Actions of the National Regulatory Authorities in 10 Low- and Middle-Income Countries Following Stringent Regulatory Authority Safety Alerts on Rosiglitazone

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Actions of the National Regulatory Authorities in 10 Low- and Middle-Income Countries Following Stringent Regulatory Authority Safety Alerts on Rosiglitazone

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Abstract

On September 23, 2010, the US Food and Drug Administration and the European Medicines Agency issued safety alerts for medicines containing rosiglitazone. The authors monitored the actions of national regulatory authorities (NRAs) from 10 low- and middle-income countries to identify the time lag between the issuance of safety alerts by these two stringent regulatory authorities and any actions by these select NRAs. Two NRAs outside Africa took regulatory actions related to safety of rosiglitazone within 2 weeks of stringent regulatory authority safety alerts. For the 7 of the 8 African NRAs where the authors could confirm the date of regulatory action, the median time lag before some regulatory action was 43 days, although there was considerable variability in time to regulatory action. Low- and middle-income countries should create or strengthen systems for timely consideration and management of emerging safety issues for products that they have registered.

Keywords

pharmacovigilance, rosiglitazone, drug safety, FDA, Africa, Asia

Introduction

On September 23, 2010, the US Food and Drug Administration (FDA) issued a safety alert indicating that the agency would require that the manufacturer develop a restricted access program for rosiglitazone under a risk evaluation and mitigation strategy.[1] On the same day, the European Medicines Agency (EMA) implemented an immediate suspension of the marketing authorization for rosiglitazone-containing antidiabetic medicines, resulting in the drug no longer being available in the European Union.[2] The FDA and the EMA took these steps on the basis of their review of data on the elevated risk of cardiovascular events associated with rosiglitazone, including acute myocardial infarction and stroke. Both the FDA and the EMA are considered to be stringent regulatory authorities (SRAs). SRAs are defined by participation in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use or its observers, such as Health Canada, or it associates, such as Australia, through legally binding mutual recognition agreement.[3]

Globally, national regulatory authorities (NRAs) must consider data on emerging safety risks against benefits in determining what medicines should be available in their countries and under what circumstances. Pharmacovigilance informs such benefit-risk decisions during the postapproval phase. However analyses of drug safety systems in low- and middle-income countries (LMICs) have reported considerable variation and gaps in the infrastructure, resources, and practices among national pharmacovigilance programs.[4,5] Notably, surveys reported variability in the types of regulatory actions taken as a result of information collected by the pharmacovigilance system in respondent countries. Many LMICs lack some

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Table 1. Regulatory actions with rosiglitazone by selected low- and middle-income countries.

Country	Regulatory Actions[a]		Communication Method	Date of Action	Lag Time,[b] d
	Suspension	Enforcement			
Ghana	Yes		Safety alert	Nov 29, 2010	67
Kenya	Yes		Safety alert (e-shot)	Oct 13, 2010	20
Namibia	Yes		Safety alert	Nov 10, 2010	48
Nigeria		Yes	Safety alert + press release	Oct 9, 2010	16
Tanzania	Yes		Not available	Nov 5, 2010	43
Uganda	Yes		Not available	Not available	N/A
Senegal	Yes		Safety alert	Oct 12, 2010	19
South Africa	Yes		Safety alert	Jul 5, 2011	285
India	Yes		Safety alert	Oct 7, 2010	14
Indonesia	Yes		Safety alert	Sep 24, 2010	1

[a]Suspension of market authorization and enforcement of risk management practices.
[b]Refers to time elapsed between stringent regulator authority alert and action by national regulatory authority, in days.

or all of the World Health Organization's (WHO's) basic elements of a pharmacovigilance system.[6] These countries often lack the capacity to conduct periodic benefit-risk analyses throughout the life cycle of products in their market. As such, when medicine safety evidence is critically reviewed and disseminated by SRAs, it has the potential for global impact. Safety information is often exchanged between regulatory authorities and the WHO, facilitated by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. For example, the WHO publishes a periodic pharmaceutical newsletter in collaboration with the monitoring program to disseminate information on safety and efficacy of pharmaceutical products. The WHO Pharmaceuticals Newsletter reported, in the fifth edition of 2010, on the new FDA restrictions on rosiglitazone and the suspension of marketing authorization in Europe. It also reported on the 2010 suspension of marketing authorization of rosiglitazone in New Zealand and new restrictions in Canada.[7,8]

