



DRUG SAFETY AND RISK MANAGEMENT PRACTICE

What Drug Companies Can Do

by Mei Sheng Duh, Sc.D., Paul E. Greenberg, and Lucia Antràs, Ph.D.

The advent of blockbuster drugs in the 1990s revolutionized American medicine. An aging population now relies on popular medications to treat a variety of common conditions, such as hypertension, high cholesterol, type II diabetes, and arthritis. One perhaps unavoidable consequence has been an increase in the number of adverse events (AEs), defined by the Food and Drug Administration (FDA) as events requiring medical intervention to prevent harm.

According to FDA's Center for Drug Evaluation and Research (CDER),¹ the number of AEs reported from 1995 to 2005 increased at a compound annual growth rate of 11.5 percent, from 156,500 to 464,000. At least partially as a result of this increase and the surge of scrutiny by public health regulators, about one-fifth of prescription drugs now carry a "black-box warning," issued by the FDA, the most serious label a drug can bear to inform prescribers and

patients of potential side effects. Moreover, an increasing number of popular drugs (most recently Merck's painkiller Vioxx and Novartis' Zelnorm for irritable bowel syndrome) have been withdrawn due to concerns over cardiac safety. It should come as no surprise to industry observers that high-stakes mass tort litigations against pharmaceutical companies are now increasingly common.

On the regulatory front, the FDA Amendments Act, signed into law in September 2007, has set forth risk identification, evaluation, and mitigation objectives for the FDA regarding postmarket drugs. The combined impact of these factors has led pharmaceutical companies to incorporate greater attention to drug safety into their pre-market approval processes as well as post-marketing surveillance.

The recent spike in reported adverse events, as an Archives of Internal Medicine study notes, is four times

steeper than the increase in the total number of outpatient prescriptions over the same eight-year period, driving researchers to search for explanations.² One contributing factor may be that many chronically ill patients now take a given drug daily over the course of many years. Another is the number of patients taking multiple prescriptions, increasing the potential for drug-drug interactions. And, unlike the small test groups in clinical trials, which tend to be homogenous and carefully selected, users of on-market drugs are highly heterogeneous, bringing a complex range of potential co-morbidities into play.

Given the inherent difficulty of pinpointing the precise cause or causes of AEs in diverse populations, pharmaceutical companies cannot realistically try to eliminate risks to all patients; instead, they must determine the best strategy for addressing the particular risk potentially associated with every new and existing drug. But risk assessment,



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A Risk Management Roadmap

1. Review clinical trials. In the wake of what happened to Zelnorm and Avandia, it is especially important that pooled analyses be carefully examined.
2. Implement a signal monitoring program, using MedWatch data, to determine if your drugs are on a watch list, and therefore likely to be under scrutiny.
3. If you get a signal, identify it and the adverse event that could potentially occur. Note that the nature of the data allows a high number of spurious signals to be sent.
4. Validate the signal with a quick, denominator-based claims analysis. The result will be a propensity score matching, adjusted for demographic variables such as age and gender.
5. If elevated risk is still being returned, a more sophisticated epidemiological study is required, to combine claims data with patient chart data.
6. Determine whether the signal was a chance finding by trying to replicate it using another claims database; if not, determine relative risk, using U.S. population data.
7. Before undertaking the most difficult and costly analysis—randomized safety trials—companies can develop an information and education program of outreach to prescribing physicians and patients.
8. Undertake randomized safety trials, if the cost-benefit analysis merits it.

which epidemiologists define as the probability of the occurrence of harm and the severity of that potential harm, requires expert judgment combined with input from many parties: company scientists and clinicians, executives, general counsel, and perhaps external counsel and strategic advisors as well.

A comprehensive approach must also take into account the unique role drug companies play not only as providers of products critical to public health and disease prevention, but also as viable businesses with obligations to shareholders. Ultimately, risk management decisions must be based on both epidemiologic concerns and business

considerations, with unwavering attention to maintaining the public's trust. In this article, we lay out a simple roadmap, based in epidemiology, that drug companies can use to design and implement a risk-management program tailored to their specific products.

Building a Risk Management Program

Pharmaceutical companies are attempting to address the challenges of on-market drug risk management within complicated and often highly charged business, social and political contexts. While drug manufacturers and healthcare providers must pledge

to “first, do no harm,” today’s demanding patients seek perfect pills that can cure the most persistent diseases.

The safety standards for pharmaceutical products are significantly higher than those imposed on nearly all other industries. As a result, even when the incidence of AEs is extremely low, drugs can still be withdrawn from the market. And, in our litigious society, if a drug is used widely, the scope alone makes it likely that litigation will ensue, even if only a small proportion of patients is affected. As University of California researcher Robert Kagan points out in *American and European Ways of Law: Six Entrenched Differences*, “the United States is distinctive in the relative ease with which entrepreneurial lawyers can aggregate tort claims by persons injured by the same product, accident, or technology into a single case, demanding millions ... or billions of dollars in damages.”³³ The business implications of possible litigation must therefore inform any risk management discussion.

