



# The Institute for Safe Medication Practices

A Nonprofit Organization Educating the Healthcare  
Community and Consumers About Safe Medication Practices

## Quarter Watch: 2008 Quarter 1

October 23, 2008

### Executive Summary

A record number of deaths and serious injuries associated with drug therapy were reported to the U.S. Food and Drug Administration (FDA) in the first quarter of 2008. Serious injuries associated with drug therapy reached a total of 20,745 new cases; reported deaths totaled 4824 cases, a 2.6 fold increase from the previous quarter.

In addition, varenicline (Chantix, Champix), an aid to stopping smoking, accounted for more reported serious injuries than any other prescription drug for a second quarter, a total of 1001 new cases, including 50 additional deaths. Varenicline was the subject of a previous Quarter Watch special report<sup>1</sup> and a separate FDA Public Health Alert about psychiatric side effects. Ranked second in reported serious injuries was heparin, a drug that helps prevent injury from blood clots. Heparin was the subject of a major product recall after a potentially lethal contaminant was identified and traced to suppliers in China. In the first quarter of 2008, the FDA received reports of 779 cases of serious injury in which heparin was the principal suspect drug.

These findings come from a program being developed by the Institute for Safe Medication Practices (ISMP) to improve patient safety through increasing our understanding of how and why drug-related injuries and medication errors occur. The results come from analyzing new adverse drug events reports submitted to the FDA. The agency releases computer excerpts of these reports for research use after personal identifying information has been removed.

However, the results of this monitoring program should be interpreted with caution because of the known limitations of these data, and the nature of the overall system through which the adverse events are monitored in the United States. Because reporting is voluntary, only a small fraction of adverse drug events that occur are ever reported to the FDA or to drug manufacturers, which then investigate and forward reports to the agency. While the sum totals of reported adverse event reports normally provide an accurate overall adverse event profile for a drug, the individual reports themselves do not prove that the drug caused the event described.

## **Trends in Reported Cases**

- Serious injuries and deaths associated with drug therapy were reported for a record total of 20,745 persons in the first quarter of 2008. The total was 38% higher than the average for the previous four quarters, and the highest for any quarter.
- Reported deaths totaled 4824 cases, a 2.6 fold increase over the previous quarter, and the highest number of deaths in a calendar quarter since 2004. Fatal cases also accounted for a larger share of all serious cases, 23% of those in the first quarter of 2008 compared to a historical average of 16%.
- Identifiable medication errors accounted for 1464 (7.1%) of all cases of serious injury. The largest numbers of cases were divided evenly between errors of administration (wrong drug, wrong dose or wrong route of administration) and overdoses (both accidental and intentional).
- Most drugs in medical use produced only a small number of reports of serious injury or death. One-half the 773 identifiable drugs tracked in the most recent quarter had six or fewer serious adverse events reported. Only 50 drugs accounted for 100 or more reported serious injuries.
- Some of the increase in quarterly totals could represent normal variation in the flow of data rather than signaling a longer-term trend in patient safety.

## **Specific Drugs**

- For a second straight quarter varenicline (Chantix, Champix) accounted for more reported serious injuries than any other prescription drug. Since approval in 2006 the drug has accounted for 3325 reported serious injuries in the U.S., including 112 deaths. In the latest quarter, the toll included numerous cases of serious injury linked to traffic accidents or falls. Other reports described other events such as blackout with a high potential to cause accidents. Following our initial report, the federal government took prompt action to ban varenicline in the most sensitive occupations such as for airline pilots and military missile crews.
- The reported contamination of the drug heparin—traced to suppliers in China—produced a sharp spike in reports. In the first quarter of 2008, the FDA

received 779 reports of serious injury including 102 deaths. The FDA recently reported receiving 238 reports of deaths over a longer period, but this is the first count of serious injuries. However, not all reported injuries were a result of product contamination.

- We investigated a new signal of a surge in reported deaths for a generic drug combination product containing acetaminophen, butalbital and caffeine (Fioricet). The drug, prescribed for tension headaches, contains a barbiturate and was reported as suspect for 156 deaths in the first quarter. Almost all reports turned out to involve questionable coding of published scientific report summarizing cases reported to the country's poison control centers in 2006, and did not signal a new safety problem.
- The 2.6-fold increase in deaths from the previous quarter was not dominated by any single drug. The most striking change was that 10 different drugs accounted for 100 or more deaths. In recent previous quarters just 1-3 drugs accounted for this toll. The 10 drugs are shown in Table 2. The risks of many of these drugs (e.g. fentanyl, oxycodone, methadone, alprazolam) have been subject of previous safety warnings from the FDA.