One of the core indicators of the Indicator-Based Pharmacovigilance Assessment Tool for assessing pharmacovigilance systems in developing countries is the average time lag between the identification of a safety signal of a serious adverse drug reaction or other significant medicine safety issue and communication of this information to health care professionals and the public.[9] Advocates for improved access to medicines in LMICs use the metric "drug lag" in indicating how long it took before an essential medicine licensed by SRAs is introduced by developing countries. At the other extreme of drug lag is "safety lag"—that is, how long it takes developing countries to react to a regulatory action taken by SRAs on a product that is also marketed in their countries. Herein, we analyzed the time lag between the safety announcements on rosiglitazone by SRAs as represented by the FDA and EMA and actions taken by NRAs from selected LMICs, using rosiglitazone as the case study.

Materials and Methods

We studied 10 NRAs: 8 within Africa—Ghana, Kenya, Namibia, Nigeria, Tanzania, Senegal, South Africa, and Uganda; 2 from outside Africa—India and Indonesia. These countries were selected on the basis of their having rosiglitazone registered in their countries and the likelihood that data might be available regarding NRA regulatory actions. We reviewed updates on global regulatory activities using Thomson Reuters IDRAC and Cortellis regulatory intelligence weekly alert,[10,11] WHO Drug Information, WHO Pharmaceuticals Newsletter, WHO Model Lists of Essential Medicines,[12] and the Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments,[13] We also searched the websites of the 10 NRAs, including their list of registered medicines, where available, and we followed up with key informants' interviews as needed to validate responses and collect additional information, as appropriate. We calculated the median time lag in days from the date of the first announcement by the SRAs (September 23, 2010, as the index date) to the date of regulatory action by the NRAs. We considered actions as any communication related to safety of rosiglitazone, not limited to safety alerts, product recalls, and withdrawals.

Results

The two NRAs outside of Africa took regulatory actions related to safety of rosiglitazone within 2 weeks of SRA action. Indonesia took regulatory action a day after the SRA's announcement and India, 14 days after. For the 7

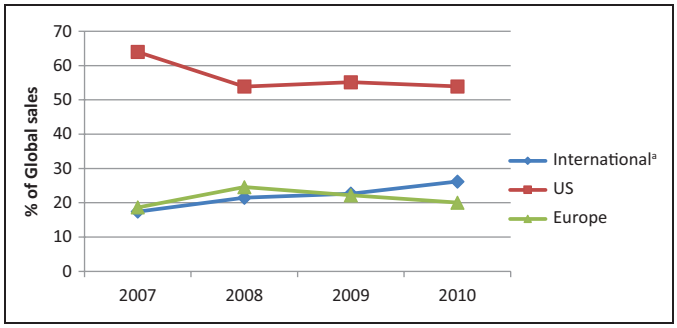

Figure 1. Regional contributions to global sales of Avandia as a percentage of global sales, 2007-2010.[22] "International" refers to non-US, non-European sales.

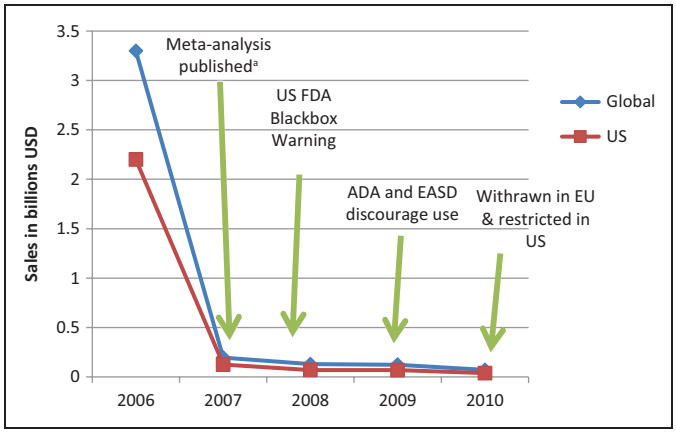

Figure 2. Sales dynamics of rosiglitazone-containing products, 2006-2010.[17] ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.

of the 8 African NRAs where we could confirm date of regulatory action, the median time lag before regulatory action in the African countries was 43 days. Although the average number of days to regulatory action is recommended as a drug safety indicator, the median better reflects the time lag across the countries studied in this instance. South Africa was an outlier with 285 days elapsed before performing any documented regulatory action.

