# Adversе Effects in Metformin Clinical and Post-Clinical Trials: A Comparative Study of the United States and Japan

Jay Campanell, Sophie Sun, Gabriel Keller

LASA ACC Biotechnology Internship, JST Sakura Science Program

## Abstract

Diabetes represents a major public health crisis in both the United States and Japan. Metformin (Glucophage, one of the most common treatments for Type 2 Diabetes (the dominant form of the disease)), has been on sale in both nations for decades. This study aims to assess the impact of the two nations' distinct regulatory environments and demography on reported adverse effects of metformin in clinical and post-clinical trials. Our study concluded that the American approval process and post-market surveillance was successful in predicting adverse events associated with metformin, while the Japanese approval process and post-market surveillance was significantly less accurate in predicting adverse effects associated with metformin.

## Introduction

How do the approval processes for adverse effects in the United States and Japan compare in their ability to predict the potential adverse effects of metformin?

Metformin hydrochloride, sold under the brand name Glucophage, is a prescription medication used to treat type 2 diabetes, a chronic medical condition in which the body cannot properly produce or process insulin. Glucophage is the most widely prescribed drug for type 2 diabetes. Glucophage decreases the amount of glucose produced by the liver and by increasing the body's sensitivity to insulin. It can also reduce the risk of cardiovascular complications associated with type 2 diabetes. Glucophage is one of the few diabetes medications that may help to reduce the risk of developing type 2 diabetes in people with prediabetes.

The FDA defines an adverse event is as any undesirable experience associated with the use of a medical product in a patient that does not necessarily have a causal relationship.

Although Glucophage is generally well tolerated, it is associated with a number of adverse reactions, including nausea, vomiting, diarrhea, abdominal pain, headache, and fatigue. Glucophage may increase the risk of lactic acidosis, a potentially fatal condition.

In the United States, Glucophage is often prescribed as a first-line treatment for type 2 diabetes, while in Japan, Glucophage is used more as a second-line treatment.

The drug was approved in the United States by the US Food and Drug Administration (FDA) in 1995, while the drug was approved in Japan by the Ministry of Health, Labour, and Welfare (MHLW) in 1997. In both countries, the drug was approved through the New Drug Application and the Japanese equivalent, the New Drug Application for Innovative Drugs.

In the United States, the FDA utilizes the Adverse Event Reporting System (FAERS) and requires drug manufacturers to conduct post-marketing studies to further evaluate safety and efficacy. Additionally, Japan has a unique system called the "JADER" database, which collects and analyzes adverse event reports from healthcare professionals and patients.

## Methods

Both post clinical trial data and approval data were used. The post clinical trial data was obtained from the US and Japan's spontaneous reporting databases. Using the OpenFDA's API calls were made to obtain all spontaneous reports recorded in the FAERS (FDA Adverse Event Reporting System) database. For Japan, the PMDA has their JADER database stored in PDF files on their website. Once data was collected from Spontaneous Report Databases (SRD) AEs of interest were chosen from the approval processes of metformin in the US and Japan. In the clinical trials, the AEs chosen to be AEs of interest had an incidence in double-blind stage 3 clinical trials of greater than 5% and that were more commonly reported in patients on the metformin medication than those taking the placebo. AEs excluded from analysis were AEs that were not seen as significant or did not show up in clinical trials to get metformin approved in each country. They were excluded because it is much harder to compare those AEs internationally due to the fact that the PMDA has much less data which gives inconsistent results with AEs at lower counts.

To determine if the AE was considered significant, disproportionality analysis was done on the databases. Because of the limitations of spontaneous reporting - observational data, underreporting is common, does not determine casualty, statistical measures to compare how unexpected a drug-event reaction is compared to the rest of the database. One of the most common methods of measuring disproportionality are proportional reporting ratios (PRRs).

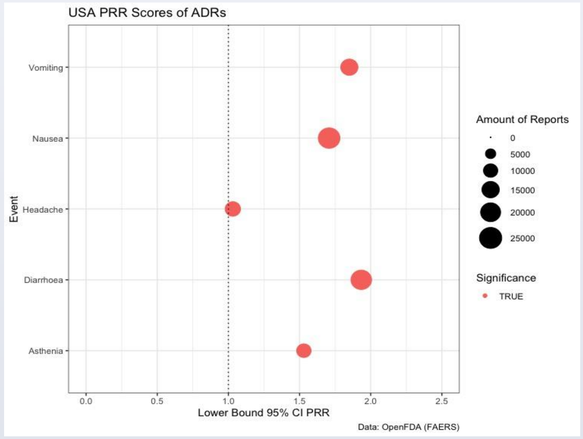
$$PRR = \frac{a/(a+c)}{b/(b+d)}$$

| | Drug of Interest | All other drugs |
|---|---|---|
| ADR of interest | A | B |
| All other ADRs | C | D |