### **Reaction Types**

- While classification of types of reactions is an emerging science, widely reported reactions included disruptions of the heart rhythm (2658 possible cases), suicide and self injury (1932 cases), and drug dependence and withdrawal (1814 possible cases).
- Drugs associated with large numbers of specific reactions include varenicline and suicide/self injury (226 possible cases), clopidogrel and hemorrhage (170 possible cases), and heparin and angioedema (103 possible cases).

### **The Adverse Event Reporting System**

- Many reports to the FDA were vague and would be difficult to analyze in depth. We found that 15% of all serious reports lacked two or more elements of basic information, such as age, gender, or substantial narrative detail about the event.
- We also detected a significant technical error in how reports were being coded by the FDA or drug manufacturers. We found instances in which follow up reports

about the same event were being miscoded as the “initial” report. We shared our findings with the FDA and revised the Quarter Watch study criteria to avoid the problem.

## **Conclusions**

While prescription drugs bring great benefits to millions of patients and most are used safely, these data show the need for additional progress to better manage the risks to patients.

For varenicline, additional action is needed to make all patients aware of the potential accident risks. We recommend that the FDA and the manufacturer add a prominent warning about accident risks to the patient Medication Guide and prescribing information for doctors. This warning should be similar to the new warnings about psychiatric side effects. While we commend the federal government for prompt action in banning varenicline in the most sensitive occupations such as for airline pilots, air controllers and military missile crews, a broader warning is still needed. Also, additional investigation and action may be needed regarding other adverse effects of varenicline, and prescribers should consider alternative treatments.

The case of heparin illustrates an example a significant safety drug problem that was promptly and effectively resolved by the drug manufacturers and the FDA once the issue was detected and understood. It also underlines the importance of the nation’s system for assuring drug product stability and purity. The scale of injury—hundreds of deaths or serious injuries in a short period--underlines the importance of strengthening oversight of drug manufacture abroad.

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## Background

Quarter Watch is pilot program developed to improve patient safety through regular monitoring of all adverse drug events reported to the FDA. The program involves developing data to address several important questions: How many people are being seriously injured or die from prescription drugs? Is the toll increasing or decreasing? What specific drugs or types of adverse events are most frequently implicated? Better understanding the risks of drugs is the key to more effective management of those hazards.

Many substantial risks—for example aircraft crashes, occupational injury, auto accidents and crime—are monitored on a systematic basis, mostly by the federal government. These risks are assessed not just to have numbers, but to measure progress, seek the reasons for favorable and unfavorable trends, and identify the pivotal targets for safety initiatives.

However, the number of individuals seriously injured or killed by prescription drugs is unknown, not calculated by a recognized statistical method, but believed to be very large. Estimates based on hospital admission studies collected over many decades calculated that 100,000 persons die annually from the complications of prescription drugs and 1 million or more may be hospitalized.<sup>2</sup> By comparison, 44,572 persons died in 2006 in motor vehicle accidents, 18,029 from homicide and 560,102 from all forms of cancer.<sup>3</sup>

The core data for Quarter Watch are computer summaries of all adverse drug event reports submitted to the FDA through the MedWatch program, and by drug companies. The agency publishes for research use excerpts of the reports from which personal identifying information has been removed.

The drug adverse event reports submitted to the FDA and stored in the agency's Adverse Event Reporting System (AERS) constitute the nation's most important tool for monitoring the safety of drugs after approval. The system contains about 4 million reports submitted to the agency since 1968 and is one of the largest and richest drug adverse event databases in the world.

The drug monitoring system, however, has some unique properties with important strengths and weaknesses. For consumers and health professionals, submission of reports is voluntary. Drug manufacturers must investigate and forward to the FDA a report about every serious adverse drug event of which the company becomes aware. But a company does not have to act unless informed of a potential adverse event by an employee, consumer or health professional. For many other types of accidents, whether auto or on-the-job, reporting is routine and systematic.

One strength of the current adverse event reporting system is its sensitivity; with tens of millions of persons able to observe a potential adverse effect of a drug the chances

are great of finding adverse effects that may have been overlooked or underestimated in testing of the drug for FDA approval. In drug testing only hundreds to a few thousand persons are exposed the drug, often for short periods of time. Individual reports may have compelling and convincing detail. For example a report may contain evidence that a medical problem started soon after drug treatment began, stopped when the drug was halted, and then returned when the drug was administered again. In addition, as the numbers of similar events increase, the weight of sheer numbers reduces the chances of a faulty signal or false alarm.