All the countries studied, except for Nigeria in the first instance, took regulatory actions to suspend the market authorization consistent with the decision of the EMA. Nigeria's Agency for Food and Drug Administration and Control—in its letter on the enforcement of risk management commitment to GlaxoSmithKline, the market authorization holder—requested that the company obtain comprehensive information on patients exposed to rosiglitazone-containing products, ensure that the products are restricted to specialist hospitals and used on a named-patient basis, and submit a report of patients' evaluation by physicians 6 months from the date of notification. The agency indicated that it would make a final pronouncement on continued marketing or otherwise of rosiglitazone-containing products by April 2011. Eventually, the agency announced that GlaxoSmithKline withdrew all rosiglitazone-containing products in Nigeria.[14] Neither the EMA nor any of the 10 NRAs reacted to the FDA's November 25, 2013, removal of some prescribing and dispensing restrictions on rosiglitazone-containing products.

We also reviewed the sales data of rosiglitazone-containing products. Figure 1 shows the percentage of sales in the US, the EU, and the rest of the world from 2007 to 2010. While the percentages of sales of Avandia were in decline in the US and the EU from 2009 to 2010, there was modest increasing trend in the rest of the world. Others noted reductions in utilization of rosiglitazone-containing products after the initial EMA press release and FDA warning on cardiovascular risk in May 2007.[15,16] Figure 2 shows the global and US sales of rosiglitazone-containing products in accordance with key safety milestones. The drop in sales is pronounced following publication of the meta-analysis.[17]

Discussion

The regulatory history of rosiglitazone serves as a case study for the need to continuously evaluate benefit-risk throughout a medical product's life cycle. The decisions by the FDA and the EMA to restrict or suspend the use of rosiglitazone were guided by available evidence as of 2010. Numerous studies underscored the adverse effects and unfavorable benefit-risk balance of rosiglitazone. In a meta-analysis conducted by Nissen and Wolski,[17] patients who were followed for at least 24 weeks from 42 different trials were analyzed. The authors found a significantly increased risk of myocardial infarction among patients treated by rosiglitazone, as compared to other medications (odds ratio [OR], 1.43; 95% CI, 1.03-1.98). The same authors updated their meta-analysis in 2010 and reported that rosiglitazone significantly increased the risk of myocardial infarction (OR, 1.28; 95% CI, 1.02-1.63), although the relation with cardiovascular mortality was not significant (OR, 1.03; 95% CI, 0.78-1.36).[18] An observational study based on Medicare claims data in the elderly reported that compared to pioglitazone, rosiglitazone increased the risk of stroke (hazard ratio [HR], 1.27; 95% CI, 1.12-1.45), heart failure (HR, 1.25; 95% CI, 1.16-1.34), and all-cause mortality (HR, 1.14; 95% CI, 1.05-1.24).[19] In the RECORD study, whose primary outcome was cardiovascular hospitalization, Home et al[20] confirmed the increased risk of heart failure among patients treated by rosiglitazone; the HR was 2.10 (1.35-3.27). On November 25, 2013, the FDA announced the removal of the prescribing and dispensing restrictions on rosiglitazone-containing drugs that was instituted in 2010. This more recent FDA action was based

