ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

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## LEADING DRUG SAFETY ISSUES OF 2012

Anticoagulants leading drug safety problem reported directly to FDA
Three anti-TNF agents dominate manufacturer reports of new, serious injuries
Fentanyl patches (DURAGESIC) prominent in product problems and medication errors
Lower limb fractures when taking alendronate (FOSAMAX) a major reported adverse event

# Executive Summary

In this report we examine the leading drug safety problems reported to the US Food and Drug Administration (FDA) for the calendar year 2012. Our ranking of the year's major issues in drug safety comes from four different perspectives on tens of thousands of serious and fatal adverse drug events.

(1) Reports that consumers and health professionals submitted directly to the FDA identified two anticoagulants, dabigatran (PRADAXA) and warfarin (COUMADIN), as the most frequent suspect drugs for the year.
(2) Cases from drug manufacturers about new, serious adverse events without adequate current warnings in the prescribing information flagged three anti-tumor necrosis factor (anti-TNF) products, etanercept (ENBREL), adalimumab (HUMIRA), and infliximab (REMICADE).
(3) The potent synthetic opioid fentanyl (DURAGESIC) in patch form was prominent in two different kinds of drug safety issues, product quality complaints and reported medication errors.
(4) Lower limb fractures and other bone disorders associated with alendronate (FOSAMAX) for osteoporosis were key results from our statistical tests to link suspect drugs with specific side effects.

In 2012, the FDA received a total of 210,648 domestic reports of serious, disabling, or fatal adverse events associated with therapeutic drugs, an increase of 16% from the previous year. Reports that consumers and health professionals made directly to the FDA declined from 21,000 to 20,310 (-3.3%) while reports originated by manufacturers increased by 18.5%, from 160,598 to 190,338.

The most striking change was a 47.8% increase in reported patient deaths, which grew from 30,725 in 2011 to 45,421 in 2012. For comparison, the reported total of 45,421 deaths compares to approximately 16,000 homicides annually, 35,000 deaths attributed to motor vehicle accidents, and 575,000 deaths from cancer.

We investigated the increase in reported patient deaths and identified a factor largely unrelated to patient safety, but indicating a substantial problem in how patient deaths are required to be reported to the FDA by drug manufacturers. The underlying reason for much of the increase was a large group of patient deaths associated with three drugs for typically fatal metastatic cancers, cases in which a drug role was either not suspected or investigated. Additional details appear below and in the full report.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all domestic, serious adverse drug events reported to the FDA. We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

Although QuarterWatch examines annual trends once a year, the normal focus is on newly-released quarterly data. For the 4th quarter of 2012, the FDA received 49,402 new domestic reports meeting the QuarterWatch criteria, an increase of 1% over the previous quarter and 11.9% over the same quarter in the previous year. The new quarter results were dominated by the increase in patient deaths that we analyzed as part of the annual results.

# The Leading Safety Problems in 2012

Achieving safer use of medication is an objective with many dimensions. It requires adequate clinical testing so the safest useful dose can be set and drug risks identified. Some patients are especially vulnerable because of disease, immune system overreaction, or because of their genetic limitations for processing some drug molecules. Product problems arise from contamination, wrong amount of active drug, quality problems with transdermal patches, inadequate dissolution, or extraneous matter. Medication errors may occur in the physician's office, hospital, pharmacy or among patients at home. In this issue, QuarterWatch seeks to capture different dimensions of drug safety through the prism of the cases that get reported to the FDA. Other approaches will be expected to provide different results. However, the major issues identified in this report all warrant greater attention at the FDA, and among physicians and patients.

## Perspective: Direct Reports to the FDA

Only about 10% of serious and fatal adverse events are reported directly to the FDA through its 800-number or online web site. (The rest are submitted by drug manufacturers based on information the companies obtain from health professionals and consumers.) We regard these direct reports as important indicators of nation-wide safety problems because they are not influenced by factors that can expand manufacturer reporting (such as marketing activities) or suppress it (hard to identify and locate generic drug manufacturers). The limitation of FDA direct reports is that the number of voluntary reports is small in comparison to the incidence of adverse drug events. In all of 2012 the FDA received only 20,310 direct reports, a number dwarfed by a risk that results in more than a million hospitalizations and more than 100,000 deaths annually. Nevertheless, Table 1 identifies five drugs with safety issues being most often directly reported to the FDA during 2012.