The data have two key limitations. First, the submission of a report does not prove that the drug caused the adverse event at issue, only that an observer suspected a connection. In addition, an individual report may include details that would lead a reasonable observer to doubt a connection between the drug and the event—or identify another factor that could possibly have caused it.

The second key limitation is that with a voluntary system, only a fraction of those events that occur are ever reported. But what share of serious adverse events ever are reported is poorly studied and may vary over time, between drugs, or for different types of adverse events. Numerous published scientific reports include a statement that no more than 10% and in some cases as little as 1-2% of events occurring are reported to the FDA.<sup>4-5</sup> However, the scientific basis for this oft-repeated assumption is not clear.

Because only a fraction of adverse events are ever reported to the FDA and because there is no system available that captures all of the adverse events that have occurred, we do not know the true number of persons who have experienced harm. We also do not the true number persons who take a particular drug and therefore it is impossible to calculate the risk of an adverse drug reaction in the general population from these data.

In addition, the nation's main system for postmarket surveillance detects some kinds of adverse drug events better than others. It performs best in detecting adverse events that appear relatively soon after treatment begins, and distinctive medical conditions that are rare unless drugs or some other toxin is involved. Examples include liver failure—destruction of so much liver tissue that survival is threatened—and severe skin reactions that indicate a runaway allergic response of the immune system. This system is least effective for events that are common in that patient population—such as heart attacks among patients at risk for coronary heart disease. Reporting can also be increased by public warnings about a newly discovered risk, and may be very low for new types of injury where a link to the drug was not previously suspected.

The number of adverse event reports cited in Quarter Watch for any specific drug is a product of three independent factors: 1) How widely the drug is used; 2) how frequently the adverse effect occurs, and 3) what fraction of events get reported. Nevertheless, the case totals provide a reasonable index of which drugs are accounting for unusually large (or very small) numbers of serious injuries and deaths. We believe, for example, that when

varenicline accounted for more reported injuries than any other drug in medical use, this was in itself a signal of a problem requiring additional investigation. Also, 100 deaths attributed to one drug in one calendar quarter is a noteworthy toll, even without adjustment for under reporting. In the United States, 100 deaths is larger than the toll of almost any hurricane, flood, expressway pileup and would exceed the average annual deaths from aircraft crashes. Put another way, the 4824 deaths reported in the first quarter of 2008 would exceed the total number of homicide victims in the same period, except that it is highly unlikely that all the drug-related deaths were reported.

We describe Quarter Watch as a pilot program because the methodology, data analysis, report content and format are evolving. Quarterly assessments have not previously been published for these or similar drug safety data.

## **Quarter Watch Methodology**

Once each calendar quarter the FDA releases computer data files containing excerpts of every drug adverse event report it has received during that period. From this mass of reports we extracted only those new reports that met the following criteria: The event occurred in the United States, described a serious adverse event or death, and were not part of a scientific study, which has different reporting requirements. We also exclude reports where the principal suspect was not a drug (a vaccine, device etc) or could not be clearly identified. Drug names were standardized as ingredient names using a system modeled on the RxNorm project from the National Library of Medicine<sup>6</sup> and include both over the counter and prescription drugs. The outcome, or severity of injury, is assigned to one of three mutually exclusive categories in this order of priority: death, disability or birth defect, and serious. The FDA defines a serious injury as one that involved hospitalization (initial or prolonged), required intervention to prevent harm, was life threatening or had other serious medical consequences.<sup>7</sup> Although many reports identify several drugs as being taken, this analysis focused only on the drug identified as the principal suspect.

In the FDA computer files, the narrative of the adverse event is replaced by a series of standardized medical terms that are assigned by the agency or the manufacturer using a special dictionary, MedDRA or Medical Dictionary for Regulatory Activities, which was developed by the pharmaceutical industry.<sup>8</sup> In this report references to types of adverse events refer to these MedDRA terms. Medication errors were identified using a standardized MedDRA umbrella term. This industry definition of medication error includes several types of intentional overdoses, such as suicide and attempted suicide, which ISMP does not regard as medication errors in its other work.

