



## PATIENT SAFETY AND PHARMACOVIGILANCE: NEW ROLE OF "PHARMACIST"

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### ABSTRACT

The recent market withdrawal of troglitazone and the pending market withdrawal of cisapride highlight the issue of the risk vs benefit ratio of marketed pharmaceuticals. Primarily through the volunteer program for reporting of adverse events, the FDA was able to document problems for troglitazone and cisapride and, in concert with the respective manufacturers, develop prescribing and monitoring guidelines for troglitazone and cisapride. With both drugs, until the recent decision to recommend withdrawal, the FDA believed the benefits of these therapies outweighed the risks of potential adverse events. Pharmacists are among the stakeholders with the FDA, in addition to physicians, other healthcare professionals, and patients, and are key to preventing and managing the risk associated with medication use. Results from pharmaceutical care research document the intuitively known benefits of pharmacist/patient interactions. It is important for pharmacists to use the MedWatch system to report suspected adverse drug events. The FDA acknowledges that risk management of medical product use is currently not without fault and many options are under discussion for improvement, including labeling changes, and different ways to communicate with healthcare professionals and patients. Whatever changes are made, however, pharmacists will always be important to maximizing the benefit and minimizing the risks of medication use.

**Keywords:** Withdrawal, Adverse Events, Pharmacovigilance, Troglitazone, Pharmacist.

### INTRODUCTION

The recent market withdrawal of troglitazone (Rezulin, Warner-Lambert) and the pending market withdrawal of cisapride (Propulsid, Janssen) highlight the issue of the risk vs benefit ratio of marketed pharmaceuticals. Primarily through the MedWatch volunteer program for reporting adverse events, the FDA was able to document problems (ie, liver toxicity and cardiotoxicity for troglitazone and cisapride, respectively) and, in concert with the respective manufacturers, develop prescribing and monitoring guidelines for troglitazone and cisapride. With both drugs, until the recent decision to recommend withdrawal, the FDA believed the benefits of these therapies outweighed the risks of potential adverse events. Nevertheless, despite labeling changes, Dear HealthCare Professional letters, and media attention, both agents continued to be prescribed and dispensed to those at risk and or without appropriate monitoring.

A recent Wall Street Journal story focused on physician culpability, making the point that doctors are overwhelmed with information, and often do not see Dear Doctor letters alerting them to drug-related problems in their voluminous amounts of mail. Furthermore, most use the hardbound Physician Desk Reference as a way to look up information in package inserts, and this book logistically cannot be updated as fast as changes in labeling occur.<sup>1</sup>

Unfortunately, pharmacists may be just as guilty as physicians in missing many serious, preventable adverse events. Patients got prescriptions from physicians for troglitazone and cisapride, but of course the prescriptions

had to be dispensed by pharmacists. In 1996, two highly publicized articles reported the results of investigations of pharmacists' activities in preventing or not preventing dangerous drug interactions with high risk of adverse events. More than 30% of pharmacists presented with prescriptions for terfenadine (Seldane, no longer on the US market) and erythromycin failed to challenge physicians or warn consumers of this well-documented, potentially fatal interaction. Other potential interactions were also ignored, again despite documentation in product labeling, standard references, and drug interaction databases.<sup>2-4</sup>

On the other hand, in these evaluations more pharmacists (at least 6 of 10 in the terfenadine/erythromycin study) screened appropriately. The FDA considers pharmacists one group of stakeholders; the others are physicians, nurses, other healthcare professionals, and patients and their caregivers. Stakeholders are essential to the FDA to manage the risks engendered whenever a new medication comes to the marketplace. The interaction of stakeholders with the FDA is primarily through MedWatch. Adverse drug events have been receiving national attention in the recent past, both for their large numbers and preventability.<sup>5-11</sup> The troglitazone/cisapride withdrawal news once again focuses the spotlight on postmarketing surveillance of newly approved drugs. The FDA approval process brings drugs to market that are safe and effective when used as labeled. It is important to remember, then, that safety does not mean zero risk. As noted in a recent FDA document:



"The Agency approves a product when it judges that the benefits of using a product outweigh the risks for the intended population and use. Labeling is given considerable emphasis because it is the chief tool the Agency uses to communicate risk and benefit to the healthcare community and patients."<sup>4</sup> The system in place is flexible enough to permit changes during the postmarketing phase of drugs, including alteration of labeling and, if needed, recommendation for drug withdrawal. With troglitazone, according to Dr. Peter Honig, an FDA drug safety official, "we had come to the conclusion that liver monitoring was necessary but it wasn't being done by practitioners. We don't know if the Dear Doctor letters weren't effective, or weren't being read, or whether physicians didn't believe monitoring was effective."<sup>1</sup> The result was the recommendation to Warner-Lambert to withdraw troglitazone from the market.

