Newsletter

Issue Num. 17 – December 2015

In This Issue

eTOX will be at DGPT & SOT 2016

82nd Annual Meeting of the German Society for Experimental and Clinical Pharmacology and Toxicology (29th February-3rd March 2016, Berlin, Germany)
55th Annual Meeting of Society of Toxicology (13-17th March 2016, New Orleans, Louisiana)

9 posters have been accepted for the upcoming DGPT (1) and SOT (8) meetings. They will cover different topics of the project: database query use cases, data analysis options, SEND implementation, cardio safety in silico prediction, model validation workflow, and extrapolation factors for risk assessment.

Season's Greetings from the eTOX team, with best wishes for 2016!

PROJECT NEWS

13th Consortium Meeting, Vienna, Austria
The meeting was hosted by Boehringer Ingelheim in Vienna on November 2nd and 3rd, 2015. Key topics were the establishment of data quality procedures, the prioritization of new data types incorporated into the eTOX database, the development of a sustainability plan for the system after the end of the project, and the first approaches of linking human safety data to eTOX data via web-services.

eTOX – iPiE connection
IMI-iPiE identified 64 compounds with ecotoxicological data which are also covered in eTOX. The corresponding eTOX datasets will be transferred to iPiE to allow analysis of correlations between mammalian and fish toxicity.

Regulatory perspective
Regulatory members in eTOX's Scientific Advisory Board recommended the addition of carcinogenicity data into eTOX in order to compare outcomes of chronic studies to cancer bioassays. Such an analysis will be valuable in the light of a revised ICH S1.

KEYNOTE

Joint efforts change the way of toxicological assessment

Message from Dr. Eckhard von Keutz, Head of Global Early Development, Bayer Pharma AG

Each scientist working in the field of non-clinical safety knows the situation: A finding is observed during a toxicological study with a new drug candidate and we are confronted with the question: have we seen this before and if so, which project was it and how did we deal with the finding? If it was not too long ago and the expert is still in the company, we have the chance to get responses to these questions. Otherwise a cumber some search in paper and pdf archives commences.

The desire for a versatile database capturing all these findings, structures and targets is obvious but as soon as we discussed such plans more seriously we immediately realized the dimension of such an endeavor in terms of time, capacity and budget.

It was therefore more than logical for us, to not only express interest in the proposal of an IMI initiative, intended to build a non-clinical database more than six years ago, but rather we volunteered to forge such a project together with other pharma companies. The **eTOX** project gained large support within EFPIA, but also encountered hurdles in dimension we had not foreseen. Aligning intellectual property protection among the 13 EFPIA companies was a time-consuming effort without any precedence; the heterogeneity of terminology used in the toxicity reports needed the development of controlled vocabulary *ab initio*. But the joint effort was worthwhile. We start to see the return of investment for this project. The database which has been created surmounts dramatically what we would have ever been able to extract and collect in-house alone at costs which would have been prohibitive. As a practical consequence, the created database has encouraged us to adjust our ways how we are looking at early drug candidates. *It is now part of a routine process at Bayer that all candidates of all early projects are assessed with a comprehensive query in the **eTOX** database based on both structural similarity and searches for similar or related targets*. The results of such searches do not only guide our selection of early safety screens or target organ investigations in early *in vivo* studies but also deliver valuable information to the project team concerning potential off-target effects.

ACHIEVEMENTS

- A Memorandum of Understanding has been signed with the **National Center for Competency Testing at EPA** granting access to selected scientists to **eTOXsys** online version. The intention is to evaluate the overlap between the **eTOX** data and EPA's **ToxCast** data and to explore whether **eTOXsys** is feasible to analyze correlations between **ToxCast** outcome and *in vivo* preclinical data.

ToxCast™
National Center for Competency Testing

- A **toxicity scoring** tool developed by FIMIM has been made available to all **eTOX** partners. This software can extract profiles of findings from multiple tables of the report database and associate those to toxicity endpoints (i.e., liver steatosis or cholestasis*)*. The final result is a quantitative scoring for every compound, describing the lowest dose at which any of the selected finding was observed (LOEL), amenable for the development of QSAR and read-across models. The first models are currently under development.

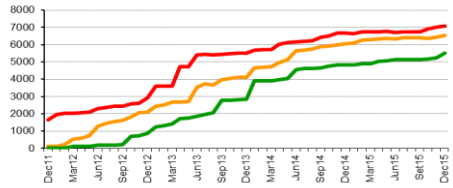
- FIMIM, in collaboration with Erasmus Medical Center is testing new web-services for extracting toxicologically-relevant bio-isosters (i.e. compounds with similar biological properties), in the context of human safety area. Linking **eTOX** compounds directly to external resources and databases is not possible for confidentiality reasons. An interesting alternative is the use of surrogate compounds; non confidential structures (e.g. marketed drugs) structurally similar to the **eTOX** compound, meeting criteria which allow a reasonable assumption of bio-isosterism. The use of such surrogate structures opens the possibility to link **eTOX** compounds to any external databases (i.e., ChEMBL or OpenFDA).

ChEMBL
openFDA

REPORT-O-METER

~~7095~~

Currently, 5518 reports of the 7095 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 (VUA-FIMIM): Linear Interaction Energy based Prediction of Cytochrome P450 1A2 Binding Affinities with Reliability Estimation. Capoferri L, Verkade-Vreeker MCA, Buitenhuis D, Commandeur JNM, Pastor M, Vermeulen NPE, Geerke DP. *PLoS ONE 2015;10(11):e0142232.*

- ARTICLE (FIMIM): Toward a unifying strategy for the prediction of toxicological endpoints. Carrio P, Sanz F, Pastor M. *Arch Toxicol 2015;340-5761.*

- ARTICLE (UNIVIE): Identification of Novel Inhibitors of Organic Anion Transporting Polypeptides B1 and B3 (OATP1B1 and OATP1B3) using a Consensus Vote of Six Classification Models. Kotsampasakou E, Brenner S, Jäger W, Ecker GF. *Mol. Pharmaceutics 2015;12(12):4395–4404.*

UPCOMING EVENTS

- **18-19.02. 2016 |** Open PHACTS workshop "Linking Life Science Data: Design to Implementation, and Beyond". Vienna, Austria.
  Info: https://www.openphacts.org/news-and-events/news-archive/2015/403-linking-life-science-data-design-to-implementation-and-beyond
- **29.02-03.03. 2016 |** 82nd German Society for Experimental and Clinical Pharmacology and Toxicology. Berlin, Germany.
  Info: http://www.gpts-kongress.de
- **13-15.03. 2016 |** 5th PhUSE Computational Science Symposium. Silver Spring, Maryland, USA.
  Info: http://www.phuse.eu/CSS-2016-Agenda.aspx
- **13-17.03. 2016 |** Society of Toxicology 55th Annual Meeting and ToxExpo. New Orleans, USA.
  Info: https://www.toxicology.org/events/am/AM2016/