**Overview**

An expert rule-based system is one of the methodologies required to support an ICH M7 compliant computational analysis. In this type of system, knowledge concerning different structural features that are associated with mutagenicity is encoded as rules in the system. If these structure-activity rules map onto the compound being evaluated, then it may indicate the compound is mutagenic.

**Alert Definition**

For all test compounds within the applicability domain of the alert reference set, a prediction is made. (i.e., the training set compounds cover the chemistry of the impurity development of the principles set forth by the Organisation for Economic Co-operation and Development (OECD) in the regulatory environment. Any remaining alerts are classified as either active or inactive. The purpose of the alert is to establish which alerts should be used to make a decision about the chemical. An expert alert reference set. SAR knowledge was derived from this data using a series of Leadscope computational methodologies. This is possible to transfer structure-activity knowledge while still protecting the intellectual property associated with individual compounds and data by using a chemical substructure SAR fingerprint. The number of false positives using the updated alert set containing knowledge derived from this analysis has decreased significantly (by over a third), resulting in a corresponding performance increase in specificity and positive predictivity. This improvement will reduce the need for laboratory testing in supporting ICH M7 submissions, ultimately reducing the time and cost associated with pharmaceutical development while still protecting patient safety.

**Applicability Domain**

The ICH M7 guideline states that the two computational methodologies should adhere to the general principles set forth by the Organisation for Economic Co-operation and Development (OECD) in the development of the models. One of these principles is “a defined domain of applicability” meaning that each model must unambiguously verify that it is capable of making a prediction for the test chemical. In the training set compounds cover the chemistry of the impurity. A prediction is made where the test chemical is unambiguously within the applicability domain of the alert based on the degree of similarity of the test chemical to the reference set.

**Results**

**Validation Test Dataset**

The test set included data from:

- 10,295 compounds from the Leadscope alert expert reference set
- The 4,021 compounds from the National Institute for Health Science, Japan
- The 6,512 compounds from the Hansen set

Duplicates across these three collections were removed resulting in a final validation test set of 14,753 compounds.

**Assessing Performance of Test Set Predictions**

Results from predicting test compounds only when experimental data was not available.

**Conclusion and Discussion**

Sharing data and knowledge derived from proprietary databases with the developers of expert alerts improves the performance of existing public alerts systems (considered acceptable by regulatory authorities for complying with ICH M7) and expands the domain of applicability for these models. It is possible to transfer structure-activity knowledge while still protecting the intellectual property associated with individual compounds and data by using a chemical substructure SAR fingerprint. The number of false positives using the updated alert set containing knowledge derived from this analysis has decreased significantly (by over a third), resulting in a corresponding performance increase in specificity and positive predictivity. This improvement will reduce the need for laboratory testing in supporting ICH M7 submissions, ultimately reducing the time and cost associated with pharmaceutical development while still protecting patient safety.

**Acknowledgments**

The authors of this poster thank Errol Ziegler and Ron Snyder for their help in developing the expert alert system as well as the participants in the knowledge sharing program.