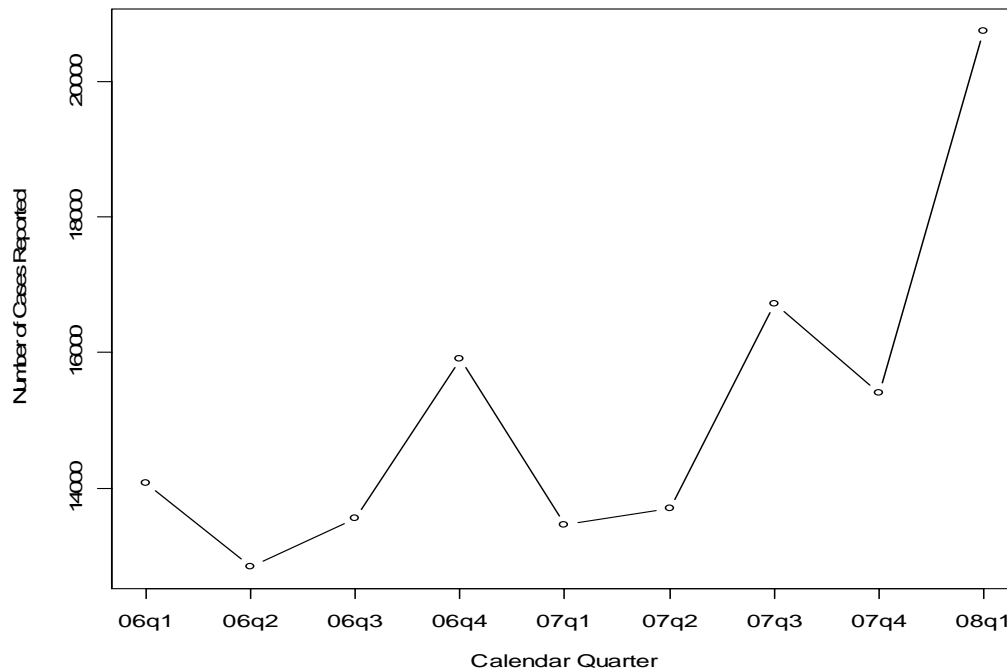
This dictionary includes additional tools for identifying types of reactions such as “suicide/self injury” that might involve several different kinds of MedDRA terms. These tools are called Standardized MedDRA Queries (SMQs) and are intended to identify

