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Post market Research of Oral Anti-Diabetic Drugs: Metformin, Glipizide, and Pioglitazone

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ABSTRACT

The aims of this study were to document the post market research of the pharmaceutical industry and the effects of labeling revisions on post market studies and outcomes of oral anti-diabetics. A literature search identified post market studies of metformin, glipizide, and pioglitazone. Labeling revisions in MedWatch® were collected as indicators of the FDA's response to post market drug safety. Data were analyzed by comparing industry and non-industry sponsored studies for the number of pre- and post-market studies, study sponsorship, drug labeling revisions, and outcomes after the drugs became generic. The number of industry versus non-industry sponsored studies was 149 (49%) and 155 (51%) for metformin; 33 (44%) and 42 (56%) for glipizide; and 85 (80.2%) versus 21 (19.8%) for pioglitazone. The differences in favorable results between industry and non-industry sponsored studies were similar for metformin and glipizide. The number of industry-sponsored studies with favorable results did not significantly increase after metformin or glipizide became generic. Studies sponsored by the manufacturer of glipizide reported significantly more favorable outcomes in comparison to studies sponsored by industry competitors (90% favorable, 10% neutral, 0% unfavorable, $P < 0.05$). For pioglitazone, significantly more favorable results were reported in industry-sponsored studies (88.2%) as compared to non-industry (66.7%) ($p = 0.008$) sponsored studies. A significant correlation exists between the number of pioglitazone's labeling revisions and the number of post market studies ($p = 0.008$). Post market research is guided by the pharmaceutical industry and by individual researchers' interests. Pharmaceutical industry-sponsored studies support the favorable use of the patented drug and show unfavorable results of the generic equivalent. A possible correlation exists between drug labeling revisions and the number of post market studies.

INTRODUCTION

Pre-market studies are used by the US Food and Drug Administration (FDA) to review a new drug application. However, pre-market studies test the drug in a relatively small number of patients and specific patient populations for a short time (Rados, 2003; National Research Council, 2007). Due to these limitations, the possibility of potentially serious adverse effects which may occur following drug release on the market cannot be excluded, and can eventually lead to drug withdrawal, or revisions of its prescribing, warnings, and contraindications (Coombes, 2007; Shah, 2007). Post market research of a new drug is essential to gain more insight into the drug's safety and efficacy. Although pharmaceutical companies are responsible for conducting post market research of their patented drugs (Melander *et al.*, 2003; Van Thiel and van Delden, 2008), they have however failed to initiate adequate post market research especially when the reported drug adverse effects in pre-market studies are not life-threatening (Fontanarosa *et al.*, 2004; Doucet and Sismondo, 2008; Ross *et al.*, 2008). Less than half of post market studies that pharmaceutical companies have committed to conduct as a condition for drug pre-approval are ever completed, and the research sponsored by the pharmaceutical industry tends to overemphasize the benefits of the patented drug while downplaying its potential risks (FDA, 2004; Fontanarosa *et al.*, 2004; National Research Council, 2007). Prior to the Food and Drug Administration Amendments Act (FDAAA) of 2007, the FDA could only mandate pharmaceutical companies to complete post market research of the drugs with pediatric indications and those

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that received accelerated approval (National Research Council, 2007). This narrow focus of mandated post market research may be due to limited FDA resources for reinforcing and evaluating post market research (National Research Council, 2007). Therefore, the FDA has launched post market surveillance programs including the Adverse Event Reporting System and MedWatch® to capture post market adverse drug events. Regardless, post market research still lags behind expectations and can be biased in favor of the patented drug particularly when the research is funded by the pharmaceutical industry (Lexchin *et al.*, 2003; Procyshyn *et al.*, 2004; Shah *et al.*, 2005; Kelly *et al.*, 2006). The Institute of Medicine's report on "Preventing Medication Errors" further emphasizes that post market research efforts are limited contrary to the FDA recommendations, and that the sponsorship of research tends to favor certain outcomes (National Research Council, 2007).

The purpose of this study was to document and evaluate the post market research studies and clinical trials related to the 3 most commonly prescribed oral anti-diabetic drugs: metformin, glipizide, and pioglitazone in the period prior to the implementation of the FDA in March of 2008 which granted the FDA more authority to require post market research.

