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The Potential Return on Public Investment in Detecting Adverse Drug Effects

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Abstract

Background—Many countries lack fully functional pharmacovigilance programs, and public budgets allocated to pharmacovigilance in industrialized countries remain low due to resource constraints and competing priorities.

Objective—Using 3 case examples, we sought to estimate the public health and economic benefits resulting from public investment in active pharmacovigilance programs to detect adverse drug effects.

Research Design—We assessed three examples in which early signals of safety hazards were not adequately recognized, resulting in continued exposure of a large number of patients to these drugs when safer and effective alternative treatments were available. The drug examples studied were rofecoxib, cerivastatin, and troglitazone. Using an individual patient simulation model and the healthcare system perspective, we estimated the potential costs that could have been averted by early systematic detection of safety hazards through the implementation of active surveillance programs.

Results—We found that earlier drug withdrawal made possible by active safety surveillance would most likely have resulted in savings in direct medical costs of \$773 to \$884 million for rofecoxib, \$3 to \$10 million for cerivastatin, and \$38 to \$63 million for troglitazone in the US through the prevention of adverse events. By contrast, the yearly public investment in FDA initiated population-based pharmacovigilance activities in the US is about \$42.5 million at present.

Conclusion—These examples illustrate a critical and economically justifiable role for active adverse effect surveillance in protecting the health of the public.

Keywords

Pharmacovigilance; investment; public health; healthcare budgets

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Introduction

Growing pressure on public investments in healthcare requires ongoing assessment of the costs and benefits of clinical and public health interventions. Following discoveries of substantial undetected side effects of several widely used medications, one area of particular importance is pharmacovigilance or post-marketing drug safety surveillance, the disciplines and programs required for identifying and controlling drug-induced illness.¹ The recent history of pharmacovigilance goes back over a half-century, when astute clinicians noted that the sedative/anti-nauseant thalidomide, widely used in pregnant women outside the US, caused major disabling birth defects.² Soon thereafter, the World Health Assembly and World Health Organization committed themselves to developing the necessary infrastructure to provide for surveillance of the safety of medicines in general use. Currently, the goal of pharmacovigilance is to safeguard the public health by identifying risks and risk factors of adverse drug events promptly, to make it possible to initiate interventions to protect patients from preventable medication-induced illness.

Nevertheless, many countries lack fully functional pharmacovigilance programs, and public budgets allocated to pharmacovigilance in industrialized countries remain low due to resource constraints and competing priorities.³ The Food and Drug Administration (FDA) division that receives spontaneous adverse drug events reports has traditionally been under-resourced and overburdened. Despite a substantial increase in FDA resources available for post-marketing drug safety monitoring mandated by the FDA Amendments Act of 2007, its budget remains small. The yearly federal budget of the FDA Office of Surveillance and Epidemiology for post-marketing safety contracts (including pharmacoepidemiology and drug utilization studies, and collaborative projects with the Centers for Medicare & Medicaid Services) has averaged about \$17,200,000 annually over the years 2012–2014 (personal communication Dr. Gerald Dal Pan, US FDA). Since 2009, an additional \$25,300,000 has been spent yearly on the FDA's Sentinel initiative, an effort to create a linked, sustainable system that draws on existing automated healthcare data from multiple sources to actively monitor the safety of medical products continuously and in real-time.⁴ The total yearly budget for FDA initiated population-based pharmacoepidemiology related activities in the US, as one measure of public investment in detecting adverse drug effects for the purpose of this study, thus amounts to about \$42,500,000, representing just 1.7% of total federal FDA funding, and 0.0015% of the US healthcare budget.⁵ This figure does not include other FDA activities related to post-market safety monitoring of drugs, such as review of spontaneous adverse event reports or review of company-initiated pharmacoepidemiological studies.