potential cases in broader categories.<sup>9</sup>

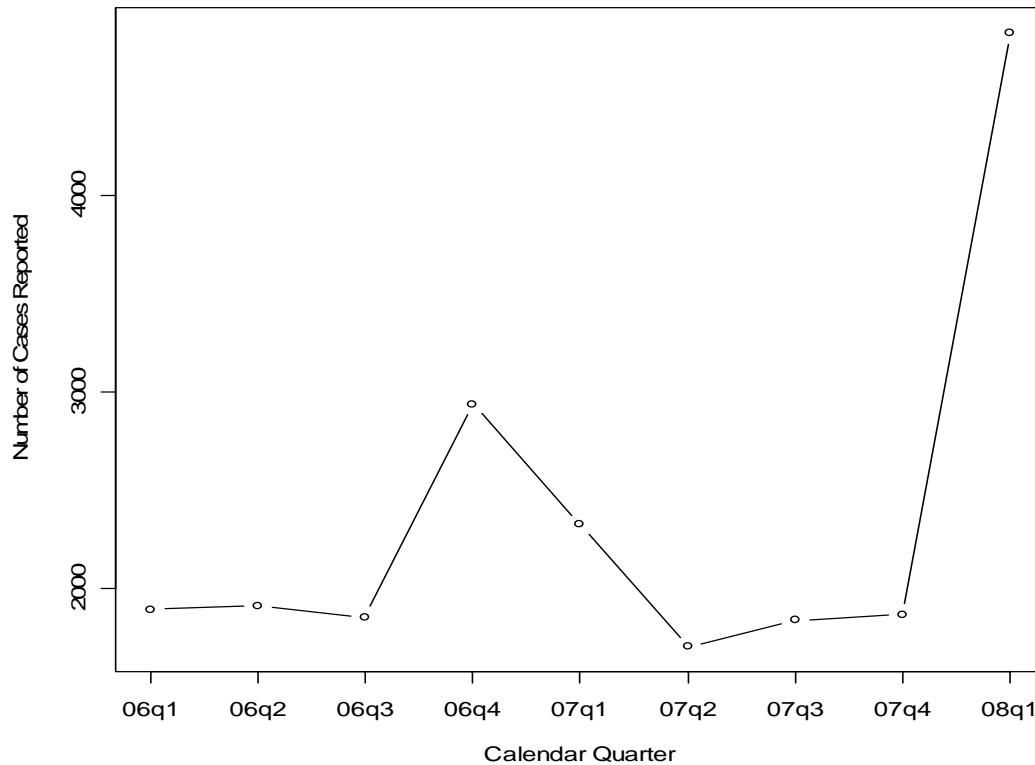
## Results

In the first quarter of 2008, the FDA received a total of 104,283 adverse event reports from all sources. After excluding foreign reports, events that did not indicate serious injury and cases from studies, Quarter Watch identified 20,745 reports of serious injury from drug therapy, a 34% increase from the 15,411 cases reported in the previous quarter, and a 38% increase when compared to the average over the previous four quarters. The longer term trend in reported serious events is shown in Figure 1. The most notable observed change occurred in deaths. In the first quarter of 2008 the FDA received reports of 4824 deaths, a 2.6 fold increase over the 1868 reported deaths in the previous quarter, and the highest number of patient deaths yet reported in a calendar quarter. Trends in reported deaths are shown as Figure 2. The figures also illustrate variability from quarter to quarter as well as portraying a more gradual upward trend over the previous eight quarters.

**Figure 1. Serious Injuries Reported to FDA by Calendar Quarter**



**Figure 2. Deaths Reported to FDA by Calendar Quarter**



### **Medication Errors**

Serious injury and deaths that involved possible medication errors accounted for 1464 new cases, or 7% of all reported injuries. The medication error total was higher than previous quarters but has been surpassed frequently since January 2004.

### **Where Reports Originate**

The FDA continues to receive a relatively small number of reports of serious directly from health professionals or consumers. Reports submitted directly to FDA's through the agency's MedWatch reporting program accounted for 3716 cases or 18% of the total for the first quarter of 2008. As in previous quarters, drug manufacturers prepare and submit most reports; in the first quarter manufacturers accounted for 17,029 (82%) of all reports meeting the Quarter Watch criteria.

## Results for Specific Drugs

The ten drugs accounting for the largest number of serious adverse events in the first quarter of 2008 are shown in rank order in Table 1.

**Table 1. Drugs Associated with Serious Injury Reports in 2008 Q1**

Drug Name	Cases	Rank
VARENICLINE	1001	1
HEPARIN	779	2
FENTANYL	631	3
INTERFERON BETA	582	4
INFLIXIMAB	463	5
ETANERCEPT	401	6
CLOPIDOGREL	297	7
PREGABALIN	280	8
ACETAMINOPHEN	273	9
OXYCODONE	272	10

Varenicline and heparin, the two drugs accounting for the most cases of serious injury, are discussed in detail in separate sections. As in previous quarters, a relatively small number of drugs have a large volume of reports. Note that only varenicline accounted for more than 1000 reports; only three other drugs had more than 500 reports. At the other end of the spectrum there are small numbers of reports for most drugs. In the first quarter of 2008 the FDA received reports involving 773 different drugs. But one-quarter of these drugs accounted for two or fewer reports. The typical drug (as measured by the median or middle value) accounted for six reports.

## Reported Drug Deaths

The 10 drugs that accounted for the highest numbers of reported deaths in the first quarter of 2008 are shown in Table 2.

**Table 2. Drugs Associated with Reported Deaths in 2008 Q1**

Drug Name	Cases	Rank
OXYCODONE	185	1
ALPRAZOLAM	163	2
ACETAMINOPHEN	160	3
ACETAMINOPHEN; BUTALBITAL; CAFFEINE	156	4
FENTANYL	131	5
MORPHINE	115	6
IBUPROFEN	114	7
METHADONE	111	8
ACETAMINOPHEN; HYDROCODONE	111	9
HEPARIN	102	10

Drugs associated with reports of death were a special focus for this quarter because of the 2.6 fold increase from the previous quarter. In addition deaths historically accounted for approximately 16 percent of reported injuries. In the current quarter deaths accounted for 23% of all cases. However, once again a large majority of drugs were associated with few or no reported deaths. Among 773 drugs with serious events reported in the first quarter, 58% had no deaths or a single death reported.

