Actions of the National Regulatory Authorities in Developing Countries Following US FDA and EMA Safety Alerts on Rosiglitazone

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Abstract

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Problem Statement: On September 23rd, 2010 the US FDA announced that it will require a restricted access program as part of a risk evaluation and mitigation strategy for the elevated risk of cardiovascular events associated with rosiglitazone. On the same day, the EMA recommended the suspension of the marketing authorizations for rosiglitazone-containing anti-diabetes medicines. One of the core indicators of the Indicator-based Pharmacovigilance Assessment Tool (IPAT) used for assessing pharmacovigilance systems in developing countries is the average time lag between the identification of safety signal of a serious ADR or significant medicine safety issue and communication to healthcare workers and the public.
Objectives: To identify the time lag between the announcements on rosiglitazone by stringent regulatory authorities (SRA) as represented by the FDA and EMA, and actions by national regulatory authorities (NRA) from selected developing countries.
Design: We reviewed the Global Regulatory Activity Digest that contains global regulatory updates. We also searched the websites of 12 NRAs including their list of registered medicines, where available, and followed up with key informants' interviews to validate responses and collect additional information, as appropriate. We calculated the average lag time in days from the date of the first announcement by the SRAs (September 23rd, 2010 used as the index date) to the date of regulatory action by the NRAs. We considered actions as any communication related to safety of rosiglitazone.
Study Population: National regulatory authorities.
Outcome Measure(s): Safety alerts and related communications pertaining to rosiglitazone
Results: We studied regulatory actions related to safety of rosiglitazone from the FDA, EMA, and 10 national regulatory authorities; 3 NRAs from outside Africa and 7 NRAs from Africa. The NRAs outside of Africa had all taken regulatory actions related to the safety alert to rosiglitazone. Of particular interest, Saudi Arabia took regulatory action to suspend rosiglitazone on March 17th, 2010 approximately 190 days before the SRAs. Indonesia took regulatory action a day after the SRAs and India 14 days after. For the 7 African NRAs, we could confirm regulatory action only for those from Namibia and Kenya. From the index date until December 2nd, 2010 when the most recent information was collected, only 2 out of 7 (29%) African NRAs have taken regulatory action or reacted to that of the SRAs.
Conclusions: The average lag time between the identification of safety signal of a serious ADR or significant medicine safety issue and communication to the public is shorter for NRAs outside of Africa. Even after 70 days from the index date, many African NRAs had no communication to consumers or healthcare providers pertaining to the safety of rosiglitazone. This IPAT indicator provides a way for assessing timely communication of safety information.
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Background and Settings

- Concerns about rosiglitazone and elevated cardiovascular risk
- Delays in applying safety alerts in developing countries
- Indicator-based pharmacovigilance assessment tool (IPAT) use in measuring the average time lag from safety signal to communication

Aims and Objectives

Identify time lag between the announcements on rosiglitazone by stringent regulatory authorities (SRA) as represented by FDA and EMA, and actions taken in response by national regulatory authorities (NRA) from selected developing countries.

Method and Study Plan

Method

- Data sources—NRA websites, drug register, key informants
- Average time lag from safety signal to communication—a core indicators of the IPAT was used to monitor the actions of the NRAs
- Calculated average lag time in days from date of first announcement by SRAs (index date) to date of regulatory action (defined as any regulatory communication) by NRAs

Results (1)

- Studied the FDA, EMA, and 12 NRAs—3 NRAs from outside Africa and 9 NRAs within
- The NRAs outside Africa took regulatory actions related to safety of rosiglitazone either before the SRA actions or within two weeks of its action
- Saudi Arabia suspended rosiglitazone on March 17, 2010—190 days before the SRAs issued announcements

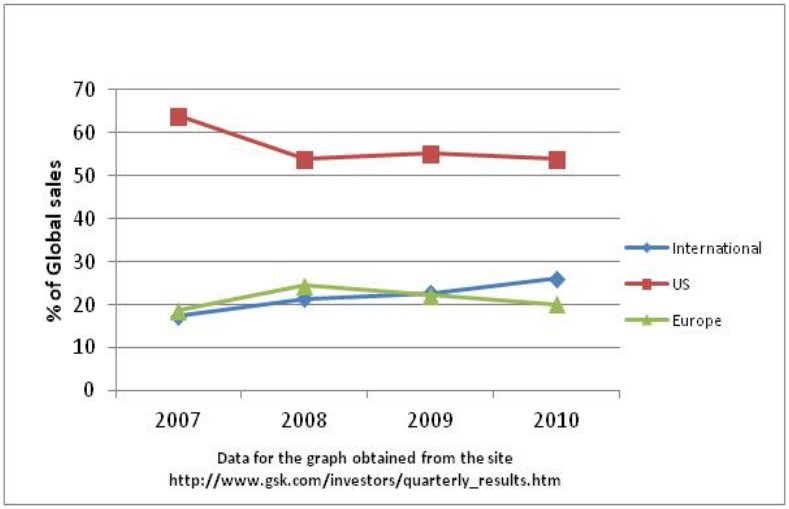
Results (2)

