MARKET WATCH

Spending On Postapproval Drug Safety

The highest drug-safety spenders among drug firms produce more new and "blockbuster" drugs than their competitors do.

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ABSTRACT: Withdrawals of high-profile pharmaceuticals have focused attention on postapproval safety surveillance. There have been no systematic assessments of spending on postapproval safety. We surveyed drug manufacturers regarding safety efforts. Mean spending on postapproval safety per company in 2003 was $56 million (0.3 percent of sales). Assuming a constant safety-to-sales ratio, we estimated that total spending on postapproval safety by the top twenty drug manufacturers was $800 million in 2003. We also examined, using regression analysis, the relationship between the number of safety personnel and the number of initial adverse-event reports. This study offers information for the debate on proposed changes to safety surveillance. [*Health Affairs* 25, no. 2 (2006): 429–436; 10.1377/hlthaff.25.2.429]

RECENT WITHDRAWALS of high-profile drugs have focused attention on the safety of marketed drugs.[1] Safety and efficacy profiles of newly launched drugs are based on the experiences of up to several thousand people in controlled clinical trials. At this level of exposure, however, clinical trials might not detect events that occur in as few as one patient per thousand.[2] Likewise, important interactions with other drugs and medical conditions might go undetected.[3] Thus, the public relies on postapproval surveillance to detect rare and unexpected reactions to new medications.

The primary postapproval method for detecting signals of adverse drug reactions is a system of spontaneous reporting.[4] In the United States, when an adverse drug event occurs and is recognized, the patient or clinician may report it directly to the U.S. Food and Drug Administration (FDA) through a MedWatch form or to the manufacturer, which is required by law to submit the data to the FDA within a specific time frame. FDA personnel enter the data into the Adverse Event Reporting System (AERS). Following signal detection and analysis, the manufacturer continues vigilance. Further actions taken by the manufacturer can include initiating new research, revising product labeling, writing a "Dear Health Professional" letter, instituting a risk management program, or withdrawing the

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product voluntarily. Potential FDA actions include recommending that the manufacturer conduct new research, requiring the manufacturer to relabel the product or write a "Dear Health Professional" letter, or withdrawing product approval.[5] The AERS received nearly 400,000 reports in 2003, but because it relies on clinicians to volunteer their time and potentially risk liability, the system underreports adverse events.[6] The FDA receives by direct report an estimated 1 percent or less of suspected adverse drug reactions.[7]

Experts have made many suggestions for improving postapproval assessment of drug safety, including alternative or complementary mechanisms to the current reporting system.[8] A first step in determining optimal policy changes is to understand current policy, including the funding of programs that address existing regulatory mandates. To that end, we present findings from a survey of drug manufacturers' postapproval drug safety efforts.

Study Data And Methods

■ **Data.** We developed a structured, Web-based survey with input from members of the Pharmacovigilance and Epidemiology Technical Group of Pharmaceutical Research and Manufacturers of America (PhRMA). The survey asked respondents to report postapproval safety efforts and costs incurred in 2003 for all drug products (prescription and over-the-counter, or OTC). The survey also asked whether 2003 costs varied greatly from 2001 or 2002 costs. We gathered data on the number of products in company portfolios, including the number of drugs for serious conditions, new drugs, and drugs approved for pediatric use. We also asked respondents to report the share of their company's safety spending in the United States, Europe, Japan, and the rest of the world.

Respondents were also asked to report the number and types of adverse events and periodic safety update reports (PSURs). For the interval since the last required report, a PSUR summarizes new adverse events from spontaneous reports, formal studies, and the biomedical literature. Although various regulatory authorities may request PSURs at different intervals, the International Conference on Harmonization has recommended a standard content and format. We classified PSURs with fewer than 100 cases as small, with 101–500 cases as medium, and with more than 500 cases as large. Case counts are those in the principal adverse-event listing, excluding nonserious listed cases. "Listed" refers to an adverse event that has already been noted officially in the Company Core Safety Information.[9]

Mindshare Interactive Campaigns administered the survey on the Internet. Beginning in 2004, we invited responses from representatives of twenty-five of the largest pharmaceutical manufacturers that sell products in the United States. We assured respondents that firm-level data would be kept confidential and that only aggregate data would be reported. The study was supported in part by a sponsored research agreement with PhRMA in which the researchers had access to all primary data and controlled the analyses and the study report.