Several commentaries and editorials have discussed the importance of pharmacovigilance activities qualitatively⁶, but little quantitative information exists regarding the potential return on investment for resources spent on pharmacovigilance. We sought to estimate the public health benefit resulting from public investment in active pharmacovigilance by analyzing three case studies. We considered the gains in terms of adverse events prevented and associated cost savings. Rather than conducting a formal decision-analytic evaluation of the benefits and costs of the entire public investment in pharmacovigilance,⁷ we illustrate the potential return on investment using three important instances of major adverse drug events

which resulted in removal of a drug from the market: rofecoxib, cerivastatin, and troglitazone. In each instance, early signals of safety hazards emerging from clinical trials, spontaneous reports or both were not well recognized, resulting in continuing exposure of a large number of patients and consequent preventable morbidity and cost, when safer and equally effective alternative treatments were available.

Case studies

Case Study #1

Rofecoxib (Vioxx) was a non-steroidal anti-inflammatory drug (NSAID) that selectively inhibits cyclo-oxygenase 2 (COX-2). It was approved by the FDA in May 1999 as an analgesic, and was voluntarily withdrawn from the market five years later by its manufacturer Merck & Co. The drug was used extensively by patients with arthritis and other conditions causing chronic or acute pain. While it reduced the risk of gastrointestinal bleeding, it was never demonstrated to have greater analgesic efficacy than other NSAIDs.⁸ Rofecoxib was withdrawn based on the results of a randomized placebo-controlled study, in which patients on rofecoxib were found to have a nearly 2-fold increase in the rate of cardiovascular events compared with those randomized to placebo.⁹ Its manufacturer claimed that this was the first reliable evidence of cardiac toxicity caused by its product.¹⁰ However, data from a cumulative meta-analysis demonstrated that evidence of the cardiovascular risks of rofecoxib were apparent from observational studies within the first year after the drug's approval,¹¹ and in data from randomized placebo-controlled trials conducted by the manufacturer as early as 3 years prior to withdrawal.¹²

Case Study #2

Cerivastatin (Baycol, Bayer), a statin used to lower serum cholesterol, was approved by the FDA in June 1997, and launched in the US market in February 1998. Within 100 days of launch, spontaneous reports identified cases of rhabdomyolysis.¹³ The product label was revised in July 1998 to include mention of rhabdomyolysis, especially in patients concurrently using fibrates. However, this early signal was not further investigated adequately.¹³ The continued high relative reporting rate for rhabdomyolysis, in particular in patients who had taken concomitant cerivastatin and gemfibrozil, led to another label change in December 1999, contraindicating the co-prescription of gemfibrozil; a pharmacokinetic and pharmacodynamics interaction study was planned. Following continued internal company analyses of the reported suspected adverse drug reactions, results from the interaction study and an observational study on the risk of myopathy, cerivastatin was withdrawn from the market by the manufacturer in August 2001.¹³ Because rhabdomyolysis is a rare and serious adverse effect unrelated to the indication for cerivastatin, the spontaneous reporting system for suspected adverse drug reactions, despite its limitations, provided useful information early on that could have been acted upon sooner.¹³

Case Study #3

Troglitazone (Rezulin, Parke-Davis) was first marketed in March of 1997 for the management of diabetes, following fast-track review by the FDA. Initial signals of an increased risk of clinically important liver toxicity based on pre-marketing clinical trials

were de-emphasized during the FDA Advisory Committee meeting and the drug was approved for sale.¹⁴ Within months concern grew about increasing reports of liver damage. By November, 135 cases of serious hepatotoxicity and 6 deaths had been reported. GlaxoWellcome, which held the licensing agreement to sell troglitazone in the United Kingdom, took its product off the market as of December 1st, 1997 after only three months of sales. At the same time, applications to market troglitazone in 26 other countries, including most of Europe, were withdrawn. In contrast, the drug remained on the market in the US with the requirement to monitor liver function on a monthly basis. In March 2000, an FDA Advisory Committee recommended that the drug be taken off the market, more than two years after the same decision was made in the United Kingdom.^{14,15}

We estimated the public health impact of these delayed withdrawals from the perspective of the US healthcare system, and considered the effect that a more active program of ongoing adverse effect surveillance could have had on these events.

Methods

An individual patient simulation framework was used to estimate the health and cost impact of the delayed withdrawals for these illustrative case studies (Table 1).