The notable change for the first quarter of 2008 was in the number of drugs accounting for 100 or more deaths. In the previous two years only 1-3 drugs accounted for 100 or more deaths. In the first quarter of 2008, all 10 highest ranking drugs accounted for 100 or more deaths. Also, note that acetaminophen (160 reported deaths) and ibuprofen (114 reported deaths) are two of the most widely used drugs in the nation with well-characterized safety profiles and tens of millions of patients. Nevertheless, an overdose of acetaminophen can result in irreversible, fatal injury to the liver, and is often implicated in intentional overdose reports. Ibuprofen, like other non-steroidal anti-inflammatory drugs (NSAIDS), carries warnings that sustained use can result in serious gastrointestinal side effects and some may increase the risk of heart attack. Another focus of Quarter Watch is to identify and investigate why drugs are accounting for large numbers of reported deaths for the first time. Heparin, as noted, was involved in a product contamination problem. Another new entrant was the combination drug (acetaminophen; butalbital; caffeine) best known as Fioricet and used to treat migraine headaches. Fioricet suddenly accounted for 156 deaths, compared to zero to one in previous quarters. The Fioricet results are also discussed separately below.

## **Specific Types of Adverse Effects**

Classifying the specific medical problem for which a drug was suspected is an emerging science. The pharmaceutical industry has devised a set of Standardized MedDRA Queries (SMQs) intended to identify cases in clinical trials and adverse drug event reports.<sup>9</sup> These criteria are intended to identify potential cases for additional review of clinical detail. While these tools have been tested for returning valid results, there is significant variation in how wide a net is cast in the search for potential adverse event cases. Several SMQs, however, appear to be specific enough to return results of scientific interest. Three examples are shown in Table 3.

**Table 3 Selected Reactions in 2008 Q1\***

SMQ/Drug	Cases
<b>Angioedema</b>	
Heparin	103
Pregabalin	58
Varenicline	52
<b>Suicide/Self Injury</b>	
Varenicline	226
Oxycodone	89
Acetaminophen; hydrocodone	87
<b>Hemorrhage</b>	
Clopidogrel	170
Warfarin	161
Heparin	88

\*Standardized MedDRA Queries (SMQ) Broad Scope

## The Adverse Event Reporting System

The nation's adverse event reporting system is only as good as the quality and quantity of reports that flow into it. One focus of Quarter Watch is to monitor how well the system itself is working, and identify areas where reporting could be improved. We classified as "vague" any report that had only a single medical term coded to describe the event, implying an extremely brief narrative, and was also missing the patient's gender or age. Among serious injuries and deaths in the first quarter of 2008, 3205 (15%) were classified as vague. In the most recent quarter, 9695/20,745 cases (47%) lacked information about the age of the patient. The quality of some of these reports may improve over time as the drug companies further investigate cases with an initial report. In the current quarter, 36,861/104,283 reports (35%) were follow up reports adding detail to a case previously reported. Quarter Watch relies on the most recent report for any particular case.

In developing the Quarter Watch pilot program, we also identified a significant problem in the coding of adverse event reports. To distinguish the original report from follow up reports that may add additional detail, the FDA provides a code to distinguish "initial" reports from "follow up reports."<sup>10</sup> In the original design of Quarter Watch, we selected only initial reports to focus on newly reported events. In reviewing and refining the criteria for selecting new reports, we discovered instances of two or more "initial" reports for the same serious adverse event. The numbers were comparatively small, but did affect item counts. We have communicated our findings to the FDA and worked around

the problem by revised our criteria for selecting reports.

## Varenicline Update

Varenicline continued to provide a striking signal of safety issues that require investigation and action. In the first quarter of 2008 the FDA received 1001 case reports of serious injury in the United States in which varenicline was the principal suspect drug. For a second consecutive quarter varenicline accounted for more reported injuries than any other drug. (See Table 1.) This compared to 988 cases in our report of the previous quarter using a slightly different methodology.<sup>11</sup>

To take further measure of the strength of the safety signal for varenicline, we made additional comparisons between varenicline and other prescription drugs. First, we explored the possibility that the market success of varenicline might partly explain the volume of serious injuries reported because millions of people had been exposed to the drug. In the first quarter of 2008, varenicline accounted for more reports of serious injury than the 10 best selling brand name prescription drugs combined. Table 6 shows serious injury reports for the 10 most frequently prescribed brand name drugs that had no generic competitors.<sup>12</sup> Varenicline accounted for 1001 cases of serious injury or death compared to 837 cases for the 10 top brand name drugs combined, and 3.5 fold more than its closest individual drug, clopidogrel, with 288 cases.