We limited the survey to postapproval safety activities; the survey did not include spending for marketing or for preapproval safety testing. It is challenging to separate preapproval from postapproval safety costs. As a rule of thumb, we considered the share of adverse-event reports to be proportional to preapproval versus postapproval safety costs. Furthermore, the survey did not include postapproval studies exploring new indications (such as the study of rofecoxib for prevention of the recurrence of colorectal polyps). Postapproval safety activities include the following: (1) handling of individual adverse-event cases reported after approval, including collection, scientific analysis, data entry into computer databases, medical review, follow-up, and reporting to worldwide regulators; (2) summary report production of aggregate postapproval adverse-event information, including PSURs; (3) safety department operations, including quality assurance, technology support, and training; (4) safety surveillance activities, including those related to postapproval risk management, safety-related

product quality complaints, including product recall for safety reasons, responses to safety questions from worldwide regulators, literature review for adverse-event information, and provision of safety information to health care professionals; (5) postapproval safety studies; (6) safety-focused epidemiologic activities (postapproval); and (7) activities required for safety-related labeling changes (excluding labeling changes for other reasons).

■ **Additional data sources.** We supplemented the data on postapproval safety resources with sales data from annual reports. Annual reports typically report drug sales separately from other categories, such as consumer and animal health products. We used data from Contract Pharma to validate the sales data, to calculate total sales by the top twenty manufacturers, and to count the number of "blockbuster" products (those with sales greater than $1 billion in 2003) per company.[10] We used sales data from Contract Pharma rather than from the PhRMA Industry Profile, because the PhRMA data exclude sales generated abroad by foreign companies. Finally, we asked the Office of Drug Safety in the FDA's Center for Drug Evaluation and Research (CDER) for its 2003 budget for postapproval safety.

■ **Data analysis.** We report descriptive statistics at the firm level. We used unweighted means that are representative of the companies in the sample but not necessarily the industry as a whole, particularly for variables with large standard deviations. When we generalized to the entire industry, we used sales-weighted data. We used the survey and sales data to estimate aggregate safety spending by the top twenty companies in 2003.

We estimated safety efforts using spending and the number of full-time-equivalent (FTE) employees. We used Pearson product moment correlation to estimate the relationship between safety efforts (that is, spending and employees) and other company characteristics (such as sales and product portfolio).

We estimated the effect of the number of initial adverse-event reports on FTEs engaged in safety activities, using multivariable regression analysis. We controlled for sales using a sales variable and an interaction term (sales multiplied by initial adverse event reports). We used FTEs rather than spending, because counts of FTEs were the most objective measure of effort available to respondents. Furthermore, all companies reported FTEs, whereas two did not report total safety spending. In a second model, we omitted the sales variables. We did not include indicator variables for blockbuster drugs and new drugs in the regression models, because we expect that these variables are highly correlated with the sales variable. We tested for multicollinearity using the variance inflation factor.

Study Results

We sent surveys to twenty-five large drug manufacturers; in general, the largest of the large responded. The eleven companies that responded accounted for 71 percent of 2003 sales by the top twenty manufacturers.[11] Six have headquarters in the United States; only four had systems in which one safety group reported to all regulators worldwide.

Mean pharmaceutical sales per company were $17 billion (Exhibit 1). On average, participating companies marketed almost 200 prescription drugs and almost 200 OTC drugs. For these companies, more than half of postapproval spending was in the United States. Exhibit 1 also reports the mean numbers of adverse events and PSURs for 2003.

On average, 57 percent of costs for FTEs were attributed to health staff and scientists. The remaining FTE costs were for management and other staff, including data management. Companies reported that, on average, 67 percent of safety spending was for postapproval safety reporting, compared with 33 percent for preapproval safety reporting. These companies spent an average of $56 million for postapproval safety in 2003 (0.3 percent of sales), with nearly 70 percent of this cost dedicated to personnel. Respondents indicated that their 2003 spending did not differ dramatically from their 2001 or 2002 spending.