MATERIAL AND METHODS

Study Design

A PubMed® literature search limited to the English language was conducted using the terms metformin, glipizide, pioglitazone, and diabetes to collect all post market research published during specific years pertaining to pioglitazone (1997-2008), glipizide (1984-2008), and metformin (1978-2008). Literature search included clinical studies, randomized controlled trials, comparative studies, multicenter studies, evaluation studies, meta-analyses, and systematic reviews.

Data on funding sources (industry or non-industry), year of study, and outcomes (unfavorable, neutral, or favorable) were collected. Information on the year and number of labeling changes was collected from the MedWatch®: The FDA Safety Information and Adverse Event Reporting Program, webpage (FDA, 2014).

Data Interpretation

Post market studies were categorized as favorable, unfavorable, or neutral for metformin, glipizide, and pioglitazone based on the following criteria:

I-A study has favorable outcomes if it shows any of the following:

1. The drug benefits outweigh its risks.
2. The drug was therapeutically superior to placebo or to other oral anti-diabetic drugs and had decreased side effects.
3. If the study did not compare the drug to placebo or to other oral antidiabetic drugs but its results encourage the use of it.
4. If the study demonstrates the drug efficacy to exceed its established efficacy or if its side effects are fewer than what is reported in the drug package insert.

II. A study has neutral outcomes if it shows any of the following:

1. The drug was therapeutically superior to placebo or to other oral anti-diabetic drugs in some aspects but inferior in other aspects, and no definitive conclusion about the drug safety or efficacy is reached.
2. The study neither discourages nor encourages the use of the drug.
3. The study demonstrates that the efficacy and side effects of the drug are comparable to its established efficacy and side effect profile.
4. The study does not determine if the drug benefits outweigh its risks.

III. A study or clinical trial has unfavorable outcomes if it shows any of the following:

1. The drug benefits do not outweigh its risks.
2. The study shows that the drug is therapeutically inferior to placebo or other drugs, or has increased side effects.
3. The study does not directly compare the drug to placebo or other drugs, and the study results discourage or limit the use of the drug.
4. The study demonstrates that the efficacy of the drug is below its established baseline or its side effects are greater than its side effect profile.

Sponsorship

Sponsorship was recorded as industry-sponsored or non-industry sponsored. Information was identified from the acknowledgement section of the paper, which when not present, the paper was read to identify the sponsorship. Sponsorship was categorized according to the following criteria:

I -Industry sponsorship was deemed present if the study met any of the following criteria:

1. It is stated in the publication that a pharmaceutical company is a sponsor in full or part of the study.
2. A drug company affiliate is listed as one of the authors.
3. One or more authors are current employees of the pharmaceutical company or were employed while the study was conducted.
4. Any author declares conflict of interest with a pharmaceutical company, including stocks holding or financial interest in the company.
5. An external agency or organization was sponsored by the pharmaceutical company to conduct the study.
6. If multiple sources or any contribution of funds are listed, the study is considered to have industry sponsorship if a pharmaceutical company was one of the funding sources.

II-A study was considered to have non-industry sponsorship if it did not fit into one of the abovementioned criteria, did not receive any funding, included but was not limited to government institutions, private foundations, non-profit organizations, academic institutions, and professional societies.

Statistical Analysis

A non-parametric binomial test was used to test if the number of studies sponsored by the pharmaceutical and non-pharmaceutical industry had a 50-50 split. Chi-square and Fisher's exact tests were used to test for relationships between industry-sponsored studies and the study results. Chi-square was used to compare if the outcomes of the post market studies were more favorable before or after the drug became generic for industry-sponsored studies and non-industry sponsored studies. Spearman's rho correlation was used to test the relationship between the number of post market studies and the number of labeling revisions in MedWatch®.

A two-sample independent t-test, binomial probability test, and Fisher's exact test were used to compare if the number of post market studies were different before and after the drug became generic. All tests were two-tailed tests, with a $p < 0.05$ considered statistically significant with a 95% confidence interval. Statistical analyses were performed using SPSS (SPSS Statistics for Windows, 17.0, 2008; SPSS Inc., Chicago, IL).