**Table 1. Most frequent drugs in direct reports to FDA, 2012**

| Rank | Drug name | Brand name* | Cases | Prominent side effect |
|---|---|---|---|---|
| 1 | DABIGATRAN | PRADAXA | 683 | Hemorrhage |
| 2 | WARFARIN | COUMADIN | 492 | Hemorrhage |
| 3 | LISINOPRIL | PRINIVIL | 378 | Angioedema & hives |
| 4 | LEVOFLOXACIN | LEVAQUIN | 330 | Tendon/joint disorders |
| 5 | DULOXETINE | CYMBALTA | 302 | Withdrawal syndrome |

*Most frequently cited brand name

For a second straight year dabigatran and warfarin are the most frequently named suspect drugs in direct reports to the FDA. (A third anticoagulant, rivaroxaban (XARELTO), ranked tenth.) * QuarterWatch has reported on the risks of anticoagulants previously and judged them to be one of the most dangerous of all outpatient drug treatments. The same property that allows anticoagulants to reduce the risk of strokes and blood clots elsewhere in the body leads to high risks for hemorrhage and other bleeding. The result is tens of thousands of emergency room visits or hospitalizations each year. It is also of concern that two years after a large volume of reports of hemorrhages began, the FDA has discounted the adverse event data and focused narrowly on the question of whether dabigatran has higher risks than warfarin. We examine the adverse consequences of anticoagulation treatment and FDA actions in greater detail in the full report.

The other drugs in Table 1 also merit additional action to reduce patient injury. Lisinopril is the most widely prescribed drug for high blood pressure, according to data from IMS Health, with more than 83 million outpatient prescriptions dispensed in 2012. In some patients, however, the drug may cause angioedema, especially swelling of the face, tongue, lips or the airway. The fluoroquinolone antibiotic levofloxacin (LEVAQUIN) is associated with tendon ruptures and other connective tissue disorders. QuarterWatch has previously described withdrawal symptoms reported among patients trying to stop duloxetine (CYMBALTA), noting that in longer term trials, 50% of patients experienced adverse effects when stopping the drug.

## Perspective: Manufacturer Reports of New, Serious Side Effects

In theory at least, a key role of the adverse event reporting system is to uncover new, serious side effects that may not have been observed or fully understood in the clinical testing prior to approval. When a drug manufacturer hears about a serious adverse event for which adequate warnings may not exist, the company is required to submit an expedited report to the FDA within 15 days. (Other adverse event reports can be submitted quarterly or annually.) Thus, manufacturer expedited reports comprise an important indicator about what drugs are most often implicated when new side effects are discovered that may require stronger warnings, restrictions, or other risk management activities.

The first, second and third ranked drugs were similar biological products called anti-TNF agents approved for uses that include rheumatoid arthritis, Crohn's disease, and psoriasis. Adalimumab (HUMIRA) ranked first with 2,962 expedited reports, etanercept (ENBREL) second with 2,958 cases, and infliximab (REMICADE) accounted for 2,623 cases. Taken together, and including other types of reports in addition to expedited cases, the three anti-TNF products accounted for 11,215 serious adverse events, including 3,324 infection cases, 342 reported skin cancers, and 119 cases of nerve fiber demyelination.

## Perspective: Product Problems and Medication Errors

Safety issues may arise for two reasons largely unrelated to the side effects of a drug. The drug may be contaminated, be over strength, under strength, or have other manufacturing defects. Medication errors may occur at any phase of the process that begins with the prescribing physician and ends with administration of the drug.

Fentanyl (DURAGESIC), a synthetic opioid that is 80 to 100 times more potent than morphine, has substantial risks independent of product problems or medication errors in prescription, dispensing or use. It contains strong warnings and restrictions because of its potential for addiction and abuse. It can produce a fatal overdose in patients who have not already become tolerant to opioids, and interacts with numerous drugs. The most widely used form of fentanyl is administered through a transdermal patch. This route of

* No reports were seen for a fourth anticoagulant, apixaban (ELIQUIS), because it was not approved until December 2012

administration adds an additional potential for injury because a lot can go wrong with a potent opioid in a small square patch.

In 2012 fentanyl was the suspect drug in 1,148 reports of serious injury associated with medication errors. Among the specific problems reported were omitting a drug dose (perhaps triggering withdrawal), putting the patch on the wrong site (absorption varies at different body sites), leaving the patch on too long, and accidental exposure to the patch by children, caregivers or others.

In addition, fentanyl was identified in 802 cases of serious injury associated with product problems (sometimes in combination with a medication error). The specific product problems were only vaguely characterized in these reports including “product quality issue”, “poor quality drug administered,” and “product adhesion issue.”

## Perspective: Linking Drugs to Specific Side Effects

We use statistical tools to search for links between drugs and specific side effects. Our approach permits identifying cases where the side effect reports were not necessarily so numerous but strongly related to particular drugs, and provides additional checks to flag associations that may have occurred purely by chance.

