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SEMINAR

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November 29, 2007  
304 Whitehead Hall  
Refreshments: 3:30 p.m.  
Seminar: 4:00 p.m.

**“HYPOTHESIS-FREE” DETECTION OF DRUG SAFETY SIGNALS**

ABSTRACT

In this presentation, I will describe the practical application of systematic analytical techniques that enable direct and immediate access to comprehensive, objective, and “hypothesis-free” views of drug safety signals. These tools dramatically speed and improve the quality and the transparency of the analyses of huge datasets.

This approach does not require the early definition of a specific hypothesis. The data collection, loading, and analytical tasks of the whole database are performed in advance. The product is a comprehensive database of signal scores coupled to graphic displays optimized to improve comprehension of the signals and context information. These tools are available for interactive use and medical validation.

For drugs already on the market, the main analytical tasks are performed using the Multi-item Gamma Poisson Shrinker (MGPS) statistical algorithm. MGPS simultaneously detects every signal of a “higher-than-expected” drug-adverse event association in FDA’s huge post-marketing safety database, the Adverse Events Reporting System (AERS). To identify signals in the data, MGPS utilizes a disproportionality analysis, combined with Bayesian shrinkage. These processes protect against generating multiple false-positive signals due to multiple independent comparisons. MGPS uses the independence model as the basis for computing the expected count. MGPS includes a Maentel–Haenszel style approach for adjusting the expected counts for potential strata heterogeneity by routinely stratifying by over 1300 categories derived from different combinations of age, sex, and year of report. Thus, the database itself serves as a background “expected”.

The MGPS algorithm was originally applied to detect fraudulent use of calling cards at AT&T and to analyze multi-item combinations of adverse drug events, drug-drug interactions, and event syndromes at the FDA in 2000. The GPS, an earlier version of MGPS, was developed and began application at the FDA in January, 1998. GPS analyzed simple drug-event pairs with an earlier version of the AERS database.

We are also exploring another statistical algorithm, the Hierarchical Bayesian Logistic Regression (HBLR), to generate signals for selected events which may be otherwise confounded by the presence of selected drugs (with their own potentially strong adverse event associations) throughout the database. Systematic logistic regression methods are more computationally intensive than the MGPS approach; for this reason they have not yet been implemented for routine, simultaneous screening of the whole safety database. Our experience indicates that HBLR may be a useful adjunct to MGPS in post-marketing safety assessments when systematically implemented, especially in polytherapy regimens, when confounding is more likely.