 2018 Roadmap



“Provide clear language regarding the acceptance of NAMs. Industry stakeholders indicate that lack of clear guidance on the status of regulatory acceptance is a significant factor impeding the use of NAMs. Industries cannot be expected to use new methods if they are uncertain about whether the data will be accepted by regulators. To facilitate use by industry, agencies should provide clear guidance on the use and acceptance of data from NAMs”.

Fontem Ventures supports this statement and welcomes a two way dialogue with the FDA on our Harm reduction approach



ICCVAM :The Interagency Coordinating Committee on the Validation of Alternative Methods

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

Conclusions



Improve the open, clear and regular dialogue with industry

Expand on collaborations for example IIVS and CORESTA

FDA should release a clear process for the qualification of new assays for Product Assessment

Identify & fast track NAMs likely to be acceptable for next generation product assessment

FDA endorsement of human relevant *in vitro* approaches, supporting a TT21C vision

Animal testing is time consuming & lacks human relevance

Request for clarity on PMTA requirements for Next Generation Products

More Information



For more information on our science, please visit our science websites:

www.ImperialBrandsScience.com

www.FontemScience.com



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