Commentary

Post-marketing safety signals: Challenges in regulatory decisions, communication & impact evaluation in developing countries

Adverse reactions to medicines and related regulatory decisions are widely publicized, and are of great concern to the society and pharmaceutical industry. Safety signals after marketing arise from spontaneous reports, clinical trials, meta-analysis, case reports, case series, analysis of large database [*e.g.* Sentinel initiative by United States Food and Drug Administration (USFDA)] and other publications. When necessary, the regulatory authorities take action so that the use of medicines has a minimum risk and maximum benefit. Such regulatory actions consist of changes in the product information in package insert/label with a change in dose, restriction on indication, highlighting safety issue, boxed warning, in rare circumstances removal of the medicine from market, if the risks outweigh benefits. Communication to healthcare professional and patients is achieved through boxed warnings and letters to prescribers.

It has been noted that regulatory review time decreased from 33.6 months during 1978-1980 (Pre Prescription Drug User Fee Act) to 10 months during 2001-2010 period in the USA[1]. In India, the time gap between the approval in European Union (EU)/internationally and approval in India decreased from nine years during 1970-1998 to two years during 1999 to 2012 period[2]. When the drugs get to the market faster due to speeding up of review system, there is increasing concern on safety. The black box warning/withdrawal in the USA increased from 21 per cent during 1978-1986 to 26 per cent during 2000-2015 period[1].

The regulatory decisions are required to be data driven, appropriately nuanced and timely to ensure patients safety, and there is increasing reliance on real-world data. In developed countries, information on risk, benefits and extent of use is readily available. However, that is not so in the developing countries.

Case of pioglitazone withdrawal from market illustrates the point.

Reports about an increased risk of pioglitazone led to its withdrawal from the French market[3]. The USFDA did not suspend the market authorization but added a black box warning for bladder cancer risks[3]. Indian drug regulatory authorities withdrew pioglitazone in June 2013[3] but then revoked the ban[3] due to lack of sufficient evidence and recommendation by the Drug Technical Advisory Board.

In view of such regulatory decisions, Pai and Kshirsagar[3] carried out a systematic review of publications on pioglitazone safety, efficacy and drug utilization in patients with type 2 diabetes in India and compared it with the data from European Medicines Agency Assessment Report (EMA-AR). No cases of bladder cancer were reported from India in VigiBase (WHO global database of individual case safety reports submitted by member countries) though there were eight cases reported in literature. The information from published literature suggested that pioglitazone was used in lower than recommended dose, mostly with metformin and sulfonylurea[3]. There was regional variation also. Pioglitazone was prescribed to 26.7 per cent patients in north and 8.4 per cent patients in the southern region in India[3]. The efficacy in clinical trials was similar to EMA-AR. Incidence of bladder cancer in pioglitazone exposed and non-exposed patients was not significantly different in an Indian retrospective cohort study[3]. Interestingly, the background incidence of bladder cancer in India was lower compared to the UK and the USA[4].

The paper noted that association of bladder cancer with pioglitazone was not significant in India[3]. However, authors commented that reporting of adverse drug reactions to Pharmacovigilance Program of India (PvPi) and studies on compliance with warnings given

in package insert and epidemiological studies with larger sample size are needed[3].

While regulatory decision itself is challenging, it is important to assess the impact of regulatory decisions on prescribing patterns and whether patient safety is being achieved. There are several methodological challenges in checking the impact of regulatory decisions. Prescribing practices are influenced by a number of different factors such as training, past experience, professional and lay press coverage of a topic, patient pressure, industry influence, in addition to random fluctuations. Further, regulatory decision is usually not sudden, but it is a consequence of professional decision culminating into regulatory action. Impact of regulatory action on prescribing pattern was studied by extracting data from Clinical Practice Research Datalink in the UK and a decrease in co-prescribing of renin-angiotensin system blockers was observed[5]. Friesen and Bugden[6] used a quasi-experimental time series analysis using citalopram prescribing data and noted decline in prescribing of high doses though there was no impact of warning on the prescribing of interacting medicines.

Published in this issue is a study done by Goyal et al[7], on the impact of regulatory spin of pioglitazone on prescription of antidiabetic drugs amongst physicians in India with multicentre, questionnaire-based observational approach. Using a validated questionnaire, the authors collected information from physicians practicing diabetes from 25 centres across India, about the impact of the pioglitazone regulatory decision on prescribing pattern. They noted that more than 50 per cent physicians prescribed pioglitazone. Interestingly, as noted in the systematic review of prescribing practices[3], Goyal et al[7] also found that the pioglitazone dose used was less than the recommended dose. Although 94.3 per cent respondents were aware of the regulatory developments regarding pioglitazone in India, 18 per cent were not aware of increased risk of bladder cancer as the cause for suspension and 55 per cent were not in favour of change in prescribing practice. Seventeen of the 416 physicians, who completed the questionnaire, came across patients who had urinary bladder carcinoma and of these, 13 had taken pioglitazone for a duration more than the recommended two years. Alarmingly, only 65 per cent physicians stated that they informed the patients about the potential risk.

Keeping dose below 28,000 mg, duration below two years, inquiring about the history of bladder disease and testing for haematuria before starting pioglitazone are the recommended risk minimization strategies. It would be important that risk minimization strategies and information on regulatory decisions are communicated to patients. Studies to evaluate impact of regulatory decisions are important to achieve the safe use of medicine. Future studies should be carried out with wider representation from all regions, urban/rural setting and specialist and non-specialist practitioners.

Information on compliance to various warnings and instruction in label package insert/also needs to be collected. Such studies can be done through questionnaire as done in this study but this suffers from recall bias and response bias. It can be collected by monitoring prescriptions. In a systematic review[8] of the drug utilization studies and analysis of nimesulide regulatory decision in India[9], it was noted that analysis of compliance to regulatory recommendation and warnings was not done during the prescription monitoring studies.

India has a National PvPi and is also a member of the WHO programme for International Drug monitoring at Uppsala Monitoring Centre. Studies such as by Goyal et al[7] evaluating the impact of regulatory decisions are welcome additions towards the objective of making medicines safer.

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