■ **Total industry spending.** Given that sales by the top twenty manufacturers were

EXHIBIT 1
Descriptive Statistics At The Company Level, 2003

Variable	Number of responding companies	Mean (standard deviation)
Pharmaceutical sales (billions of dollars)	11	17.4 (10.52)
Portfolio (number of drugs)		
Prescription drugs	10	183.6 (186.78)
Over-the-counter drugs	10	197.6 (204.01)
Drugs for serious conditions	9	17.6 (15.19)
New drugs	9	8.1 (5.16)
Blockbuster drugs (2003 sales greater than $1 billion)	11	3.8 (2.89)
Drugs approved for pediatric use	9	39.6 (44.76)
Share of postapproval safety spending		
United States	10	0.6 (0.22)
Europe	10	0.2 (0.15)
Japan	10	0.1 (0.09)
Rest of world	10	0.1 (0.09)
Adverse events (thousands)		
Initial nonserious	10	27.8 (18.45)
Initial serious, expedited	10	7.4 (7.56)
Initial serious, not expedited	10	11.1 (13.59)
Follow-up nonserious	10	13.9 (14.31)
Follow-up serious, expedited	10	8.4 (13.20)
Follow-up serious, not expedited	10	13.0 (10.87)
Periodic safety update reports		
Small (fewer than 100 cases)	11	67.6 (84.26)
Medium (101 to 500 cases)	11	40.1 (58.52)
Large (more than 500 cases)	11	25.3 (23.33)
Share of costs by employee type		
Physicians	10	0.2 (0.09)
Other health staff	10	0.3 (0.20)
Scientists	10	0.1 (0.08)
Management	10	0.1 (0.05)
Other staff	10	0.3 (0.24)
Full-time-equivalents	11	298.1 (159.01)
Share of spending on postapproval safety	11	0.7 (0.11)
Share of sales for postapproval safety	9	0.003 (0.001)
Postapproval safety spending for personnel (millions of dollars)	10	38.1 (18.77)
Nonpersonnel postapproval safety spending (millions of dollars)	9	16.6 (14.85)
Postapproval safety spending (millions of dollars)[a]	9	55.72 (31.82)

SOURCE: Unweighted descriptive statistics at the company level for 2003 using survey data and company annual reports.
[a] One respondent declined to estimate nonpersonnel and total costs, so the averages for personnel and nonpersonnel do not add to the average total.

$267.6 billion in 2003 and assuming a constant safety-to-sales ratio of 0.003, we estimated that these manufacturers spent $800 million on postapproval safety in 2003.[12]

■ **Correlations.** Safety spending and number of FTEs were significantly correlated with sales and number of adverse-event reports, new drugs, and blockbuster drugs (Exhibit 2). On the other hand, numbers of prescription drugs, OTC drugs, drugs for serious conditions, and pediatric drugs were not correlated with safety efforts. These measures do not control for a given drug's sales volume or novelty.

The number of FTEs directed at postapproval safety ranged from 38 to 550 (mean [standard deviation], 298 [159.1]) per firm. The company with the fewest FTEs also had the fewest initial adverse-event reports and the lowest sales in the sample. The company with the most FTEs had the most initial adverse-event reports and the highest sales in the sample. There is evidence of economies of scale, in

EXHIBIT 2
Correlations Between Variables Measuring Postapproval Safety Effort (Spending And Staff) And Other Variables Of Interest