Utilization measures

We first identified from the literature and media reports the total number of prescriptions dispensed in the US for rofecoxib,¹⁶ cerivastatin,¹⁷ and troglitazone¹⁸ over the product lifespan of each. Next, we identified the total number of quarters each drug spent on the market in the US based on the marketing start date and the date of withdrawal.¹⁹

Epidemiologic measures

We identified key publications in the peer-reviewed literature reporting on the incidence rates and their 95% confidence intervals for the outcomes of interest for each of these three drugs along with the background rate in a control group.^{20–22} Users of NSAIDs, users of other statins, and non-users of troglitazone (i.e., general population) were selected as controls for rofecoxib, cerivastatin, and troglitazone users, respectively.

Pharmacovigilance measures

We identified the time point in the lifespan of each of these three drugs at which a pharmacovigilance signal for the outcome of interest would have been identified (the “signal detection quarter”) had an active prospective monitoring system been in place. We present two scenarios: a best-case (earliest signal detection) and a worst-case scenario. For rofecoxib and cerivastatin, the best-case scenario was based on previously published studies using actual contemporaneous healthcare utilization data sources which reported the quarter during which a signal would have been detected if prospective safety monitoring using a Sentinel-like approach had been in place.^{19,23} To do this, we performed a series of retrospectively conducted sequential cohort studies, with new data added on a quarterly basis, to determine the time point by which sufficient data had accrued to detect the suspected association between a drug-outcome pair. For troglitazone, in the absence of a

published estimate of the best-case scenario using actual data, we used the date of withdrawal of this agent from the UK market as the best-case scenario.²⁴ For the worst-case scenario, we conservatively selected the quarter of signal detection as one year after the earliest evidenced signal detection time points discussed above for rofecoxib and troglitazone, and 9 months for cerivastatin (in light of the actual drug withdrawal date).

Adverse event cost measures

For the outcome of interest in each drug-outcome pair, we identified the direct medical costs for that event as reported in the literature.^{25–28} We estimated a standardized, inflation-adjusted cost for each outcome in 2014 US dollars (the year for which the public investment in drug safety monitoring was estimated). In the case of acute liver failure caused by troglitazone, we included costs for liver transplant in 87% of the cases and costs of caring for hepatocellular damage for the remaining patients.¹⁸ We have conservatively estimated that once a given drug was withdrawn it would have been replaced by a potentially equally costly substitute (e.g., celecoxib for rofecoxib, atorvastatin for cerivastatin, or pioglitazone for troglitazone). Thus, we did not consider the likely savings to the healthcare system of switching to an effective generic drug (e.g., naproxen, simvastatin, or metformin, respectively) once the costly but unsafe drug had been withdrawn.

Simulation Model

The model uses quarterly cycles. Each cycle, we estimated the total number of patients exposed to the drug of interest assuming a linear increase in drug uptake over time.²⁹ We estimated the probability that an individual patient experienced an event in that quarter while on the drug of interest versus the comparator drug by sampling from the event rate distributions, which were parameterized as a beta distribution. Costs were assigned by sampling from a normal distribution, assuming a standard deviation equal to 10% of the mean estimated event cost. Costs were discounted at 3% per year. This process was repeated until the total number of quarters the drug was on the US market was reached. The simulation was then replicated under the best- and worst-case scenario in terms of signal detection, and the difference in excess events and costs were estimated. Results of probabilistic sensitivity analyses are based on 100 replications with random draws from the distributions, allowing for the estimation of 95% credible intervals (both confidence and credible intervals are denoted by CI hereafter). The model was implemented in Arena Version 15.00 (2007 Rockwell Automation Technologies, Inc., Milwaukee, WI).

Results

Utilization measures

Of the three drugs we studied, rofecoxib was the most widely used, with approximately 105 million prescriptions filled by US patients over > 5 years of marketing. The total number of prescriptions filled for cerivastatin and troglitazone were 11.2 and 12.9 million over their 3.5 and 3 years of marketing, respectively.

