ESTP Newsletter 2014 (2)

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Dear ESTP Members,
In our Summer issue, we will read three topics which are directly linked to the new initiatives that your ESTP Executive Committee has launched in 2013:

- *SEND*
  (by Charlotte Keenan)
- *Clinical Pathology & Biomarkers*
  (by Aida Diaz-Bayon)
- *Computational Toxicology/Pathology 2.0*
  (by Alessandro Piaia)

The articles summarize the purpose and activities of each committee. We wish to thank all authors for providing an update.

Have a great reading!

Zuhal Dincer
On behalf of ESTP Executive Committee

INHAND collaboration with SEND

Dear ESTP members,

During 2012, International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) Global Editorial Steering Committee (GESC) representatives attended meetings with representatives of the FDA Center for Drug Evaluation and Research (CDER), Clinical Data Interchange Standards Consortium (CDISC), and the National Cancer Institute (NCI) Enterprise Vocabulary Services (EVS) to initiate integration of INHAND terminology as the preferred terminology for SEND (Standard for Exchange of Nonclinical Data). SEND is a formal mechanism for submitting data from non-clinical studies to the FDA electronically and in a standardized format. INHAND GESC assists the SEND Controlled Terminology (CT) committee in providing definitions for base processes and modifiers associated with the INHAND published terminology. INHAND ad hoc members of the SEND CT committee will participate in this endeavour and take issues to the full GESC and/or appropriate INHAND Working Group for resolution. The GESC may also call on experts in the field to assist in any aspect of their role as a 'Scientific Advisory Board'. The interest in utilizing the INHAND nomenclature, based on input from industry and government toxicologists as well as information technology specialists, signifies the potential for wide acceptance of this nomenclature.

The initial list for the SEND code-list of non-neoplastic (NONNEO) microscopic pathology contains terms from published INHAND organ systems. The list will continue to grow as INHAND publishes additional organ systems. Some terms on the NONNEO code-list may look different from how they have been

presented in the INHAND publications. Terms on the NONNEO code-list are for the most part generic and can be used across tissues, where appropriate. INHAND published terms have been modified to fit the SEND standard in some cases by being broken into base process and modifiers. For example the INHAND term Necrosis, zonal would be separated into NECROSIS for population in MISTRESC (Microscopic Standardized Result) and ZONAL in MIDISTR (Microscopic Distribution). Tissue specific terms from INHAND are included on the NONNEO code-list when it is important to use the exact term representing a spectrum of tissue changes (example – chronic progressive nephropathy). Tissue specific terms may include reference to a particular tissue in the preferred term as well as in the definition if needed. Additional general base process terms not yet included in INHAND publications have also been added to the NONNEO code-list to make the first list as comprehensive as possible. In the process of mapping terms from INHAND to SEND, some inconsistencies have been noted for the same term across several organ systems (example – thrombus vs thrombosis). These will be harmonized using the new change control process and the most current terminology will be available on the goRENI website.

Due to the interactions with the SEND project and future needs to serve in an advisory role, GESC will become a permanent standing committee of the various Societies of Toxicologic Pathology with a defined appointment and term of members and establishment of several new roles, due to the expectation for ongoing interactions with the SEND project and future needs to serve in an advisory role. GESC will act as a clearing house for comments and requests for updates to the INHAND terminology from the SEND CT committee as well as from the memberships of each Society.

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Clinical Pathology and Biomarkers Committee

Dear ESTP Members,

This new committee is made of 15 members located across the three continents and with varied backgrounds (Pharmaceutical and Agrochemical industry, and CROs). The group is quite diverse, with some people's interests being new/emerging biomarkers, whilst others are more traditional clinical pathology data evaluation/interpretation. In our midst are anatomic pathologists and clinical pathologists, most are ESTP and/or ESVCP (European Society of Veterinary Clinical Pathology) members. Some are active participants in various relevant consortia or working groups.

Our first meeting was held on 11th April 2014 and we now meet monthly for an hour. Claudio Petterino has been identified as our liaison with the ESVCP. One of the first subjects the group discussed was the current activities of Consortia working on Safety Biomarkers: e.g. Critical Path Institute - Predictive Safety Testing Consortium (PSTC), Health and Environmental Sciences Institute (HESI), Innovative Medicines Initiative - SAFE-T. All agreed that we did not want to duplicate efforts already ongoing elsewhere but that we should keep abreast of their progress.

The group's agreed aims are:

- To create a group of motivated people interested in bringing together clinical and anatomical toxicological pathology disciplines
- To increase the visibility of clinical pathology/safety biomarkers in the toxicological pathology arena
- To create and enhance interactions between the ESTP and sister societies (e.g. BSTP), ESVCP (European Society of Veterinary Clinical Pathology), ECVCP (European College of Veterinary Clinical Pathology), and

ACCP (Association of Comparative Clinical Pathology) members
- To share *clinical pathology and biomarkers* knowledge in preclinical safety assessment between the ESTP and ESVCP/ECVCP/ACCP members
- To promote the development and use of novel biomarkers in preclinical studies
- To identify and facilitate training opportunities to enhance the clinical pathology knowledge of anatomical pathologists involved in preclinical safety assessment.
- To keep up-to-date on Best Practices and regulatory documents related to clinical pathology and biomarkers, in the context of safety evaluation and in association with the relevant clinical pathology societies

