

Piloting Post-market Surveillance of Saxagliptin with FDA Adverse Event Reporting System and MedDRA-Based Adverse Event Diagnostics



C. Cao², D. Choi⁴, O. Dang², S. De², T. Guo³, L. Huang³, R. Kurtzig², J. Li¹, A. Taylor⁴, R. Tiwari³, J. Zalkikar³

¹FDA OCS, ²FDA OSE, ³FDA OB, ⁴IBM

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 MedDRA-Based Adverse Event Diagnostics (MAED) as an additional tool for post-market safety 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 comparison options. This pilot explored whether the transformation of FDA Adverse Event Reporting System (FAERS) data for MAED-LRT use was possible. We also examined the utility of the output generated from MAED-LRT to aid in identifying potential signals compared to that of Empirica Signal.

Method

We included data elements from the FAERS database relevant to MAED-LRT. 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.

Acronyms:

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

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

Adverse Event (AE) Preferred Term	MAED-LRT: P-value	Empirica: EB05	OSE Comment
Otosclerosis	0.002	46.197	Not Labeled
Pancreatitis	0.002	11.05	Labeled
Pancreatitis acute	0.002	7.423	Labeled
Blood glucose increased	0.006	5.131	Indication/Disease/Treatment Related
Blood glucose decreased	0.002	3.304	Indication/Disease/Treatment Related
Glomerular filtration rate decreased	0.002	3.654	Indication/Disease/Treatment Related
Angioedema	0.002	3.424	Labeled
Hypogammaglobulinaemia	0.002	3.729	Not Labeled
Oedema peripheral	0.002	2.159	Labeled
Oedema mouth	0.002	2.272	Labeled
Rash	0.002	2.061	Labeled
Upper respiratory tract infection	0.002	1.697	Labeled
Swelling face	0.002	1.615	Labeled
Weight decreased	0.002	1.388	Labeled
Acute lymphocytic leukaemia	0.002	1.354	Not Labeled
Urticaria	0.002	1.326	Labeled
Aortic aneurysm	0.028	1.243	Not Labeled
Lip swelling	0.002	1.161	Labeled
Headache	0.002	1.139	Labeled
Gastrointestinal disorder	0.028	1.881	Labeled
Swollen tongue	0.006	1.097	Labeled
Drug dose omission	0.004	1.086	Not Labeled
Swelling	0.028	1.085	Labeled
Eye swelling	0.002	1.003	Labeled

Table 2: Evaluation of MAED-LRT AE Terms Not Identified by Empirica Signal with EB05 > 1

AE Preferred Term	MAED-LRT: P-value	OSE Comment
Biliary polyp	0.002	Not Labeled; all clinical trial cases
Injection site pain	0.002	Not Applicable; saxagliptin only available as tablet
Drug ineffective	0.002	Not Labeled; common AE in FAERS
Decreased appetite	0.002	Not Labeled; direct effect of drug
Lactic acidosis	0.002	Not Labeled; possibly confounded by concomitant use of metformin
Pneumonia	0.002	Not Labeled; respiratory infections labeled (potential for elevation)
Dehydration	0.002	Labeled
Cardiac failure congestive	0.002	Not Labeled; Saxagliptin shown to increase rate of hospitalization for heart failure in Cardiovascular Outcomes Trial (CVOT) ⁴
Cardiac disorder	0.002	Not Labeled; Saxagliptin did not increase or decrease ischemic events in CVOT ⁴
Cerebrovascular accident	0.002	Not Labeled; Saxagliptin did not increase or decrease ischemic events in CVOT ⁴ ; added to labeling in Japan ⁵
Anaphylactic shock	0.002	Labeled
Coronary artery disease	0.002	Not Labeled; Saxagliptin did not increase or decrease ischemic events in CVOT ⁴
Myocardial infarction	0.002	Not Labeled; Saxagliptin did not increase or decrease ischemic events in CVOT ⁴
Non-cardiac chest pain	0.002	Not Labeled; Saxagliptin did not increase or decrease ischemic events in CVOT ⁴
Pruritus	0.002	Labeled
Urinary tract infection	0.002	Labeled
Bladder cancer	0.006	Not Labeled; possibly confounded by concomitant use of pioglitazone
Cardiac arrest	0.018	Not Labeled; Saxagliptin did not increase or decrease ischemic events in CVOT ⁴
Anaphylactic reaction	0.022	Labeled
Constipation	0.024	Not Labeled; common and non-serious AE
Acute myocardial infarction	0.028	Not Labeled; Saxagliptin did not increase or decrease ischemic events in CVOT ⁴
Hypersensitivity	0.028	Labeled

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 $p \leq 0.05$; hence, 500 was used to reduce the runtime.

As shown in Table 1, common AE terms were identified by MAED-LRT with $p \leq 0.05$ and Empirica Signal with EB05 ≥ 1 .

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.⁴ Cerebrovascular accident was added to labeling for Saxagliptin in Japan.⁵

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 drug safety surveillance tool, more testing is required.

References:

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