- Indonesia took regulatory action a day after the SRAs
- India took action 14 days after SRAs
- For the 9 African NRAs that registered rosiglitazone, the average time lag before regulatory action was 55 days
- From the index date until August 5, 2011—a total of 316 days (nearly 10 months)—the other African NRAs that had also registered rosiglitazone have not taken any regulatory action or reacted to actions of the SRAs

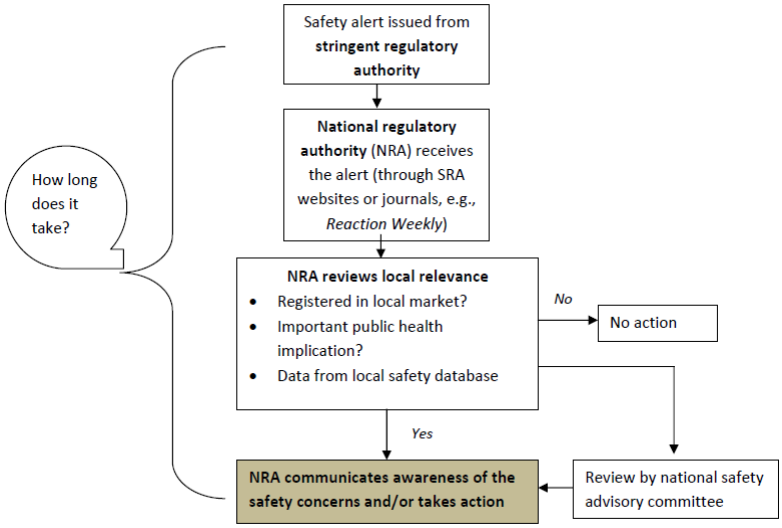
Results—Regulatory Action on Rosiglitazone (3)

Country	Action		Communicated	Date	Lag time (DAYS)
	Suspension of market authorization	Enforcement of risk management practices			
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 and 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	July 5, 2011	285
India	Yes		Safety alert	Oct. 7, 2010	14
Indonesia	Yes		Safety alert	Sept. 24, 2010	1
Saudi Arabia	Yes		Safety alert	March 17, 2010	190

Regional Contributions to Global Sales



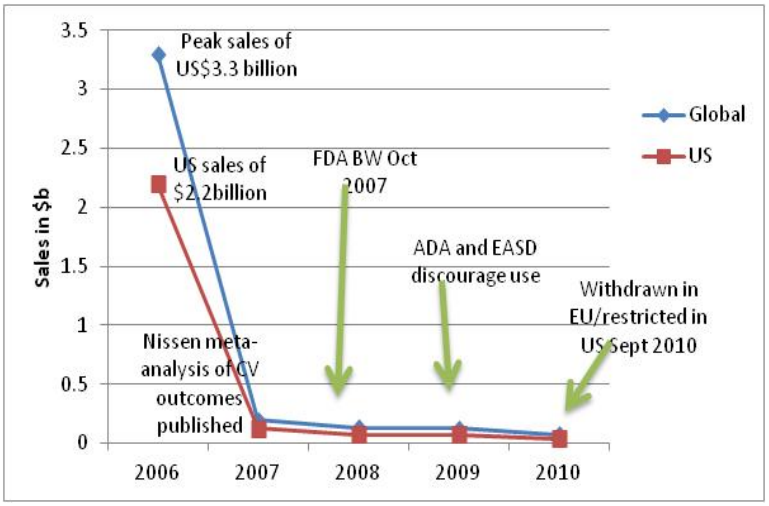
Reacting to Emerging Safety Issues



Summary

- Average time lag for safety communication is shorter for NRAs outside Africa
- Even after 10 months from the index date, many African NRAs had not communicated anything regarding the safety of rosiglitazone to consumers or health providers
- IPAT indicator provides a way for assessing timely communication of safety information.

What drives change in utilization?



Policy Implications and Conclusions

- Developing countries should create systems for timely management of new safety issues, particularly for products they have registered and that are being used by their citizens
- Tools to improve the timely use of safety data for local decision making are needed
- Pharmacovigilance performance metrics like IPAT should be used by countries to monitor the development of their safety systems