The group plans to reach its aims by:
- having monthly meetings by teleconference
- exchanging information on and discussing any potential new *in vitro* and *in vivo* techniques, biomarkers
- creating and establishing strong links between ESTP and ESVCP / ECVCP / ACCP / other relevant societies
- in collaboration with ESTP, ESVCP, ECVCP, ACCP, and other relevant societies:
    - identifying educational needs/wishes from members of the combined societies
    - proposing educational opportunities, workshops, speakers to Scientific Organising Committees (SOCs)
    - providing clinical pathology/anatomical pathology - related lectures/educational material that would fit with and broaden the conferences / training / workshop programs and attract members to conferences
    - being willing and able to help the relevant meetings' SOCs

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In Silico Computational Toxicology and Involvement of Pathologists

Dear ESTP Members,

We are living in an era where toxicology science and the way to generate and handle data are rapidly changing. Therefore toxicologic pathologists' way to use their skills to contribute to the drug and chemical discovery and development process is also changing. The need for these changes has been originated internally to different companies/industries because of increasing costs of discovery and development of drugs and products. With drugs, current methods appear unable to predict adverse events constantly or lack of efficacy in humans which leads to a high incidence of post-marketing withdrawal. Also regulatory agencies are more and more challenging for the new submission documents, due to a growing concern that many of the new basic science discoveries may not quickly yield more effective, more affordable and safe products for humans. Final but no less important reason is an increased public awareness and ethical concern on the use of animals in toxicological experiments giving rise to a steadily expanding request for alternative methods.

Many different tools and technologies have been developed since this era started and they are generating more and more sophisticated methods. One of the largest themes is represented by the *in silico* (computational) toxicology, which is a growing field to model ADME and toxicological hypothesis, development and testing.

The best definition of *in silico* toxicology comes from EPA which defines it as: "*integration of modern computing and*

information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals". Moreover the FDA insights in this gives the flavour on the perceptions by regulatory agencies (taken from Challenges and Opportunities Report - March 2004): "*there are currently significant needs, but also significant opportunities, for developing tools that can more reliably and more efficiently determine the safety of a new medical product. As biomedical knowledge increases and bioinformatics capability likewise grows, there is hope that greater predictive power may be obtained from in silico (computer modelling) analyses such as predictive toxicology. Some believe that extensive use of in silico technologies could reduce the overall cost of drug development by as much as 50%.*". (http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm)

Many computational approaches are now available to predict toxicity and they are represented by expert systems and specific methods. The expert systems are a comprehensive repository of experts' knowledge and therefore the power of those systems are related to the amount of high quality information of the relative datasets, and their quality ultimately relies on the time and efforts taken by experts to collect and curate data. The specific methods (data driven system) rely on algorithms of ligand-based modelling, such as quantitative structure activity relationship methods (QSAR), and structure-based modelling of atomic ligand-target interaction. As the two algorithms are often integrated to further validate individual models, today the two main algorithms are often combined.

It has been with this premise and the recognition that individual companies may possess only a relatively small database, that both public initiatives and joint venture between public and private initiatives have started, developing novel software tools based on larger database, with the aim to exploit the existing historical safety data to better predict - by using computational methods - the safety of new candidate medicines for patients and new products and food ingredients (among others some good examples are given by the international QSAR foundation http://www.qsari.org/; the CAESAR project www.caesar-project.eu, the BioIntelligence program http://europa.eu/rapid/press-release_IP-09-778_en.htm or the IMI eTOX project http://www.imi.europa.eu/content/etox).

In those contexts it is clear that a major contribution to the development of these tools is given by the scientists with large experience in toxicology, knowledge management, bioinformatics, chemoinformatics, biostatistics and software development from industry and academia. One example is given by the eTOX initiative, which started with a sharing of information, in the shape of preclinical reports, among the different contributing companies and generating a toxicological database with high structural in vitro and in vivo data. One of the first needs the project experienced was the need to navigate the large amount of shared legacy data generated, since the "verbatim" approach in their extractions generated a large amount of synonyms and copies with slight changes, to an extent that they were totally unusable by modellers. In that context a group of pathologists have been dedicating time to curate those terms and created a histopathology-ontology to allow synonyms to be brought together and creating also grouping and linking terms implying pathological mechanism of development. Moreover, the usage of those data from modellers will also get help from the scientific contribution and guide that toxicologic pathologists can give.

It becomes therefore clear that there is and/or could be an underlining important contribution of toxicologic pathologists to this process; not least, pathologists can also be considered as one of the key experts to interrogate these new tools and interpret their results.

To explore the potential extent of toxicologic pathologists involvement in *in-silico* (computational) toxicology, the related challenges and the potential need for additional training in toxicological pathology, a group "Bioinformatics/*in silico* Tools" has been formed in the context of ESTP, working group to evaluate the future of Toxicologic pathology (Pathology 2.0). At this stage it is composed by Thierry Flandre, Frieke Kuper, Heike Marxfeld, Frederik Schorsch, Alok Sharma, Robert Sills, Manuela Stolte, and myself, Alessandro Piaia.

It has been with a mixed sense of great expectations and hope for a bright future for all toxicologic pathologists and our society. I have written this letter to remark a field which is growing and gaining more and more interest, and also to highlight the key contributions of our society and each member can and should give. And I am looking forward to working with this team.

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Message from the President

Dear Friends,
It will be a great pleasure to welcome you to our second Joint European Congress of the ESVP, ESTP and ECVP (Berlin, Germany, August 27–30, 2014). This will be our 12th European Congress of Toxicologic Pathology. This conference, aptly named "Cutting Edge Pathology" will bring you the most up-to-date advances in pathology with presentations in areas of toxicopathology of the endocrine and endocrine regulated organs, nanotoxicology, regenerative medicine and cancer. It will be again a great moment where our three organisations are also united and will offer us a chance to meet friends and make new ones.

Thanks for joining us
Frédéric SCHORSCH
Your chairman

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