Epidemiological and pharmacovigilance measures

For rofecoxib users, a meta-analysis of randomized controlled trials²⁰ found that the incidence rate of acute myocardial infarction (MI) was 5.7 per 1,000 person years (PY) (95% CI, 4.0 – 7.9 per 1,000 PY), compared to 2.1 per 1,000 PY (95% CI, 1.0 – 3.7 per 1,000 PY) in non-selective NSAIDs users. It has been demonstrated that with an active pharmacovigilance program in place, a signal for the rofecoxib-MI association would have been detected after just one year of marketing.²³ We selected this time point as the best-case scenario for signal detection; it indicates that approximately 8 million PY of exposure to rofecoxib occurred after the point that an active pharmacovigilance program would have detected the drug's risk. We estimate the corresponding number of avoidable cases of MI attributable to rofecoxib during this period at 27,489 (95% CI, 10,930 – 45,244). Following a similar approach for the worst-case scenario (signal detection after two years of marketing), the estimated number of avoidable cases of MI attributable to rofecoxib would have been 24,562 (95% CI, 9,614 – 39,814).

For patients prescribed cerivastatin, the incidence rate of rhabdomyolysis was 53.4 per 100,000 PY (95% CI, 14.6 – 136.8 per 100,000 PY), while for other statin users the incidence rate was 4.4 per 100,000 PY (95% CI, 2.0 – 8.2 per 100,000 PY).²¹ Based on published estimates from actual healthcare utilization data, the best-case scenario of signal detection for this case-example was 2.5 years post-marketing.¹⁹ This would mean that an estimated 437,260 excess PY of exposure to cerivastatin occurred after the signal could have been detected, resulting in 190 (95% CI, 43 – 383) avoidable cases of rhabdomyolysis. In the worst-case scenario, the signal would have been detected after >3 years of marketing, resulting in 53 (95% CI, 10 – 130) avoidable cases of rhabdomyolysis attributable to cerivastatin.

In the third case-example, the incidence rate of acute liver failure was 240 per 1,000,000 PY (95% CI, 6.3 – 1,386 per 1,000,000 PY) for troglitazone users and 0.3 per 1,000,000 PY (95% CI, 0.1 – 0.9 per 1,000,000 PY) in the general population.²² The best-case scenario of signal detection after one year, based on the market withdrawal date in the UK, resulted in 264 (95% CI, 24 – 803) avoidable acute liver failure cases attributable to troglitazone. The worst-case scenario of signal detection after two years of marketing resulted in 162 (95% CI, 14 – 474) avoidable acute liver failure cases.

Cost measures

The highest cost of events prevented was estimated for rofecoxib (\$773 to \$884 million), as MI is a common event. The costs of events prevented were lower for cerivastatin-induced rhabdomyolysis (\$3 to \$10 million) and for troglitazone-induced acute liver failure (\$38 to \$63 million), as both of these events had low incidence rates. The uncertainty with respect to the precise magnitude of these savings is reflected in the 95% credible intervals, which are presented in Table 2.

By contrast, at current rates of expenditure, the total cost of active pharmacovigilance for all marketed drugs is \$42.5 million per year.

Discussion

Using analyses of actual healthcare utilization data that were available at the time such decisions would have been made, we estimated the reductions in morbidity and healthcare costs that could have been realized through use of a practical, near-real-time method of active drug safety surveillance. Our analyses demonstrate a pivotal and economically justifiable role for active pharmacovigilance in protecting the health of the public. While current yearly investment in such an approach in the US is estimated at about \$42.5 million, earlier withdrawal of unsafe drugs based on increased active surveillance would have resulted in savings of \$773 to \$884 million for rofecoxib, \$3 to \$10 million for cerivastatin, and \$38 to \$63 million for troglitazone in direct medical costs alone. Beyond these direct medical expenditures, our analysis did not consider the additional human cost in terms of the morbidity, loss of functional capacity, and mortality that could have been avoided.