### "PHARMACIST" IN NEW ROLE

Intuitively, pharmacists are an important part of the risk vs benefit assessment process, because we see patients when they get new prescriptions filled and any time they return for a refill. During any of these interactions, assessments of potential drug interactions and any adverse event is possible. Additional inquiry is possible into whether proper monitoring (eg, liver enzyme testing) is being performed. Any time there are new labeling changes and particularly when a drug is withdrawn from the market, it is key for pharmacists to take the time to ensure that patients get a change in therapy (if needed) but continue to take medications for chronic conditions. Pharmaceutical care (a more formal name for pharmacist counseling and education of patients, along with monitoring drug therapy) research results support this thinking. Nau and associates used a Health Belief Model premise that patients judge benefit of a preventive health behavior by perceived threat reduction of a specific health problem. They demonstrated that asthma patients followed by pharmacists believed that pharmaceutical care intervention was more effective in preventing problems compared with those not receiving pharmaceutical care intervention<sup>12</sup>.

A number of pharmacist groups have developed structured pharmaceutical care programs, which target patients at high risk to develop adverse events. These include primarily those with chronic conditions (eg, asthma, hypertension, and hypercholesterolemia). Nau's group evaluated patients followed closely by pharmacists in an anticoagulation clinic and found that patients perceived a reduction of the risk of warfarin-related problems because of their interactions with pharmacists, particularly, knowing that their blood levels were being closely watched.<sup>13</sup>

Fischer and colleagues<sup>14</sup> worked with participants who all were taking multiple medications for chronic medical conditions. In this 6-month study, participants received initial drug therapy assessment, plan for drug therapy

goals, education, interventions with other health care professionals if appropriate, and follow-up care. Findings included not only that participating patients reported receiving more information from pharmacists on all aspects of their medication but also improvement in compliance and better awareness of potential adverse events from their medications.

MedWatch is the best known postmarketing risk assessment FDA program. Available by means of mail, phone, FAX, or the Internet, MedWatch, which is the FDA Medical Products Reporting Program, takes the reports received and forwards them to the appropriate FDA center for evaluation. The FDA wants to hear about serious adverse events. These events include when the patient outcome is death, life-threatening, reason for hospitalization or for prolonged hospitalization, disability (eg, organ failure requiring transplantation), congenital anomaly, or require some kind of intervention (change of drug therapy, treatment with other drugs, or other therapies). They are very much interested in relatively new drugs, because adverse event information for these agents is limited to patients exposed to the new drug during clinical trials (usually less than 10,000 patients). The number of patients receiving new drugs rises dramatically when a new drug hits the marketplace.<sup>4</sup> Do not be intimidated if you do not have the complete information, and report even if you are not certain the product caused the event.

The FDA acknowledges that risk management of medical product use is currently not without fault, and many options are under discussion for improvement, including labeling changes and different ways to communicate with healthcare professionals and patients.

### CONCLUSION

Despite the considerable experience and expertise that have been developed by national reporting centers, those involved in pharmacovigilance face major challenges to satisfy increased consumer expectations. The changes in risk-benefit that emerge during a drug's marketed life will need to be more effectively identified and communicated to clinicians and patients. International surveillance may benefit by becoming more proactive, utilizing linked observational data where available. This will require a considerable increase in funding and staffing. Pharmacovigilance is currently being strengthened with the introduction of enhanced authorities regarding postmarket safety of drugs, with the power to require postmarketing studies, to order changes in a drug's label and to restrict distribution of a drug. Furthermore, newly marketed drugs may soon be given provisional approval until considerable experience is gained in clinical practice and a comprehensive safety profile established.

A weakness of current product information is the lack of identification of core information or key messages, which are buried in the voluminous print of less important information. Merely listing ADRs is not enough. Comprehensive information is required on risk factors,



the type of monitoring required (if this will help prevent or enable earlier detection of an ADR), the expected incidence and how to manage the ADR. Ideally, all key information, especially regarding safety, should be highlighted and presented at the top of the datasheet under a subheading such as Critical Information for Prescribers. These data should include not only a thumbnail of the basic pharmacology, indications, important contraindications and interactions but also information to guide the prescribing doctor toward a reasonably informed risk-benefit assessment. For many drugs, only four or five core adverse reactions that have the potential to cause significant morbidity or mortality may need to be mentioned here. Absolute risk reduction, numbers needed to treat and numbers needed to harm should be included where these data are available. Such information could be a guide to discussing the pros and cons of treatment with individual patients and make it clearly evident, for example, that the risk-benefit issues when deciding on treatment of a simple fungal infection of the toenails, are quite different to those of a serious systemic infection. Just as black box warnings can help to alert prescribers and users to critical safety information, safety update amendments should be readily identifiable in bold print, preferably under a subheading such as Safety Updates.

Current methods of communicating safety warnings may have limited impact, not only on prescribing practices, but also on patient awareness. Patient information leaflets, written in lay language, are also currently in standard format and could be more user friendly, highlighting risk-benefit issues and key safety information.

Increased emphasis on education is required at all levels. Drug safety and pharmacovigilance should be included in undergraduate medical and pharmacy curricula and postgraduate educational programmes, and medical students should be taught how to communicate risk-benefit issues to patients, although we have yet to determine the best way to do this. While prescribing is a core skill that should be taught to every medical student, reporting and participation in ADR monitoring schemes must also be promoted as a fundamental professional responsibility.

The recent drug withdrawals of troglitazone and cisapride have once again put the spotlight on methods to evaluate the risks of new drugs. The FDA's MedWatch program is currently the best way for pharmacists and others to report adverse drug events. Whatever changes may be made in the future, however, pharmacists will always be important to maximizing the benefit and minimizing the risks of medication use.

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