Results

Metformin

There were 304 metformin studies with 183 (60.2%) studies that showed favorable outcomes, 62 (20.4%) were neutral, and 59 (19.4%) were unfavorable (Table 1). Industry-sponsored studies were 149 (49%) (55% favorable, 22.8% neutral, 22.2% unfavorable) as compared to 155 (51%) non-industry sponsored studies (65.2% favorable, 18.1% neutral, 16.9% unfavorable) ($p > 0.05$). There were significantly more studies that included metformin after it became generic as compared to the time before its patent expired (239 vs. 65 studies, respectively; $p < 0.05$). This increase was significant in the industry and non-industry sponsored studies ($p < 0.05$ for both). The number of favorable outcomes was similar between industry and non-industry sponsored studies ($p > 0.05$). Favorable outcomes were also similar in industry or non-industry sponsored studies that were conducted before and after metformin patent expiration ($p > 0.05$). There were no significant differences between studies sponsored only by the manufacturer of metformin (*Bristol-Myers Squibb, NY, NY)* as compared to those co-sponsored by the manufacturer or those sponsored by industry competitors, or non-industry sponsors ($p > 0.05$). There were 8 MedWatch® labeling revisions for metformin, but no relationship was found between the number of post market studies and the number of MedWatch® labeling revisions.

Glipizide

There were 75 glipizide studies with 33 (44%) industry-sponsored studies (63.6% favorable, 18.2% neutral, 18.2% unfavorable) and 42 (56%) non-industry sponsored studies (40.4% favorable, 31% neutral, 28.6% unfavorable) ($p > 0.05$) (Table 2). There was no significant increase in the percentage of industry-sponsored studies that showed favorable outcomes after glipizide became generic ($p > 0.05$). The number of studies conducted did not differ before and after glipizide's patent expiration ($p > 0.05$). After glipizide became generic, the number of non-industry sponsored studies significantly decreased from 29 to 13 studies ($p < 0.05$), and the number of industry-sponsored studies increased from 12 to 21 studies, but this difference was not statistically significant ($p > 0.05$). Favorable outcomes were similar between industry and non-industry sponsored studies before or after glipizide patent expiration ($p > 0.05$ for both). In comparison to studies sponsored by industry competitors, studies sponsored by the manufacturer of glipizide (Pfizer, NY, NY) reported significantly more favorable outcomes (90% favorable, 10% neutral, 0% unfavorable, $p < 0.05$). There were no MedWatch® labeling revisions for glipizide.

Table. 1: Metformin Results.

Metformin Studies	Number of Studies	Study Outcomes (%)			
		Favorable	Neutral	Unfavorable	*p*- value
Total	304	183 (60.2)	62 (20.4)	58 (19.4)	
Before generic	65	46 (70.8)	14 (21.5)	5 (7.7)	
After generic	239	137 (57.3)	48 (20.1)	54 (22.6)	< 0.001[a]
Industry-sponsored	149	82 (55)	34 (22.8)	33 (22.2)	0.774[b]
					0.31[c]
Before generic	35	24 (68.6)	7 (20)	4 (11.4)	0.132[d]
After generic	114	58 (50.9)	27 (23.7)	29 (25.4)	< 0.001[e]
Non-industry sponsored	155	101 (65.2)	28 (18.1)	26 (16.7)	
Before generic	30	22 (73.3)	7 (23.3)	1 (3.4)	0.084[f]
After generic	125	79 (63.2)	21 (16.8)	21 (16.8)	< 0.001[g]
Industry-specific sponsor					
Manufacturer only	17	12 (70.6)	3 (17.6)	2 (11.8)	0.858[h]
Manufacturer co-sponsor	20	11 (55)	4 (20)	5 (25)	0.539[I]
Competitor	112	59 (52.7)	27 (24.1)	26 (23.2)	0.365[i]

For all values, $p < 0.05$ is considered statistically significant.

[a] *Comparing the total number of studies before and after metformin generic.*
[b] *Testing if there is a 50-50 split between the number of industry and non-industry sponsored studies.*
[c] *Comparing favorable outcomes between industry and non-industry sponsored studies*
[d] *Comparing favorable outcomes of industry-sponsored studies before and after metformin became generic.*
[e] *Comparing the number of industry-sponsored studies before and after metformin became generic.*
f *Comparing favorable outcomes of non-industry sponsored studies before and after metformin became generic.*
g *Comparing the number of non-industry studies before and after metformin became generic.*
h *Comparing favorable outcomes of studies by Bristol-Myers Squibb to non-industry sponsored studies.*
I *Comparing favorable outcomes of studies sponsored by Bristol-Myers Squibb only to studies co-sponsored by Bristol-Myers Squibb.*
j *Comparing favorable outcomes of studies by Bristol-Myers Squibb and competitors sponsored studies.*

