Pioglitazone suspension and its aftermath: A wake up call for the Indian drug regulatory authorities

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Pioglitazone, the commonly used antidiabetic drug was placed under suspension in June (June 18, 2013). The suspension was promulgated in the Government gazette.[1] It was not recommended by the Drug Technical Advisory Board (DTAB). There has been no mention of the Pharmacovigilance Program of India (PVPI) reporting suspicious signals for pioglitazone. The medical fraternity debated the appropriateness of the decision. Doctors worried on the lack of affordable replacement for pioglitazone. The pharmaceutical industry was taken aback by the suddenness of the decision. The diabetic population was a mute spectator to this entire event. The backlash from the medical fraternity and pharmaceutical industry was swift. Accusations of improper review and not following the procedures flew thick. The institution of the Drugs Controller General (DCGI), India, was at the center of this backlash. The apex drug regulator's action of suspending a common and widely used drug looked ill-informed. A fortnight of heated media discussions and accusations forced the DCGI on the defensive. Finally, the nation was informed that the suspension was being revoked and pioglitazone would now be available again with an updated warning for the patients.[2] In a month, the office of the drug regulator went from being generally regarded as a scientifically oriented body to it being perceived as an ill-informed, over-zealous organization.

Pioglitazone has been used globally for two decades. It has proven efficacy as an antidiabetic and is especially valued in the Asian–Indian patients, who have a high level of insulin resistance. It is the member of a family of molecules that has been besieged by bad luck right from the start. Troglitazone an early member of this family was withdrawn within 3 years of its introduction in the market for propensity to cause liver failure.[3] Rosiglitazone, another member of the same family was dropped because of the associated risk of myocardial infarction.[4] Within this, cursed family pioglitazone carved out a reputation for being an affordable and effective antidiabetic. But the family heritage soon caught up and initial reports hinted at an increased risk for bladder cancer. The PROactive trial first reported the finding of an increased risk of bladder cancer [14 vs. 5] in patients taking pioglitazone to those in the placebo arm.[5] A more recent update on the same study reported no observed increase in bladder cancer risk in the pioglitazone arm.[6] Another study from the Kaiser Permanente Northern California diabetes registry reported that use of pioglitazone for more than 2 years was weakly associated with increased risk for bladder cancer.[7] A large study from the United Kingdom reported no increase in bladder cancer with pioglitazone use.[8] The findings thus have been varied. The Indian media widely quoted the ban on the sale of pioglitazone in France and Germany. The suspension in France was based on the findings of a population-based cohort study, which reported that 'pioglitazone exposure was significantly associated with increased risk of bladder cancer'.[9] The USFDA in June 2011 mandated the introduction of information on the increased risk for bladder cancer in the pioglitazone label. It based the decision on the interim analysis from the Kaiser Permanente Northern California diabetes registry and also acknowledged the French a population-based cohort study.[10]

With this background, the suspension of pioglitazone by the Indian drug regulator looks to have been heavily influenced by actions taken elsewhere on the globe. Globally the debate on the pioglitazone and bladder cancer saga is still on, and

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the causality has never been clearly established. The decision also reflects a lack of understanding of the full impact of nonavailability of this drug on the Indian patients. How was the decision on suspension of pioglitazone reached? The due process has been review and recommendation by the empowered DTAB on such matters. A check on the CDSCO website for the past minutes of the meeting of DTAB does not show any discussion on pioglitazone.[11] There is full minuted discussion on Analgin, another drug placed under suspension along with pioglitazone. This raises serious concerns. Was DTAB the highest technical body under DCGI not aware of the consideration to suspend pioglitazone? This fact alone should ring warning bells in the pharmaceutical regulatory corridors of India. Can a decision like suspending pioglitazone, be taken without DTAB's approval? Is this an isolated case or this is a symptom of deeper malaise: A rot that has set in the system? The full details of the events preceding the suspension of pioglitazone, DTAB, and DCGI's role in these events need to be investigated and brought forward. This will assure the medical fraternity and the pharmaceutical industry that due procedures are followed in taking decisions. Any lacunae that may be identified will only help in strengthening the system by due corrective measures.

The popular press reported on another facet to this suspension of pioglitazone. An eminent Indian diabetologist, it is reported, wrote to the Prime Minister (PM), highlighting the cases of bladder cancer that were seen by him in patients on pioglitazone.[12] A short correspondence of eight cases of bladder cancer in patients with pioglitazone use by the concerned diabetologist and his group also appeared in an Indian journal.[13] The letter then found its way to the health ministry. Assuming the letter to PM was written in good faith, the matter could be looked upon as another example of institution deferring to individuals. But it gets murkier, as the media also reports that the said diabetologist received a monetary grant for educational programs. This grant came from a pharmaceutical giant, whose gliptin class of drug stands to gain directly from the suspension of pioglitazone. Now it is not clear, whether the letter to PM mentioned this conflict of interest. The only way to know is for the letter to be released in the public domain. This report and the events that followed raise many questions. What was the PM's role in this suspension? When there is an entire institution that looks after drugs and related issues, why was the letter addressed to the PM? Did the eminent diabetologist report these cases to PVPI? Did the DCGI follow due process in deciding on the suspension of pioglitazone?

In hindsight, this entire fiasco of suddenly suspending an established and commonly used drug looks murky, ill-informed and at its worst an attempt to make scarce a drug while costlier alternative is made available. Professional conflicts of interest, bypassing set practices of review, undermining institutional independence, and the list goes on. In the recent past, we had cases of drug approvals being given based upon recommendation by eminent doctors of the country. Only the recommendations were verbatim copies and full of spelling errors.[14] Recently we had amendments to the Drugs and Cosmetics Act that classified as clinical trial injury – failure of investigational product to provide intended therapeutic effect – a statement that negates the entire premise of conducting a clinical trial.[15] How can we know if the investigational product will provide therapeutic benefit before we have done the trial? The Indian patients, medical fraternity and the pharmaceutical industry expect better from the apex drug regulator of the country. We need a system that bases its decisions on evidence and conducts the business of regulating the drugs industry in a scientific and ethical way: A regulatory system that is vigilant, ever alert to quality, safety and ethical issues.

The government needs to investigate the pioglitazone suspension. The people of India deserve a complete and truthful report. Only then can such recurrences be prevented.

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