One result for the year 2012 was the strong association between the osteoporosis drug alendronate (FOSAMAX) and 1,327 reports of bone and joint injuries, including femur fractures and osteonecrosis of the jaw. Bone and joint injuries were reported 186 times more frequently than would be expected given the total number of reports for this drug, and the chances of a spurious association approached zero. This was one of the strongest drug-adverse event relationships observed in 2012.

Interpreting this signal requires caution because of no certain answers to a key question: Does this osteoporosis drug increase bone density, but over the long term render the femur and other bones more vulnerable to atypical fractures that may heal slowly? In addition, fractures are expected in an older population with osteoporosis.

The FDA considered duration of treatment in 2010 and concluded that the benefits versus risks after 3-5 years of treatment were unknown. It required a warning stating “Optimal duration of use has not been determined” and adding, “Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use.”

The 1,327 cases reported in 2012 cannot resolve the question of whether long-term use of alendronate is beneficial overall, or harmful. It does provide a signal highlighting a key weakness in the system that allows millions of people to be exposed to long-term drug treatment where long term risks and benefits have not been determined.

## Problems in the FDA Adverse Event Reporting System

The FDA describes the adverse event reporting system (FAERS) as the cornerstone of postmarket surveillance of approved drugs. Our earlier study showed these data account for a majority of new warnings, restrictions, and other safety actions. Because of this key role, one QuarterWatch objective is to identify weaknesses and outline positive steps to improve this drug safety system.

In 2012, FDA policy and regulation caused the FAERS system to receive thousands of patient death reports from manufacturers in which a drug role was either not suspected, not investigated, or both. The most striking examples are the 2012 results for three cancer treatments.

Last year Roche reported 15,192 patient deaths associated with three drugs for locally advanced or metastatic cancers, erlotinib (TARCEVA), bevacizumab (AVASTIN), and capecitabine (XELODA). Just these three drugs accounted for 33% of the 45,421 reported deaths among 713 monitored drugs. In addition,

12,028 of these death cases, or 79%, were uninformative because they contained just the event term "Death," which is an expected outcome in advanced or metastatic cancers. The company told us patient deaths came from newly discovered records in a patient assistance program in operation for years that indicated that the cancer patients had died.

The problem originates in an FDA regulation that defines a patient death as an adverse drug event that has to be reported. Companies with extensive patient contact for marketing or other purposes will therefore learn of patient deaths. Under current policy and procedures, these deaths are frequently reported without information whether the drug was suspected of having contributed to the death.

The drug safety costs of this regulatory breakdown are substantial. The only national system we know of that provides surveillance of patient deaths associated with drug therapy is being contaminated by thousands of reports in which a drug role was not necessarily suspected. The magnitude of the problem is large. In 2012, 47% of all reported patient deaths were uninformative reports containing the single event term "Death."

## About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The FDA's adverse event reporting data combine reports originated by drug manufacturers with cases submitted directly by consumers and health professionals through the agency's MedWatch program. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. However, given numerous reports with credible detail, adverse event data may have important scientific weight in a broader assessment of causality. A majority of new warnings, restrictions, or other major actions to manage the risks of drugs are based on these data. The reporting rate for FAERS is unknown, and published estimates in specific cases range from around 1% to 15%, and up to 30% in unusual cases of enhanced reporting. We use the term *signal* to mean evidence that, in our judgment, is substantial enough to warrant publication but requires further investigation to determine the frequency of occurrence and to establish a causal relationship to the suspect drug. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement at the end of this report expands our description of this project and its staff.

## Conclusions

The 2012 adverse event report data show, in our judgment, that a major priority in drug safety should be to reduce the serious and fatal hemorrhages resulting from treatment with anticoagulant drugs, particularly in the older population with atrial fibrillation. We have previously identified several approaches to improve safety. For dabigatran, this includes reassessing the one-dose-fits-all strategy to prevent overdoses in vulnerable, older patients; more intensive monitoring of kidney function; and better information to alert physicians about managing the risks of an anticoagulant drug without an emergency antidote for serious bleeding. For warfarin, safety could be increased by better monitoring of anticoagulant effects, increased vigilance for warfarin's numerous drug interactions, and better patient selection. In the full report we also review FDA actions that have deemphasized the risks.

On the other hand, the FDA has launched an ambitious drug safety initiative to use its power to mandate risk management programs to educate physicians about safe use of long-acting opioid drugs, including the fentanyl patches highlighted in this report. This new use of FDA regulatory powers also contains provisions to assess its effects on safety. These results will inform not only this drug safety initiative but may help determine whether other safety initiatives should be designed using this model.

