Nonclinical Data Interconnectivity for Endpoint Predictivity (NICE)

Project Scope

Explore means by which nonclinical and clinical data can be interconnected in ways that facilitate their use for identifying hazards and risks of pharmaceuticals. Key parameters for interconnecting clinical with nonclinical data include drug class, pharmacologic class, pharmacologic target and /or mechanism of action. An outcome of this project could be guidance for the US FDA and the pharmaceutical industry regarding design/analysis of SEND datasets to allow for nonclinical data to be associated with metadata that accurately describes the drug's mechanism of action, target and/or pharmacologic class. In addition, strategies for interconnecting nonclinical with clinical data, based on pharmacologic class, could be developed. In addition, strategies for searching for and identifying pharmacologic class effects for adverse events and toxicities could be developed.

Specific topics to consider include:

- What are accepted terminologies/nomenclatures for pharmacologic class and/or mechanism of action ? How are these developed ?
- What in silico tools/databases are available for interconnecting clinical adverse events/toxicities with nonclinical toxicity data using pharmacologic class ?
- Can guidance be developed regarding the use of in silico/computational tools for interconnecting pharmacologic class with clinical and nonclinical data ?
- What resources are available regarding this topic ?
- Useful databases and references for data analysis/searching will be included on this Advance Hub site

Project Activities Completed in 2014

- Various case examples of pharmacologic class/targets were selected in which clinical and nonclinical safety data were likely available in the public domain
- Publicly available databases (eg, DailyMed, Drugs@FDA, Drug Bank)
- Two different commercial analytical tools were evaluated (Instem's Safety Intelligence Program and Elsevier's Pharmapendium)
- The following questions were asked. What types of data are available and unavailable ? Can relationships be developed between clinical and nonclinical safety data ? What limitations exist regarding these analyses ?

Summary and Suggestions

- Availability of nonclinical and clinical safety data in public databases is highly variable and difficult to search
- Publicly available data are oftentimes summary level, versus primary datasets
- FDA NDA summaries of approved drugs have the greatest amount of nonclinical and clinical data. However, the data are not organized by pharmacologic class, the data are difficult to develop relationships between nonclinical and clinical data sets, automation with analysis /searching is not apparent, and data available based on FDA assessment of primary source data
- Commercially available software tools provide significant advantages for searching and data analysis; address disadvantages indicated above to varying degrees of success
- Key challenges for evaluating relationships between nonclinical and clinical safety data include the following: 1) relating doses in toxicology studies with human doses, 2) comparing drug exposures between animal and human studies, 3) differences in terminology/ontology between nonclinical and clinical data, 4) variances/inconsistency in terminology across studies, 5) mapping animal toxicology findings (especially pathology) to human adverse events and vice-versa, and 6) ability to search based on pharmacologic class/mechanism of action is not always apparent as some pharmacologic classes/mechanisms of action are too broad for effective searching (eg, kinase inhibitors)
- Associating nonclinical safety data with pharmacologic class information (MOA = mechanism of action, PE = physiologic effect, CS = chemical structure, and/or EPC = established pharmacologic class) or targets could aid with the following: 1) identifying common toxicities with a pharmacologic class, 2) identifying relationships between nonclinical and clinical data, 3) provide an alternative to therapeutic area for categorizing drugs, and 4) provide a means to anticipate undesirable effects that may be associated with the drug or pharmacologic class
- Pharmacologic class information (MOA, PE, CS and/or EPC) should be included as metadata associated with SEND datasets; 1) use the Veterans Administration National Drug File - Reference Terminology (NDF-RT) as a guide, and 2) include known pharmacologic target for the drug

Note: this project is derived from the combination of 2 former projects in the Nonclinical WG: Endpoint Predictivity and Data Interconnectivity

Accomplishments

- The following article was recently published by members of the Nonclinical Working Group:

Kasturi J, Brown AP, Brown P, Madhavan S, Prabakar L, Wally JL. Interconnectivity of disparate nonclinical data silos for drug discovery and development. Therapeutic Innovation & Regulatory Science, OnlineFirst version 22 April 2014

http://dij.sagepub.com/content/early/2014/04/21/2168479014531421.abstract.

Links to Select Drug Databases

- DailyMed for FDA approved drug labels

http://dailymed.nlm.nih.gov/dailymed/index.cfm

- Drug Bank - open source for drug and pharma target information in tabular format

http://www.drugbank.ca/

- FDA summary reviews of NDAs

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

- TOXNET - Toxicology Data Network (toxicology information on numerous chemicals)

https://www.nlm.nih.gov/toxnet/index.html

- European Medicines Agency

http://www.ema.europa.eu/ema/

- FDA Orange Book (generic drug products)

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

- TG-Gate - Life Science Database Archive (Japanese site for misc information on approved drugs, pathways, pharmacology, etc)

http://dbarchive.biosciencedbc.jp/en/open-tggates/desc.html

Relevant Publications

- Kropp TJ et al. FDA engages collaborators to address nonclinical data challenges. Therap Innov & Reg Sci 2013; 47(1):41-5
- Kasturi J et al. Interconnectivity of disparate nonclinical data silos for drug discovery and development. Therap Innov & Reg Sci 2014; 48(4):498-506
- Bai and Abernethy. Systems pharmacology to predict drug toxicity: integration across levels of biological organization. Annu Rev Pharmacol Toxicol 2012; 53:451-473
- Chen M et al. FDA-approved drug labeling for the study of drug-induced liver injury. Drug Discovery Today 2011; 16(15/16):697-703
- Parkinson J et al. Application of data mining and visualization techniques for the prediction of drug-induced nausea in man. Tox Sci 2012; 126(1):275-284
- Briggs K et al. Inroads to predict in vivo toxicology - an introduction to the eTOX project. Int J Molec Sci 2012; 13: 3820-3846
- Valerio LG. In silico toxicology for the pharmaceutical sciences. Tox Appl Pharmacol 2009; 241:356-370
- Cases M et al. Editorial: Improving data and knowledge management to better integrate health care and research. J Int Med 2013; 274:321-328
- Olson H et al. Concordance of the toxicity of pharmaceuticals in humans and in animals. Reg Toxicol Pharmacol 2000; 32:56-67
- Tamaki C et al. Potentials and limitations of nonclinical safety assessment for predicting clinical adverse drug reactions: correlation analysis of 142 approved drugs in Japan. J Toxicol Sci 2013; 38(4):581-598