Table. 2: Glipizide Results

Glipizide Studies	Number of studies	Study Outcomes (%)			
		Favorable	Neutral	Unfavorable	*p*- value
Total	75	38 (50.7)	19 (25.3)	18 (24)	
Before generic	41	18 (43.9)	11 (26.8)	12 (29.3)	
After generic	34	20 (58.8)	8 (23.5)	6 (17.7)	0.490[a]
Industry-sponsored	33	21 (63.6)	6 (18.2)	6 (18.2)	0.298[b]
					0.144[c]
Before generic	12	6 (50)	3 (25)	3 (25)	0.388[d]
After generic	21	15 (71.4)	3 (14.3)	3 (14.3)	0.163[e]
Non-industry sponsored	42	17 (40.4)	13 (31)	12 (28.6)	
Before generic	29	12 (41.4)	8 (27.6)	9 (31)	0.838[f]
After generic	13	5 (38.5)	5 (38.5)	3 (23)	0.019[g]
Industry-specific sponsor					
Manufacturer only	10	9 (90)	1 (10)	0 (0)	0.023[h]
Manufacturer co-sponsor	8	4 (50)	3 (37.5)	1 (12.5)	0.157[i]
Competitor	16	8 (50)	3 (18.8)	5 (31.2)	0.1[j]

For all values, $p < 0.05$ is considered statistically significant.
[a] *Comparing the total number of studies before and after glipizide became generic.*
[b] *Testing if there is a 50-50 split between the number of industry and non-industry sponsored studies.*
[c] *Comparing favorable outcomes between industry and non-industry sponsored studies.*
[d] *Comparing favorable outcomes of industry-sponsored studies before and after glipizide became generic.*
[e] *Comparing the number of industry-sponsored studies before and after glipizide became generic.*
[f] *Comparing favorable outcomes of non-industry sponsored studies before and after glipizide became generic.*
[g] *Comparing the number of non-industry sponsored studies before and after glipizide became generic.*
[h] *Comparing favorable outcomes of studies by Pfizer to non-industry sponsored studies.*
[i] *Comparing favorable outcomes of studies sponsored by* Pfizer *only to studies co-sponsored by* Pfizer.
[j] *Comparing favorable outcomes of studies by* Pfizer *and competitors sponsored studies.*

Table. 3: Pioglitazone Results.

Metformin Studies	Number of Studies	Study Outcomes (%)			
		Favorable	Neutral	Unfavorable	p- value
Total	106	89 (84)	14 (13.2)	3 (2.8)	
Industry-sponsored	85	75 (88.2)	7 (8.2)	3 (3.6)	
Non-industry sponsored	21	14 (66.7)	7 (33.3)	0 (0)	< 0.001a
					0.008b
Industry-specific sponsor					
Manufacturer only	49	43 (87.8)	6 (12.2)	0 (0)	0.049c
Manufacturer co-sponsor	18	17 (94.9)	1 (15.6)	0 (0)	0.664d
Competitor	18	15 (83.3)	0 (0)	3 (16.7)	0.692e

For all values, $p < 0.05$ is considered statistically significant.
a *Testing if there is a 50-50 split between the number of industry and non-industry sponsored studies.*
b *Comparing favorable outcomes between industry and non-industry sponsored studies.*
c *Comparing favorable outcomes of studies by Takeda to non-industry sponsored studies.*
d *Comparing favorable outcomes of studies sponsored by* Takeda *only to studies co-sponsored by* Takeda.
e *Comparing favorable outcomes of studies by* Takeda *and competitors sponsored studies.*

Pioglitazone

There were 106 pioglitazone studies with 85 (80.2%) industry-sponsored studies (88.2% favorable, 8.2% neutral, 3.6% unfavorable) as compared to 21 (19.8%) non-industry sponsored studies (66.7% favorable, 33.3% neutral, 0 unfavorable) ($p < 0.05$) (Table 3). Industry-sponsored studies showed significantly more favorable outcomes as compared to non-industry ($p < 0.05$). There were no significant differences in the favorable outcomes between studies sponsored by the manufacturer (Takeda Pharmaceuticals, Deerfield, IL) and non-industry sponsored studies ($p > 0.05$). There were 16 labeling revisions for pioglitazone, with a relationship between the number of pioglitazone studies and the number of MedWatch® labeling revisions ($p < 0.05$).

