Newsletter

Issue Num. 18 – March 2016

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Second eTOX Hackathon

7-10th March. 2016. Barcelona

***eTOX** Second Hackathon was held this month in Barcelona, hosted by FIMIM. In this event the participants were organized in three different teams - each team working on a predefined/ specific challenge. The common goal of all teams was to advance in the definition of the modelling strategies of the **eTOX** project.*

PROJECT NEWS

eTOX at SOT 2016

eTOX presented 8 posters at the 55th Annual Meeting of the Society of Toxicology, held between the 13th and 17th of March in New Orleans.

Feedback was received both from pharmaceutical companies and regulatory institutions. Whereas company representatives were interested in the day-to-day use for early compound assessment, regulatory agencies asked about details on database set-up and ways to get access to the database.

All posters can be viewed at the eTOX website: http://www.e-tox.net/sot2016.html

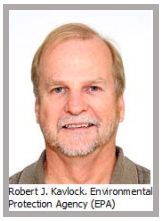
eTOX and EU-ToxRisk

On Jan 13th to 15th the kick-off of the EU-ToxRisk project took place in Egmont aan Zee, NL. EU-ToxRisk (http://www.eu-toxrisk.eu/) is an international consortium of 39 partner organisations funded by the European Commission to work on the integration of new concepts for regulatory chemical safety assessment. There is a high degree of overlap of both partners and objectives between eTOX and EU-ToxRisk. eTOX was presented during the kick-off by T. Steger-Hartmann. The next step will be the preparation of a Memorandum of Understanding.

KEYNOTE

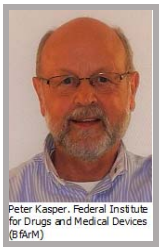
SAB joint keynote: The eTOX project from regulatory perspective

Message from R. Kavlock, M. Pasanen, P. Kasper



Robert J. Kavlock. Environmental Protection Agency (EPA)

Markku Pasanen. European Medicines Agency (EMA)



Peter Kasper. Federal Institute for Drugs and Medical Devices (BfArM)

Over the last six years the IMI **eTOX** project has created a **well-curated, versatile preclinical database** (**eTOX** db) which can be used as a **source for "read-across"** approaches and a collection of predictive models (**eTOXsys**) with the aim of significantly improve our ability to predict the safety and liabilities of new medicines. Partner pharmaceutical companies are already exploring the use of these new tools in early phases of the drug development process in order **to identify potential risk of new drug candidates** as early as possible. However, from a regulatory point of view, the more interesting question is whether (or when) these new promising prediction models are mature enough to be used for regulatory decision-making processes. This leads to the question on the **requirements for regulatory acceptance of new *in silico* predictive systems** in safety assessment. The OECD principles for the validation of QSAR models (such as a defined endpoint, an unambiguous algorithm, a defined domain of applicability, or appropriate measures of predictivity) can be considered as basic criteria for regulatory acceptance. However, equally important for a regulatory fit-for-purpose evaluation is a clear definition of the intended context of use of a prediction model. The level of scrutiny in the evaluation process would very much depend on the defined application scenario, for instance whether the new model is used (1) merely in addition to a traditional safety assessment approach, (2) for mode of action and/or human relevance analysis of adverse animal findings, (3) as essential part of an integrated testing strategy, or (4) a one-to-one replacement of a specific toxicity study in animals.

While the outcome of a prediction model for regulatory decision making may be accepted on a case-by-case basis by a regulatory authority (e.g., during a Clinical Trial Application), a broader application of a specific prediction model in regulatory safety assessment or even the incorporation into a regulatory testing guideline will need a **more formal acceptance process**. A possible pathway for EU-wide regulatory

KEYNOTE

(continuation)

acceptance is offered by the EMA as described in the **Guideline on Qualification of Novel Methodologies for Drug Development.** The EMA qualification procedure might also be of interest as a component of the development of commercial products and would give support to sustainability of newly developed prediction tools. Similarly, the recent experience of the FDA in qualifying biomarkers may be of relevance.