The signal linking alendronate to femur fractures highlights a fundamental flaw in the overall system by which drugs are tested and approved. To obtain new drugs more quickly and at lower cost, long term benefits and risks are seldom determined. In this case, 18 years after marketing approval, the optimum duration of treatment with alendronate is still unknown, and in some large patient subgroups a question remains whether benefits outweigh the risks.

The FDA should make it a priority to revise reporting requirements to improve the validity of patient death reports associated with drug therapy. Unintended consequences of its current regulations have substantially compromised the value of its safety surveillance of patient deaths.

Overall, we determined that that the 16% increase in serious, disabling, and fatal adverse events was primarily a reporting system problem rather than a signal of deterioration in patient safety. The perspectives on drug safety in this report identify specific problems and drugs that warrant attention to reduce the risk of injury from prescription drug therapy.


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## Contents

# Methods Summary

QuarterWatch seeks to improve patient safety through publishing the results of our regular monitoring and analysis of serious adverse drug events reported to the FDA. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source. [1]

Our publication examines domestic adverse drug events that are specifically coded as "serious," which means under FDA regulation events that resulted in death, permanent disability, a birth defect, involved hospitalization, were life threatening, required intervention to prevent harm, or had other medically serious consequences. [2] We exclude reports from foreign sources, cases from clinical studies, which have different reporting requirements, and events in which the injuries were not coded as serious. We standardize drug names to an ingredient name based on the National Library of Medicine RxNorm project [3] and do not distinguish between different routes of administration or dosage forms unless otherwise stated.

We focus on case reports received by the FDA for the first time in the calendar quarter or year under study. The actual events may have occurred earlier. When case reports are revised or updated we use the most recent version while retaining the original report date.

In these data, the adverse events that occur are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[4] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[5] We also group adverse event terms using MedDRA categories called High Level Terms (HLTs) and High Level Group Terms (HLGTs) that combine related but more specific medical terms. The QuarterWatch database was updated in November 2012 to MedDRA version 15.1.

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by IMS Health Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

> "The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2012 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities."

The QuarterWatch totals for the quarter include a category of drugs with special reporting requirements, restricted distribution, or active surveillance programs that either result in a much higher reporting rate or capture adverse events in which drug involvement is not necessarily suspected. These special category drugs are included in the total number of reports but are otherwise excluded from comparisons and rankings. In this report the term "regularly monitored drugs" means those remaining after the special reporting drugs have been excluded.

Reported totals for any calendar quarter, specific drug, or adverse event may change over time because thousands of reports are revised, entered into the FDA system late, or subject to changes in the QuarterWatch or FDA coding or report criteria. To compensate, all historical comparisons and trends over time are recalculated every quarter and may differ from previously reported totals. The term *signal* as used in QuarterWatch means evidence of sufficient weight to justify an alert to the public and the scientific community, and to warrant further investigation.

The QuarterWatch master database of all adverse event reports submitted to the FDA is maintained on a MySQL open source database (http://www.mysql.com/) and analyzed with the R Package for Statistical