Variable	Postapproval safety spending	FTEs
Postapproval safety spending	1.00	0.88***
Full-time-equivalents (FTEs)	0.88***	1.00
Pharmaceutical sales	0.93***	0.84***
Number of adverse events		
Initial nonserious	0.73**	0.77**
Initial serious, expedited	0.57	0.62
Initial serious, not expedited	0.75**	0.60
Follow-up nonserious	0.77**	0.66**
Follow-up serious, expedited	0.79**	0.65**
Follow-up serious, not expedited	0.47	0.64**
Portfolio		
Prescription drugs	0.62	0.52
Over-the-counter drugs	0.17	0.39
Drugs for serious conditions	0.36	0.39
New drugs	0.86***	0.77**
Drugs approved for pediatric use	0.47	0.48
Blockbuster drugs (2003 sales greater than $1 billion)	0.93***	0.79***

SOURCE: Authors' analysis using survey data and company annual reports.
**$p < .05$ ***$p < .01$

that the company with the fewest FTEs had the highest number of FTEs per initial adverse-event report (0.017). The company with the most FTEs had the second-lowest number of FTEs per initial report (0.005).

We further examined these relationships in regression analysis (Exhibit 3). We estimated that a company has four additional FTEs for every thousand additional initial adverse-event reports. In other words, a company has one additional FTE for every additional 251 reports ($p = .10$). Companies with higher sales have more FTEs. However, the interaction term is neither statistically nor economically significant, which indicates that if two companies have an equal increase in their initial adverse-event reports, they will have about the same number of additional FTEs, despite differences in company sales. To better understand this relationship, one might imagine that a company with higher sales starts with more safety employees than a company with lower sales but that they add employees at about the same rate as initial adverse-event reports increase. In the second model, we found that a company will hire an additional FTE for every 223 initial adverse-event reports ($p = .002$).

Discussion

Despite concerns about the adequacy of current methods of drug safety surveillance, there have been no studies quantifying the total resources devoted to postapproval safety. We found that manufacturers spent 0.3 percent of sales on postapproval safety in 2003. This proportion seems low compared with the 15.6 percent of sales on research and development (R&D, which includes preapproval safety efforts) in 2003.[13] On the other hand, the absolute dollar amount spent by industry on postapproval safety in 2003 was considerable ($800 million for global postapproval safety efforts by the top twenty manufacturers).

In the same time period, the total budget for the Office of Drug Safety in the FDA's CDER was $22.1 million for the United States only.[14] The Office of Drug Safety is responsible for creating, maintaining, and analyzing the AERS

EXHIBIT 3
Regression Analysis Of Postapproval Safety Activities

	Model 1		Model 2	
Independent variables	**Coefficient**	***p* value**	**Coefficient**	***p* value**
Constant	−8.560	.913	96.747	.108
Initial adverse-event reports (thousands)	3.990	.095	4.478	.002
Pharmaceutical sales (millions)	0.013	.088		
Interaction term: sales multiplied by initial adverse events	0	.190		
R^2	0.84		0.73	

SOURCE: In model 1, the authors regressed the effect of the number of initial adverse-event reports on full-time-equivalents (FTEs) engaged in safety activities, controlling for sales using a sales variable and an interaction term (that is, sales multiplied by initial adverse-event reports). Model 2 is identical to model 1, except for the omission of the sales variables.

database (including data mining); conducting epidemiologic investigations; working with sponsors to support risk management efforts; and assessing medication errors. Technological tools to automate initial screening of AERS help minimize the cost of that system.[15] Spending on preapproval review at the FDA has increased considerably since enactment of the Prescription Drug User Fee Act (PDUFA) in 1992, but the impact of recent extensions to the act that increase funding to the CDER for postapproval safety is not yet known.[16]

The cost-effectiveness of postapproval safety surveillance cannot be determined without an assessment of effectiveness, which was beyond the scope of our study. There does, however, appear to be consensus that some information is not accessible from spontaneous reporting systems, such as long-term effects of medications, reliable comparisons between products, and rare adverse effects associated with older drugs.[17] Indeed, our data indicate that cost is associated with the number of new products but not the total number of prescription drugs. Although spontaneous reporting can assist in signal detection for rare cases of severe toxicity, such as those seen with cerivastatin and terfenadine, it is less effective in detecting adverse events that are commonly manifest in the population, such as cardiovascular complications of COX-2 inhibitors.[18] In the latter case, randomized clinical trials directed at new indications for COX-2 inhibitors shed light on the association.[19] However, the FDA has limited funding and authority to require epidemiological investigations and randomized trials under conditions of general use that could test hypotheses when a potential adverse reaction has been suggested.