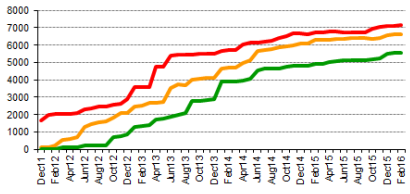
The data initially collected in the **eTOX** project is mainly focusing on systemic toxicity from repeat dose studies in rodents and non-rodents and includes notable success in forging a common ontology amongst diverse data generators. However, **extension to other endpoints** would significantly broaden areas of potential regulatory applications. The integration of data from safety pharmacology, pharmacokinetics, pharmacodynamics, reproductive-developmental toxicity and carcinogenicity studies are beyond the end of the project, but are strongly supported by the SAB for future investments. Of particular importance from a regulatory point of view is the **linkage of the non-clinical database to human safety information**, and we appreciate the initial efforts in this area. These efforts are expected to be of significant benefit in increasing the reliability of toxicity prediction and reduce cases of severe toxicity-related adverse events in late stage drug development or even of marketed products.

Finally, **continued education of regulatory non-clinical assessors** would be vital for the implementation of computational toxicology methodologies into the regulatory arena. Experience among regulators with *in silico* predictions for regulatory purposes is currently limited to the use of QSAR systems for predicting mutagenicity of impurities according to ICH M7. It is clear that guidance documents and training workshops would be needed to accompany broader application of *in silico* prediction tools to establish a common scientific understanding of their strengths and limitations in risk assessment and regulatory decision making.

This year the IMI1 **eTOX** project has reached its 7th and final year of duration. Follow-up activities with continued up-date of **eTOX** platform and involvement of regulatory scientists are essential to further explore the impact of the outcome of the project on the future of regulatory safety assessment. We encourage further commitments of transparency and public access of the underlying data and models as means to ensure that the potential impact is maximized.

REPORT-O-METER 7139

Currently, 6647 reports of the 7139 cleared for sharing within the consortium have finished the extraction data process and are available in the **Vitic Nexus eTOX database**.



Cleared Reports submitted to CROs or in-house facilities for data extraction

Extracted Reports with processing by CROs or in-house facilities completed

Vitic Reports with data available at Vitic Nexus database

PUBLICATIONS

A full list of publications is available on http://www.etoxproject.eu

- ARTICLE (UNIVIE): Flagging drugs that inhibit the bile salt export pump. Montanari F, Pinto M, Khunweeraphong N, Wlcek K, Sohail MI, Noeske T, Boyer S, Chiba P, Stieger B, Kuchler K, Ecker GF. *Mol Pharmaceutics 2016;13(1):163-71.*
- ARTICLE (VUA): Improving the iterative Linear Interaction Energy approach using automated recognition of configurational transitions. Vosmeer CR, Kooi DP, Capoferri L, Terpstra M, Vermeulen NPE, Geerke DP. *J. Mol. Mod 2016;22(1):1-8.*
- ARTICLE (CT): The In Vitro Pharmacological Profile of Drugs as a Proxy Indicator of Potential In Vivo Organ Toxicities. Remez N, Garcia-Serna R, Vida D, Mestres J. *Chem Res Toxicol 2016. In Press.*

UPCOMING EVENTS

- **14.04.2016 |** Streamlining Drug Discovery and Development: Leveraging data analysis and modelling for design. San Francisco, USA. Info: http://goo.gl/yZyEoL
- **26.06-01.07.2016 |** Drug Safety Gordon Research Seminar and Conference, Easton, MA, USA. Info: https://www.grc.org/programs.aspx?id=16738
- **15-17.08.2016 |** 6th Pharmacovigilance Congress. Toronto, Canada. Info: http://pharmacovigilancecongress.pharmaceuticalconferences.com/conference-brochure.php
- **4-7.09.2016 |** 52nd Congress of the European Societies of Toxicology (EUROTOX 2016), Istanbul, Turkey. Info: www.eurotox2016.com