Background
As part of ongoing surveillance of post-market drug safety, the Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND) jointly review relevant data, summarize findings, and, when necessary, develop a plan to further investigate potential new safety issues for products regulated by the Center for Drug Evaluation Research (CDER). 1 Various data mining tools, such as Empirica Signal, are available to aid in post-market drug safety surveillance efforts. 2

OSE, in collaboration with both the Office of Biostatistics (OB) and the Office of Computational Sciences (OCS), examined the feasibility of using MAED-Based Adverse Event Diagnostics (MAED) as an additional tool for post-market surveillance. MAED employs the likelihood ratio test (LRT) based method for signal detection. 3 MAED-LRT also allows users to subset the products or events in an analysis, thereby providing more minimal user input.

We focused on Saxagliptin as an additional tool for post-market safety surveillance. In contrast to Scirica 4 and cardiovascular outcomes in patients with type 2 diabetes mellitus. 5

Method
We included data elements from the FAERS database relevant to Saxagliptin. We focused on Saxagliptin and compared it to other drugs used to treat diabetes, excluding insulin.

A SAS script was written to transform FAERS data into the appropriate data structure and format required by MAED-LRT. The feasibility of transforming the FAERS data was assessed by considering whether the data could be transformed for MAED-LRT use, and the extent of automating the transformation to require minimal user input.

We executed the MAED-LRT analysis twice: once running 500 simulations and another running 1000 simulations. Adverse event (AE) terms with a P-value of ≤ 0.05 were considered potential signals from MAED-LRT. These signals were then compared with potential signals that had a Bayes geometric mean (EB05) between 1 and 2, and the EB05 > 2 from Empirica Signal. As shown in Table 1, common AE terms were identified by MAED-LRT with p < 0.05 and Empirica Signal with EB05 ≥ 1.

Table 1: Common AE terms from MAED-LRT with p ≤ 0.05 and Empirica with EB05 ≥ 1

Table: Evaluation of MAED-LRT AE Terms Not Identified by Empirica Signal with EB05 > 1

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Discussion
Data extracted from FAERS can come in various formats, but not as the MAED compatible sas7dbat. Due to the limitation of other data formats, we used the latest excel format (.xlsx) to house the data before transformation. Transformation of the data was feasible because the automation required only two user parameters.

Signal detection using MAED-LRT has the potential to add value to post-market drug safety surveillance. In contrast to Empirica Signal, it identified cardiac failure congestive and cerebrovascular accident as signals. Furthermore, the user can compare one drug with a group of comparators used to treat the same medical condition and identify potential signals while adjusting for underlying diseases.

While MAED-LRT shows promising results as an adjunctive post-market safety surveillance tool, more testing is required.

Results
Transformation of FAERS data for MAED-LRT use was achieved using a SAS program that requires two user parameters: the location, and the name of, the FAERS data. MAED-LRT analysis for 500 and 1000 simulations produced the same AE terms for p ≤ 0.05; hence, 500 was used to reduce the runtime.

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Table 2 further explored the utility of MAED-LRT analysis by assessing the clinical significance of AE terms not identified in Empirica Signal with EB05 ≥ 1. Fifteen of the 22 AE terms were identified as potential signals because they were not labeled. Cardiac failure congestive was also identified from CVOT. 6 Cerebrovascular accident was added to labeling for Saxagliptin in Japan. 7

References

Acronyms:
FDA = Food and Drug Administration; IBM = International Business Machines Corporation; SAS=Statistical Analysis Software; MAED = Medical Dictionary for Regulatory Activities

Disclaimer: The views expressed in this presentation are those of the authors and do not necessarily represent the policy of FDA.