Our analyses have certain limitations and strengths. We have not calculated a complete return on investment across all available drug treatments, but rather provide an illustration using three examples. They illustrate different scenarios for return on investment by contrasting common versus rare outcomes, and signals detected by clinical trials versus spontaneous reports. We also did not account for adverse events that were detected during this time period and did not lead to drug withdrawal but to better use of the drug. On the other hand, our estimates of the current yearly costs of active drug safety surveillance activities in the US represent the total public outlay of funds to the FDA for this purpose. Consequently, the potential total cost savings of a comprehensive pharmacovigilance system are markedly underestimated. In addition, we have likely underestimated the clinical costs generated by the drug-adverse event cases as we only have accounted for direct medical expenditures. Indirect costs, such as lost productivity for patients and caregivers, were not considered. However, it should be recognized that by far the largest cost savings were attributable to rofecoxib because of the frequency with which it was being prescribed, the amount of time it remained on the market, and the amount of excess risk. It is impossible to predict how often such rofecoxib-like situations will occur per decade. But it is clear that major adverse drug events are not rare events. Investment in active drug surveillance offers protection against the occurrence of such events, which are bound to recur.

We made a number of simplifying assumptions in conducting the analyses: for example, we assumed 30-day dispensings, and a constant risk over time. The best-case scenarios assume that the signals would result in immediate withdrawal of the drugs, and that there is no lag time between dates of service and the time that data become available. The rate of liver disease for the comparator group in the troglitazone analysis is an estimated rate in the general population, which includes patients with and without diabetes. By being transparent about the calculations and underlying assumptions, others can evaluate the impact of changing these assumptions.

Large-scale active monitoring systems are not only intended to inform regulatory decisions, but also to alert stakeholders to patterns that warrant closer investigation. A concern is therefore the risk of generating an intractably large number of false-positive alerts. Through the use of various design and analytic techniques, the risk of false-positive alerts due to bias

can be minimized.¹⁹ Careful selection of an alerting algorithm will reduce the risk of generating false-positive alerts due to chance. The trade-off between false-positive and false-negative alerts will need to be considered in devising and applying such decision rules, since a multipronged alerting rule will increase the probability of a false-negative alert.¹⁹ It should be noted that there is also a non-monetary cost associated with false positive and false negative alerts; namely loss of public confidence in the drug regulation system. Therefore, it remains critical to allocate resources to methodological research focused on developing rules that provide optimal balance between false positive and false negative alerts.¹⁹

While we included a delay between the alert and the decision to withdraw in our simulation to account for the time needed to further investigate and confirm the alert, we did not explicitly account for false-positives and false-negatives. The costs of false-positives would include those associated with the conduct of the further investigation. The costs of false-negatives would be equivalent to a further delay in withdrawal, which would result in avoidable adverse events and associated morbidity and costs.

The “safety” of a given drug is not absolute, but is rather a relative measure as to whether the risk associated with its use is in some acceptable proportion to its benefit. Although a comprehensive risk-benefit analysis assessing the safety profiles of these drugs relative to their potential benefits was outside the scope of our analyses, better use of emerging data when these drugs were on the market might have revealed a loss of this balance between benefits and risks. The effect of lowering LDL cholesterol with cerivastatin, at the initially approved doses, was smaller than that achieved with other already available statins, and it was never approved for preventing clinical outcomes of cardiovascular events.¹³ Troglitazone did not reduce HbA_{1c} either as monotherapy or as additive therapy more than existing medications.¹⁵ Rofecoxib was not more effective than other NSAIDs as an analgesic or anti-inflammatory agent; its benefit in reducing gastrointestinal complications was modest and very similar to that achieved by addition of a proton-pump inhibitor to other NSAID regimens.³⁰

In December 2016, the 21st Century Cures Act was signed into law. The law contains several provisions designed to reduce the amount and rigor of clinical testing required before new drugs and devices can be approved. It places greater emphasis, for example, on biomarkers and surrogate endpoints, and non-randomized evidence to support new uses of existing drugs. Such focus on speed of approval may require further investments in a high-quality pharmacovigilance system to reliably evaluate risk-benefit tradeoffs of treatments for indications approved using these alternative pathways.³¹

Our findings demonstrate the importance of supporting the current efforts of pharmacovigilance with proactive safety monitoring of newly marketed medications, and following up on potential safety concerns raised in randomized controlled trials. Fast and transparent communication and decision making once the signal has been confirmed are also important, with such activities fully integrated into the regulatory process. Much methodological work is already underway in the FDA Sentinel initiative and its related activities³² and more is needed to clarify the best way of implementing such near-real-time

safety surveillance activities using the increasing number of ever-larger databases, analyzed by new methods^{19,23,33} in increasingly fast analysis cycles.