Pharmaceutical companies clearly need to develop a pragmatic approach to managing the safety of on-market drugs. Unfortunately, they can't yet turn to any standard protocols for help in managing risk during the post-marketing period. In 2005, the FDA published some nonbinding recommendations on pharmacoepidemiologic assessment, but this guidance does little more than define basic concepts, stating, for example, that “pharmacovigilance principally involves the identification and evaluation of safety signals.”³⁴

Absent formal guidelines, pharmaceutical companies must strike a balance between benefit and risk. That means evaluating the positive treatment efficacy of products that will

help the majority of patients who take them alongside the potentially negative side effects, or AEs, which typically occur in a minority of patients. Ideally, drugs would be administered only to patients not likely to suffer side effects; however, the ability to predict this accurately and consistently is well beyond the limits of current medical knowledge and technology. In addition, a side effect that might appear to be a random adverse event at one point in time may later—with hindsight bias (the medical equivalent of Monday-morning quarterbacking)—be interpreted as a signal of an adverse event that should have been detected and managed. Once researchers begin linking adverse events to the known properties of a drug, it becomes easy for critics to accuse drug companies of not having done enough to safeguard the public all along.

In designing risk management strategies, drug company executives need to conduct a cost-benefit analysis based on multiple possible scenarios. H. Gregg Claycamp, Associate Director for Risk Analysis and Strategic Policy Assessment at CDER and an expert on risk management, suggests that any such program must, at a minimum, address the following questions:

- Does the risk exceed an acceptable level? Or is it already below current regulatory concerns ... or has it been reduced by risk management programs to a currently acceptable level?
- What steps might be taken to reduce or eliminate remaining risks?
- What is an appropriate balance among risks, benefits, and resources to manage risks?⁵

The broad nature of these considerations underscores the fact that assessing the needs of a risk manage-

ment program continues to be largely a qualitative effort, dependent more on judgment calls than on fact-based findings. Determining the appropriate risk-benefit balance always involves the judgment and preferences of the decision maker as well as some uncertainty around the true benefits and risks of a given drug. Quantitative methodologies, building upon existing methods

Strategic Decisions in Balancing Risk and Benefit

Pharmaceutical companies may decide, based on corporate strategy, to manage the results of an AE signal related to one drug retrospectively, while they may need to choose a proactive approach with regard to a different drug. Some drug companies develop safety programs that are implemented from the moment drugs

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for analyzing cost-effectiveness, could serve as a possible way to allow decision makers to evaluate the net benefit of a drug given different risk-benefit acceptability thresholds.⁶

As noted earlier, the context in which these decisions are being made has changed significantly: the risk benefit calculus often now takes place under intense scrutiny from public health crusaders, industry watchers and regulators, competitors, media and the general public. In the face of this pressure, some companies are beginning to adopt more formal quantitative methods for weighing risk and benefit, identifying thresholds for drug safety in much the same way that they evaluate drug cost-effectiveness. The impact and results of these methods are, however, still being studied, and defining the relative term “acceptable risk” therefore remains for many companies a qualitative challenge.

enter the product pipeline, preferring to gather and analyze data in advance of potential FDA requests or investigations.

Whatever the approach selected, each program needs to be appropriate to the specific nature of the risk. Whenever a pharmaceutical company identifies a signal of a potential side effect (from monitoring MedWatch for example,) it will often develop and document a response. However, since risk management programs can be extremely expensive, companies cannot afford to follow up on every signal, or to investigate each to the same extent. Consider the case of two drugs for which the manufacturer has identified similar AE signals, one with a history of annual sales in the \$5 billion range, and a newer product with first-year sales of \$100 million. A very different risk-benefit ratio may apply to each, resulting in two separate risk management approaches.

For some pharmaceutical companies, the threat of lawsuits over product safety is the primary catalyst for establishing a risk management strategy. In litigation, a proactive approach can be key. A solid risk management program will have identified and assembled a set of well-researched studies, published in reputable health care journals, well in advance of any suits being filed. This might involve gathering data-based evidence on the population level—in other words, epidemiological evidence, not just clinical trial outcomes. Such evidence can be used to demonstrate, for example, the incremental risk of a specific drug relative to established baselines. As was the case in the Vioxx trials, having this kind of evidence in hand at the outset can help companies attain critical early wins in mass torts.

Conclusion

With Americans taking more prescription drugs each year, concern about

drug safety is unlikely to diminish, and pharmaceutical companies may be forced to devote greater resources to risk management programs. However, the precise shape of programs implemented can be expected to evolve in accordance with advances in both science and risk management.

In the future, part of every company's risk management strategy may involve reducing the number of AEs, for example, by applying new insights into the genetic basis of drug safety problems. That's the goal of the newly established International Serious Adverse Events Consortium, funded by seven of the world's largest drug companies, that is already searching for a genetic cause of liver-toxicity and plans to focus next on heart and kidney problems related to drug side effects. But the science of pharmacogenetics is still in its infancy, and its impact on policy-making

and drug regulations will not fully be known in the foreseeable future. In the interim, in order to survive and succeed, drug companies may have to focus as much energy on strategic risk management as they historically have on such core areas as drug development, innovation, and growth. ▲

- 1 FDA, CDER Report to the Nation, Post-marketing adverse event reports, 2005
- 2 See <http://archinte.ama-assn.org/cgi/content/abstract/167/16/1752>
- 3 Robert A. Kagan, "American and European Ways of Law: Six Entrenched Differences." Institute of European Studies, <http://repositories.cdlib.org/ies/060407>
- 4 FDA, available at <http://www.fda.gov/CDER/GUIDANCE/6359OCC.pdf>
- 5 Gregg Claycamp, *Perspective on Quality Risk Management of Pharmaceutical Quality*, DRUG INFORMATION JOURNAL 353; Vol 41, Issue 3, July 1, 2007
- 6 Lynd LD, O'Brien BJ. *Advances in Risk-Benefit Evaluation Using Probabilistic Simulation Methods: An Application to the Prophylaxis of Deep Vein Thrombosis*. J CLIN EPIDEMIOL. 2004 Aug;57(8):795-803.

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