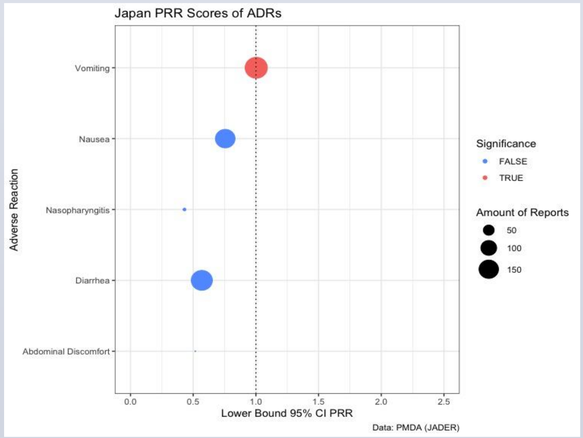
To get close to detecting real world data, spontaneous reporting databases were used because they are the most widely used tool for post market surveillance of medications and both the US and Japan have structured systems with data available to the public for analysis. To detect if a drug-event reaction should be considered significant from the data in the SDRs one of the European Medical Agency's (EMA) signal detection parameters was used. The parameters used are if the lower bound of a 95% of the PRR scored is greater than 1 and the number of observations is greater than 5. It was selected due to the ease of calculating significance with the available data and because of its reputable reliability found in clinical studies conducted by the EMA for the most effective signal detection methods. PRRs were calculated for all adverse events of interest for metformin, those found to be possibly significant in Phase 3 of Clinical trials. Adverse events were then tested for if they were significant, if the adverse event proved significant then the clinical trials were predictive of the drug in the real world and if it proved to not be significant then the clinical trials were not predictive of real world situations.

## Results

For the United States, the adverse effects that were considered to be significant in the clinical trials given to the FDA for metformin approval were diarrhea, nausea/vomiting, abdominal discomfort, flatulence, asthenia, indigestion, and headaches. Out of those adverse effects, all were seen to be significant with a 95% CI lower bound value of greater than 1 (flatulence and indigestion were not found in the FAERS database).




The adverse effects found in Phase 3 Clinical Trials for Japan were diarrhea, nausea, abdominal pain, vomiting, anorexia, nasopharyngitis, and increased blood lactate. Out of those the only one found to be significant with a lower bound PRR score of greater than 1 was vomiting (anorexia and increased blood lactate were not found as adverse reactions in JADER).




Overall the observations/reported adverse events amount had much smaller values in Japan's database when compared to the United States.

## Discussion

The US regulatory system proved to be much better at predicting real-world adverse events than Japan, with all of the adverse events coming back as significant compared to only one from Japan. The function of the spontaneous reaction databases could have been a factor in this result as well. Japan's JADER database mainly focuses on serious reactions and the majority of reports come from healthcare officials. It can be hard to enforce healthcare officials to report because of how busy they are therefore only more serious AEs are reported. The AEs investigated and predicted in clinical trials all are mild such as diarrhea and headaches and thus medical officials in Japan could have been less likely to report such reactions causing the count to be significantly lower in the database than compared to the true value giving a lower PRR score than what is necessarily true. The FAERS database also has a considerable amount of reports directly from consumers (roughly half of the database) therefore less severe reactions could be more readily reported making the database more reflective of real-world circumstances and giving more accurate PRR scores.

## Acknowledgements

We would like to thank Mr. Oleniczak for supporting us on this project. We would also like to thank all of our generous hosts during our exchange trip in Japan, especially Imaeda-san from Pfizer for organizing and hosting the trip, Shimatani-san from Pfizer for providing partial funding for the trip, and Dr. Narukawa from Kitasato University who pointed us towards disproportionate analysis as a way to compare the countries. We would also like to thank the following: (PMDA) Chief Executive Yasuhiro Fujiwara, Dr. Sato Junko, Togashi Mika, Hiroto Inuzuka, Miho Sato, Ms. Ogawa, Shinichi Okudaira, Ehara Teruyoshi, and (Kitasato University) Takeshi Hirayama, Yoshinori Kobayashi, Misa Oyama. We had the pleasure of meeting many more fantastic people at Pfizer, the PMDA, and Kitasato University that are regretfully not listed.

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