DISCUSSION

Type 2 diabetes mellitus is a chronic disease that is associated with high morbidity and mortality (American Diabetes Association, 2008). Drug therapy and lifestyle modifications are the main interventions in the management of diabetics (Nathan *et al.*, 2009). The need for safe and effective anti-diabetic drugs has led to increased pharmaceutical research for new drug classes for the treatment of type 2 diabetes. Following the introduction of thiazolidinediones, post market reports emerged about the possible exacerbation of congestive heart failure (rosiglitazone; pioglitazone) and myocardial ischemia (rosiglitazone), in some patients taking these drugs. The drugs labeling was revised to include black box warnings and precautions that emphasize these potential risks (GSK, 2007; Takeda Pharmaceuticals, 2009). These examples highlight the need for pharmaceutical companies to engage in post market research in order to ensure drug safety in a larger patient population with co-morbid conditions.

This study documents the post market research for the 3 most commonly used anti-diabetic drugs metformin, glipizide, and pioglitazone. For metformin, only 25% of the industry-sponsored studies involved the manufacturer. This low number confirms the concerns of the Institute of Medicine that drug companies are

falling short from conducting post market research (National Research Council, 2007). Favorable outcomes reported with metformin were about similar for industry and non-industry sponsored studies. This might be explained by the high benefit to low risk ratio of metformin as compared to other oral anti-diabetic drugs (Bolen *et al.,* 2007). After a drug becomes generic, its manufacturer may lose interest in financially supporting post market research. However, results of this study indicate otherwise, with the majority of metformin studies conducted after metformin became generic. This is not surprising because the introduction of new oral anti-diabetic drugs has triggered comparative effectiveness studies with metformin, because of its superior safety profile and its long term benefits in reducing diabetes-related myocardial infarction and death especially in overweight diabetic patients (Gillies and Dunn, 2000; Holman *et al.*, 2008). Industry and non-industry sponsored studies were more likely to show favorable results and less likely to be unfavorable before metformin became generic. We speculate that in the earlier years of metformin availability, studies may have focused on its beneficial anti-diabetic effects and its relative safety. As post market experience is gained, studies may have begun to report the drawbacks of metformin that coincided with metformin going generic. Unfavorable results significantly increased after metformin became generic which might be attributed to increased market competition for oral anti-diabetic drugs, with more unfavorable results reported in studies that used metformin as a benchmark to the new oral anti-diabetic drugs. In 2002, there were numerous studies sponsored by the manufacturer on an extended release and combination forms of metformin (Blonde *et al.,* 2002; Garber *et al.,* 2002; Strowig *et al.,* 2002). This might have been an attempt by the manufacturer to use the new metformin dosage forms to extend its patent life and make up for the anticipated large drop in revenues after metformin patent expires. The competition between pharmaceutical companies for the market of oral anti-diabetic drugs may also offer another plausible explanation for the sudden increase in metformin studies. There were studies by the manufacturer of exenatide to promote its new oral anti-diabetic drug, and by the manufacturers of metformin, pioglitazone, and rosiglitazone to protect the position of their drugs (Cook *et al.,* 2007; Goldstein *et al.,* 2007; Nelson *et al.,* 2007; Nichols and Gomez-Caminero, 2007; Rasouli *et al.,* 2007), which may have largely contributed to the high number of industry-sponsored studies in 2007. For glipizide, most post market studies were not sponsored by the pharmaceutical industry. This may be due to the large number of post market studies that were conducted after the patent of glipizide expired. Industry-sponsored post market studies with glipizide tended to show favorable results. This might be explained by a potential conflict of interest by the investigators whose research was supported by the pharmaceutical company, and possible publication bias whereby unfavorable results were not published. In a review of clinical trials for the treatment of multiple myeloma, results that favored a new therapy were more likely to be reported by industry-sponsored studies (Davidson, 1986; Freedman, 1987; Djulbegovic *et al.,* 2000). Moreover, only 5% of industry supported analyses reported unfavorable conclusions in an economic analysis of new cancer drugs, whereas 38% of not-for-profit studies reported unfavorable results (Friedberg *et al.,* 1999). The number of non-industry sponsored studies decreased after glipizide's patent expired, while favorable results remained relatively constant. Whereas other industry-sponsored research by the competitor increased in number and favorability after glipizide's patent expiration, these can be attributed to increased market share after glipizide became generic. Lastly, manufacturer's sponsored studies and the percent of favorable outcomes increased after glipizide's patent expired. However, many of these studies compared the regular glipizide to the manufacturer's extended release formulation which were not distinguished in this study.