**Table 4. Reported Serious Adverse Events for the Most Frequently Prescribed Brand Name Drugs in 2008 Q1**

Brand Name	Rank	Generic Name	Cases
LIPITOR	1	ATORVASTATIN	188
LEXAPRO	2	ESCITALOPRAM OXALATE	39
SINGULAIR	3	MONTELUKAST	89
NEXIUM	4	ESOMEPRAZOLE	30
PLAVIX	5	CLOPIDOGREL	288
VYTORIN	6	EZETIMIBE; SIMVASTATIN	79
ZYRTEC	6	CETIRIZINE	18
PREVACID	8	LANSOPRAZOLE	4
DIOVAN	9	VALSARTAN	34
ZETIA	10	EZETIMIBE	68
Total			837

We also compared the reports for varenicline with two other pharmaceutical treatments for smoking cessation. We found 17 reports of serious injury in the first quarter of 2008 for all pharmaceutical products containing nicotine—such as chewing gum and transdermal patches. We found no reports in that period for Zyban, the brand name and dosage form under which the antidepressant drug bupropion is sold for smoking cessation. However, we identified 44 reports of injuries for bupropion that did not specify the brand name or indication, and therefore might have been prescribed for smoking cessation.

In May ISMP issued a special report on varenicline describing a strong safety signal seen in the adverse event data.<sup>1</sup> It should be noted that the 2008 first quarter data had already been submitted to the FDA at the time of the ISMP report, but had not yet been released for research use. At the same time the FDA also issued a Public Health Advisory on Chantix warning of serious psychiatric side effects including changes in behavior, attempted and completed suicides.<sup>13</sup> It also required a mandatory Medication Guide to warn patients of these risks.<sup>14</sup>

The ISMP report identified signals of additional kinds of side effects, notably serious accidental injuries, and recommended that the FDA and the manufacturer, Pfizer, investigate this and other signals. Other possible risks that required investigation to confirm included diabetes, potentially life-threatening interruption of the heart rhythm, heart attacks, strokes, and moderate and severe allergic reactions.

ISMP's concern about the risk of accidents was confirmed in serious adverse events reported in the first quarter data for 2008. These included 15 cases with MedDRA standardized medical terms indicating road traffic accidents. These new traffic accident cases included medical terms describing a spectrum of possible effects of varenicline that might have been responsible, such as seizure, disturbance of vision, panic attack and impaired judgment. The 2008 reports also included 52 additional cases with MedDRA terms indicating various kinds of blackouts or loss of consciousness, which have high potential for accidents. Some reported blackouts implied a sudden disruption of the heart rhythm while others appeared to be associated with psychiatric symptoms.

Three U.S. government departments have addressed ISMP's most immediate safety concern, the risk of accidents by individuals operating aircraft or vehicles and in other occupations where a lapse in alertness or motor control could lead to massive injury. The Federal Aviation Administration has banned the use of Chantix by airline pilots,<sup>15</sup> the Department of Transportation has limited its use among truck drivers,<sup>16</sup> and the Department of Defense has prohibited its use by aircraft and missile crews.<sup>17</sup>

In the same period, the FDA used its new legal powers to require Pfizer to take two additional safety actions.<sup>18</sup> Using new legal authority granted by Congress in September 2007, the FDA required Pfizer not only to issue a stronger warning about psychiatric side effects, but also to survey consumers to ensure the warning was being received and understood. In addition, the FDA required Pfizer to conduct a new clinical study of psychiatric side effects. Previously, the FDA had no legal authority to require new clinical studies after approval, nor could it require companies to study how effectively consumers and doctors received and understood safety warnings. This is one of the first known uses of the FDA's new legal authority.

The varenicline reports for the first quarter of 2008 may have been affected by the increasing amount of publicity the drug received regarding psychiatric adverse events. In

February of 2008 the FDA issued a press release and Public Health Advisory declaring “it is increasingly likely that there may be an association between Chantix and serious neuropsychiatric symptoms.” The previous November the agency had indicated that it was investigating such reports, following media attention to the September 2007 death of a musician who was shot to death after screaming and pounding on the door of his girlfriend’s neighbor. The musician had consumed substantial amounts of alcohol and was taking Chantix.<sup>19</sup> We believe that the publicity may have stimulated additional reports for varenicline as more doctors and patients learned about the potential link between the drug and psychiatric side effects. However, the number of injuries associated with varenicline remains very large and many reported injuries concerned other risks of the drug such as accidents, seizures and moderate and severe allergic reactions.