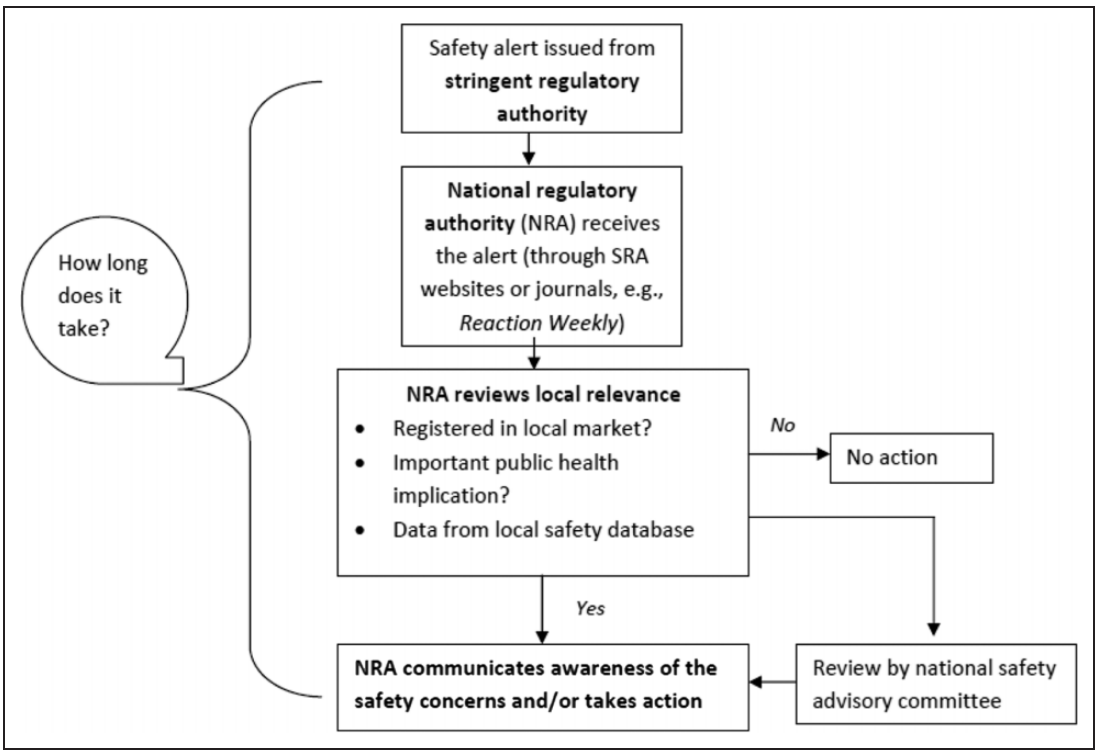

Figure 3. Proposed process for national regulatory authorities to react to emerging safety issues.

on reevaluation of the RECORD trial conducted by the Duke Clinical Research Institute.[21]

Determination of the benefit-risk balance of medicines should be an ongoing activity throughout a medical product's life cycle. As new information becomes available, regulatory decisions can be issued, qualified, or even reversed. These decisions should be based on thorough analysis of available safety information. With regard to measuring safety time lag, the delays in the observed NRA actions may be explained by the lack of a systematic approach for utilizing safety alerts from external sources, a situation that was revealed by the recent evaluation of African pharmacovigilance systems in sub-Saharan Africa.[4] Better global collaboration among NRAs is needed along with improved information exchange practices.

In this study, we considered regulatory actions as any communication related to safety of rosiglitazone. A system for scanning emerging safety issues could have triggered timely communication to health care professionals in LMICs. Figure 3 proposes a process for NRAs to react to emerging safety issues. It is also conceivable that the inconsistency in the actions taken between the US (restriction of use) and the EMA (full suspension) may have created some ambivalence among regulators from LMICs.

Our study is limited by the relatively small number of countries assessed. Although this limits generalizability, we believe that our findings remain informative and illustrate the presence and utility measurement of a safety lag between SRAs and LMICs with weaker drug regulatory systems. We were unable to verify the reasons for delayed regulatory actions across the countries studied, particularly in South Africa: a country with more resources relative to the others and where more timely regulatory action would have been expected. Although all the NRAs in our study eventually suspended the market authorization, this case highlights the importance of building strong pharmacovigilance systems, as the benefit-risk considerations may vary across countries according to disease epidemiology and products available in the local market.

Conclusion

LMICs should create systems for timely identification and management of emerging safety issues, especially for products that they have registered and their populations are using. One of the challenges in the practice of pharmacovigilance is to globally reduce safety lag inequity. The harmonization of standards, the use of common terminologies, and the sharing of information can help reduce safety lag and continued exposure

to potentially harmful products. A systematic approach for risk management based on external safety alerts and the use of tools may improve the timely use of safety data for local decision making in LMICs. Pharmacovigilance performance metrics such as the Indicator-Based Pharmacovigilance Assessment Tool should be used by countries to monitor their safety systems.[9]

Author Note

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Declaration of Conflicting Interests

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