For pioglitazone, most post market studies were sponsored by the pharmaceutical industry. This might be explained by the fact that pioglitazone was still patented during our study period and the manufacturer had vested interest in supporting post market studies. Industry-sponsored studies were likely to show favorable results. This might be explained by a potential conflict of interest of the investigators whose research was supported by the manufacturer, a possible research design bias that alters the study methodology to show positive results, and a publication bias that favors the release of only positive outcomes. Studies that were fully sponsored by the manufacturer were more likely to show favorable results when compared to the non-industry sponsored studies, whereas competitor sponsored studies showed more unfavorable results. An association between pharmaceutical industry funding and positive research outcomes in favor of the manufacturer's product has been documented, and may be due to research efforts reliance on industry funds (Shah *et al.,* 2005; Kelly *et al.,* 2006). This study also shows a trend in increased number of post market studies from 1997 to 2008. Although the exact reason is unknown and the black box warning was not added to pioglitazone labeling until 2007, we speculate that this might have been triggered by the 3 MedWatch® reports about pioglitazone in 2003. A high number of 21 post market studies were published in 2006, followed by 18 studies in 2007. There were another 3 labeling revisions in MedWatch® in 2006 and 2007, which may have lead to adding a Black Box Warning to pioglitazone labeling in 2007. In summary, this study is unique in several aspects: it focused on controlled trials and studies of the group of the 3 mostly prescribed oral anti-diabetic drugs over an extended period (1978-2008); it assessed the effects of competitor sponsored studies; evaluated the results before and after the drug became generic; and it is the first study to attempt evaluating the relationship between MedWatch® reports and the number and outcomes of studies that followed. Study results show that post market research of oral anti-diabetic drugs increased with the increasing rate of type 2 diabetes. Sponsorship by pharmaceutical companies is a strong impetus for post market research, with a potential bias favoring positive outcomes for the patented drug (Lexchin *et al.,* 2003; Procyshyn *et al.,* 2004; Shah *et al.,* 2005). This study also suggests a possible relationship between the

number of labeling revisions in MedWatch® and the number of post market studies. Further analysis of the MedWatch® data is still needed before this can be ascertained. Lastly, although such an approach has its own limitations, we believe that the pharmaceutical industry should proactively attempt to predict potentially serious drug adverse events through the known biomarkers of the particular drug at the conclusion of phase III trials, rather than reactively evaluating such reactions after they occur.

This study presents certain limitations. It included published clinical trials and studies from PubMed® which may not include other related research that is listed in other scientific databases. Further, the study was not designed to determine the exact reasons to the trends in post market studies, thus we could only speculate about the most likely reasons for why they occurred. This study looked at data that emerged primarily from the period prior to when the FDAAA took effect in March of 2008. The FDAAA empowered the FDA with additional authorities to require post market studies and clinical trials, safety label changes and Risk Evaluation and Mitigation Strategies (REMS). Fain et alexplored the fulfillment of the post market studies from 2007 to 2011 (Fain *et al.*, 2013). The authors obtained data from the biological license and new drug application from the FDA annual reports published in the Federal Register. The trends identified in their study included a decrease in the number of studies not yet started, an increase in the number of completed studies that fulfilled the post marketing obligation and an increase in the number of delayed studies. Their study was limited by the fact that it was not designed to statistically evaluate the FDAAA's effect on compliance with post marketing commitments. More studies are needed to evaluate the current post marketing data after the FDAAA implementation for the medications we discussed in our study and to look at general trends of post market studies fulfillment.

CONCLUSION

Post market research is guided by the pharmaceutical industry and by the researcher's priorities and interests. When supported by pharmaceutical companies, post market studies show favorable outcomes of the patented oral anti-diabetic or report unfavorable outcomes with the generic drug. A correlation may exist between the number of post market studies and labeling revisions. We speculate that predicting patient vulnerability through a better understanding of biomarkers can assist in setting the appropriate priorities for conducting post market research, and the utilization of biomarkers could enhance the quantity and quality of such research.

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