## **Heparin Cases**

In the first quarter of 2008 the number of reported serious injuries identifying heparin as the principal suspect drug increased 19 fold from the previous quarter, rising from 42 cases to 779 cases. Heparin is a drug most often administered intravenously or by injection to prevent or dissolve blood clots and is widely used in connection with surgery and kidney dialysis. In the previous two years the number of reported serious injuries associated with heparin treatment fluctuated between 22 and 80 cases per quarter. The number of reported deaths grew from 4 in the fourth quarter of 2007 to 102 in the first quarter of 2008. The number of reported deaths in which heparin was a principal suspect fluctuated between 2 and 18 cases per quarter in the previous two years.

The crisis involving heparin began in early January 2008 when the FDA learned about potentially life-threatening allergic and hypersensitivity reactions which involved nausea, vomiting, and a sudden drop in blood pressure. The events were initially traced to products of the Baxter Healthcare Corporation—which first detected a problem and had already begun to recall some lots of its heparin products.<sup>21</sup> The adverse events were ultimately traced to a contaminant, oversulfated chondroitin sulfate, introduced into heparin by a supplier in China that provided the drug to Baxter and several other pharmaceutical companies. The suspect compound was so similar to heparin that it was not detected in standard quality assurance testing.

The FDA’s own update which included more recent data than available to Quarter Watch cited a total of 238 deaths of which the agency identified 149 cases with symptoms that might link it to allergic reaction. Baxter Healthcare said the report character and volume were similar to what it had observed. The company also said it had analyzed numerous case reports and found that many were too vague to assess whether contamination had been involved while others contained details suggesting contamination was unlikely to have contributed to the reported event. Contamination is not the only source of adverse events associated with heparin treatment. Most notable is increased risks of hemorrhage or bleeding, a result of heparin’s effect in boosting the body’s ability to

dissolve blood clots.

Baxter has recalled all of heparin products packaged in vials and has not their resumed manufacture.<sup>20</sup> The case of heparin contamination dramatizes the importance of an element of the safety net that normally receives little attention. One element of FDA regulation of drugs involves elaborate chemical reviews and inspections to ensure the drug molecule is stable and produced in consistent concentrations or strength. The heparin disaster, according to later reviews, occurred because the contaminant was not detected by normal purity testing, and because the foreign facility in China where the key ingredient was manufactured did not undergo full FDA inspections.<sup>21</sup>

## **Acetaminophen/butalbital/caffeine**

One Quarter Watch technique is to use statistical tools to identify new signals appearing for the first time in a new calendar quarter. In the first quarter of 2008 a combination drug product acetaminophen/butalbital/caffeine (Fioricet) crossed a warning threshold for exceeding five deaths in one quarter for the first time. In fact, the product accounted for 156 deaths reported in a single quarter and was ranked fourth in deaths among all prescription drug products, an additional signal of a possible safety concern. (Table 2)

Further analysis of these reports revealed that they all had been submitted by one manufacturer—Watson Pharmaceuticals—on the same date in February and cited the same event date in January 2006. We contacted Watson and learned that the reports were submitted in compliance with an FDA requirement to survey the medical literature for case reports appearing in scientific journals. In December of 2007, the American Association of Poison Control Centers' published an annual report that included a tally of 1229 fatalities resulting from accidental exposure to pharmaceutical products.<sup>22</sup> A large majority of these cases involved suspected suicides and some identified illegal drugs as principal suspect.

However, a review of the poison control centers' report disclosed only four cases of a verified death attributed to acetaminophen/butalbital/caffeine combination product. We shared this analysis with Watson Pharmaceuticals and requested that the company review the remaining 152 death cases. The company indicated that it had submitted a report for any fatality case in the poison control centers report containing acetaminophen, alone or in combination with any other drug, on grounds that it might possibly have been the company's product. We believe this was a mistake, given that the poison control centers had already conducted an independent review of each fatality case reported. We recommend that Watson work with the FDA to improve the accuracy of future adverse event reporting based on this source.

We conclude the 154 Fioricet cases that only identified the common ingredient of acetaminophen are an instance of over reporting. As noted earlier, a voluntary system normally results significant *underreporting*. The Fioricet reports are a rare instance of

overreporting.

We believe that systematic inquiry into new signals is beneficial even if (as in this case) it does not uncover evidence of a new risk to patient safety. Identifying and eliminating abnormal reporting should improve the quality of the overall postmarket surveillance system over time.

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