Our results indicate that safety spending and FTEs are highly correlated with new products and blockbusters. New products may generate more adverse-event reports because clinicians are more likely to report adverse events for products with which they are less familiar. Higher sales volume indicates exposure of more patients and thus greater odds that adverse events may occur with the products, even if there is no causal relationship. Finally, manufacturers with more sales, new products, and blockbusters likely have higher profits. Higher profits provide more resources for spending on safety and greater incentive to spend on safety to avoid litigation.

■ **Comparisons with other studies.** Although this is the first systematic assessment of spending on postapproval safety by drug manufacturers, two other studies are noteworthy. First, Joseph DiMasi and colleagues estimated that postapproval R&D costs over a given drug's lifetime were $140 million.[20] Our estimates differ greatly for at least three reasons: (1) DiMasi and colleagues estimated cost per drug, whereas we estimated cost per company; (2) they estimated lifetime costs of products, whereas we estimated annual costs; and (3) they included postapproval costs beyond safety efforts, and we did not.

Second, a benchmark study by World Class International—a consulting firm that specializes in process, technology, and outsourcing—found that the number of initial adverse-event reports per total global head count in drug safety for 2003 ranged from 100 to 400.[21] Ignoring outliers, the typical range was 250 to 350. Our finding that companies hire an additional FTE for every 251 initial adverse-event reports is consistent with those findings.

■ **Limitations.** The data are self-reported and were not audited, so manufacturers might have had an incentive to misreport costs. However, we do not believe that the data were misrepresented, based on four observations. First, the study was conceived at an invited meeting convened by the Centers for Education and Research on Therapeutics (CERTs), sponsored by the Agency for Healthcare Research and Quality. There was consensus among attendees (representing academe, the FDA, and industry) that such a study should be performed to inform the discussion of the optimal postapproval system and providing a benchmark on cost. Second, manufacturers reported spending 0.3 percent of sales on postapproval safety, so this is unlikely to be a public relations effort. Third, six responses were submitted before the September 2004 withdrawal of rofecoxib, when public pressure was lower. These six manufacturers reported spending an average 0.3 percent of sales on postapproval safety—approximately equal to that by the full sample. Fourth, the finding on FTEs per initial adverse-event report is consistent with the benchmark study.

The study has other limitations. First, the sample consists of PhRMA members that tend to be large and medium-size pharmaceutical companies; hence, the findings are not necessarily representative of smaller companies or those in the biotech sector. On the other hand, because our sample covers more than 70 percent of the sales of the top twenty manufacturers, it should be a reasonable estimate of total industry spending. Second, the data cover only one year. Respondents indicated, however, that spending in 2001 and 2002 did not differ dramatically from 2003. Third, respondents might have neglected to allocate some infrastructure costs. However, we do not believe that this omission by some respondents would greatly alter our results. Fourth, because of the challenge of separating preapproval from postapproval safety costs, we suggested the following rule of thumb: The ratio of preapproval to postapproval reports equals the ratio of preapproval to postapproval costs. However, if more effort is associated with a preapproval report than a postapproval report, then actual postapproval costs will be lower than we estimated. Fifth, the scope of the study is limited only to postapproval safety activities by PhRMA members and the Office of Drug Safety; it omits costs borne by physicians and other reporters, non-PhRMA members, and regulators in other countries.

THERE IS GREAT NEED for postapproval surveillance in the United States, because this is the country of preferred launch for new drug compounds and for innovative compounds in particular.[22] U.S. patients receive obvious benefits from earlier access to innovative drugs, but novel drugs are subject to greater risks, and many risks become fully known only with widespread use of the drugs.[23] An Institute of Medicine committee is studying the effectiveness of the U.S. drug safety system with an emphasis on the postapproval phase.[24] Our study can provide information for the debate on proposed changes to the system and a baseline for future studies on the impact of new regulations.

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