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Table 1

Measures of pharmacovigilance activities for rofecoxib, troglitazone, and cerivastatin

Comparator group	Rofecoxib & Acute Myocardial Infarction non-selective NSAIDs	Cerivastatin & Rhabdomyolysis other statins	Troglitazone & Acute Liver Failure non exposure to troglitazone
Utilization measures			
Total number of prescriptions dispensed in the US over the lifetime of the drug	105,000,000 ¹⁶	11,172,000 ¹⁷	12,900,000 ¹⁸
Number of quarters on the US market	21 ¹⁹	14 ¹⁹	12 ¹⁹
Epidemiologic measures			
Incidence rate for the event of interest in the comparator group	2.1 per 1,000 PY ²⁰ (95% CI, 1.0 – 3.7 per 1,000 PY)	4.4 per 100,000 PY ²¹ (95%CI, 2.0 – 8.2 per 100,000 PY)	0.3 per 1,000,000 PY ²² (95%CI, 0.1 – 0.9 per 1,000,000 PY)
Incidence rate for the event of interest among users of the drug	5.7 per 1,000 PY ²⁰ (95% CI, 4.0 – 7.9 per 1,000 PY)	53.4 per 100,000 PY ²¹ (95%CI, 14.6 – 136.8 per 100,000 PY)	240 per 1,000,000 PY ²² (95%CI, 6.3 – 1,386 per 1,000,000 PY)
Pharmacovigilance measures			
The quarter when signal would have been detected with a well-functioning pharmacovigilance program (the “signal-detection” quarter)	Best-case scenario 4 ²³	Best-case scenario 10 ¹⁹	Best-case scenario 4 ²⁴
	Worst-case scenario 8	Worst-case scenario 13	Worst-case scenario 8
Cost measures			
Direct cost of each event of interest (2014 US\$)	\$35,573 ²⁵	\$57,421 ²⁶	\$289,277 (liver-transplant) ²⁷ \$29,306 (decompensated cirrhosis) ²⁸

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Table 2

Cost savings associated with adverse events prevented due to pharmacovigilance activities for rofecoxib, troglitazone, and cerivastatin

“Signal-detection” quarter	Rofecoxib & Acute Myocardial Infarction			Cerivastatin & Rhabdomyolysis			Troglitazone & Acute Liver Failure		
	Best-case scenario	Worst-case scenario	8	Best-case scenario	Worst-case scenario	13	Best-case scenario	Worst-case scenario	8
Total number of additional prescriptions dispensed after signal detection	100,454,545	88,636,364		5,320,000	1,489,600		11,246,154	6,946,154	
Number of excess person-years of exposure after signal detection	8,256,538	7,285,181		437,260	122,433		924,341	570,917	
Number of avoidable cases based on pharmacovigilance (95% credible interval)	27,489 (10,930 – 45,244)	24,562 (9,614 – 39,814)		190 (43 – 383)	53 (10 – 130)		264 (24 – 803)	162 (14 – 474)	
Estimated cost savings attributable to pharmacovigilance programs	\$884,027,340	\$773,204,143		\$9,896,480	\$2,752,197		\$62,905,529	\$38,151,638	
(95% credible interval)	(\$328,848,010 – \$1,521,128,985)	(\$287,374,732 – \$1,330,656,279)		(\$2,360,852 – \$21,113,231)	(\$570,147 – \$6,538,982)		(\$5,942,033 – \$202,311,625)	(\$3,346,466 – \$120,159,681)	

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