The Food and Drug Administration Predictive Toxicology Roadmap and its Implementation

Public Hearing Request for Comments

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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.

Limited Guidance

Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

DRAFT GUIDANCE

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Toxicology data from the literature

▼ Toxics analysis of constituents and other 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

OECD Test Guidelines Programme

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
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.
In vitro Pre-clinical Assessment

In vitro regulatory toxicology

OECD

In vitro Pre-clinical and clinical bridging studies

TT21C

In vitro regulatory toxicology

In vitro Pre-clinical Assessment

Novel human relevant in vitro assays

In silico modelling

Clinical samples

CVD endpoints
Cancer endpoints
COPD endpoints
Organ interactions
AOP Development
Regional lung deposition
In silico modelling QVIVE

Scratch wound
CTA
3D lung models
2 compartment models
Organ-on-a-chip

Monocyte adhesion/migration
Mechanistic Reporter Assay

Systems Toxicology approach

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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
Solutions

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!
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
Conclusions

- FDA should release a clear process for the qualification of new assays for Product Assessment
- Expand on collaborations for example IIVS and CORESTA
- 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
- Improve the open, clear and regular dialogue with industry
More Information

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

www.ImperialBrandsScience.com

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