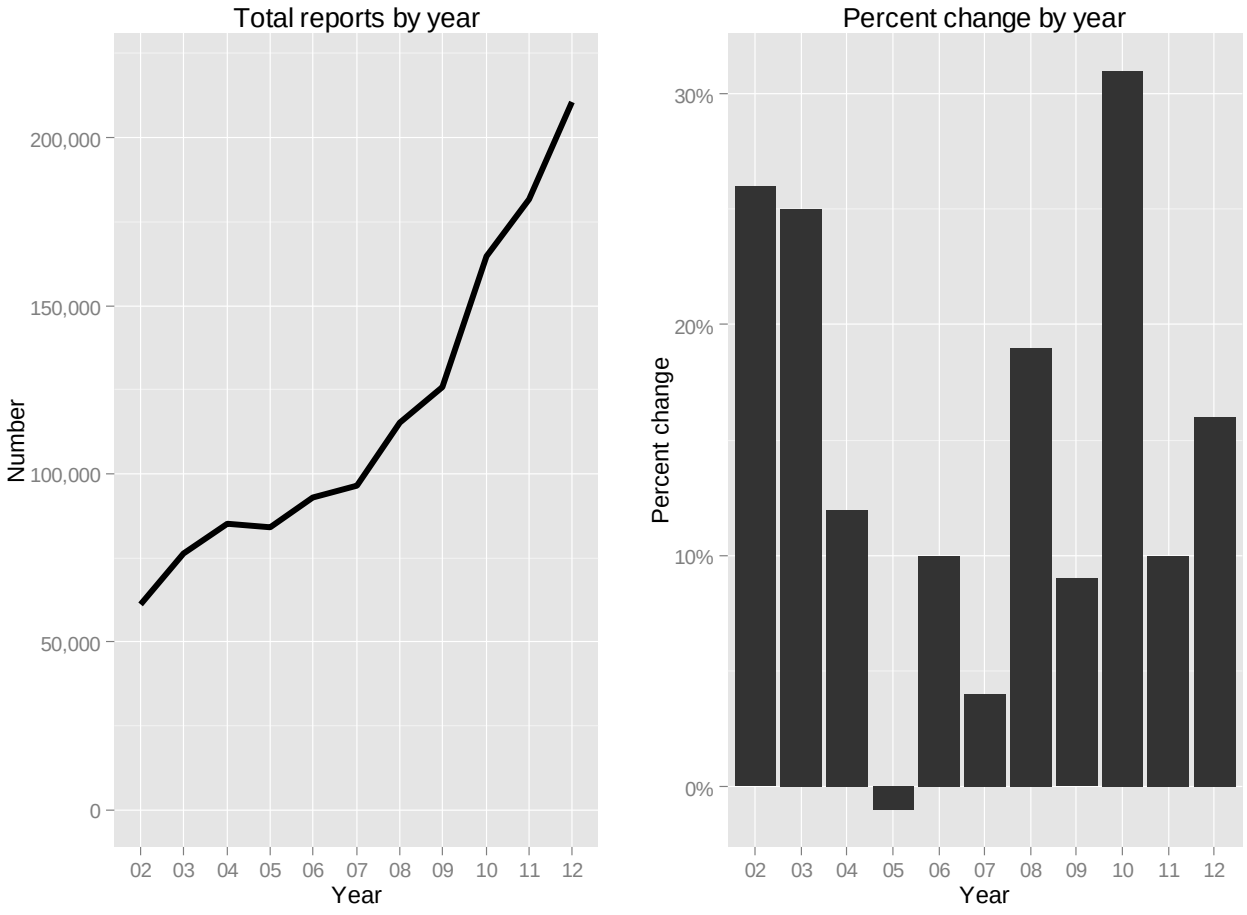
Computing (http://www.r-project.org/). A full technical description of our methodology can be found on the QuarterWatch web pages (http://www.ismp.org/quarterwatch/detailedmethods.aspx).

This is the first QuarterWatch report to utilize source data from the FDA's new computer and software system for collecting and monitoring all the adverse event reports that it receives. The agency calls the new system FAERS (or FDA Adverse Event Reporting System) to distinguish it from its predecessor AERS (or Adverse Event Reporting System). While the new data have a different format and somewhat different field definitions, it has not affected the basic QuarterWatch selection criteria. However, technical problems in the new data create new obstacles for others who wish to duplicate our results. An additional summary of changes appears on the QuarterWatch web page "Detailed Methods."

# Results

In 2012, the long-term trend continued in the steady and substantial rise in domestic serious, disabling, and fatal adverse drug events reported to the FDA. The total of 210,648 reports was a 16% increase from the 181,598 cases in the previous year. The 16% annual increase was similar to the long-term trend over the previous decade, which averaged 13.5%. The biggest jump in the decade came in 2010 with a 31% increase; in only one year, 2005, did report volume decrease, a drop of 1.3%. The annual percent changes and trend over time are shown in Figure 1.

**Figure 1. Total reports and percent change in serious, disabling and fatal reports by year**



These general trends do not immediately display two sub trends of note. FDA direct reports—an important risk index—have actually declined 17% from a peak of 24,724 in 2008 to 20,310 reports in 2012. A second trend is an increasing share of reports from consumers (rather than health professionals)—both from consumers who report side effects directly to the FDA or contact drug manufacturers, who then prepare the reports. Since 2002 the consumer share of all reports has doubled, increasing from 20% of all reports in 2002 to 43.8% in 2012.

### Upward Trend Examined

Our examination of the reasons for the 16% increase showed that the largest share of the change could be explained by a problem in adverse event *reporting* rather than a substantial new drug safety issue. The 2012 results were substantially increased by 15,192 reports of patient deaths submitted by Roche for three oncology drugs, erlotinib (TARCEVA), bevacizumab (AVASTIN), and capecitabine (XELODA). As reported in greater detail below, most of the case reports came from several years of direct contact with patients.

That said, new treatments did expand the totals; three drugs newly approved in 2011 accounted for 4,640 cases in their first full year on the market: the anticoagulant rivaroxaban (XARELTO) accounted for 2,081 new cases, telaprevir (INCIVEK), a new treatment for hepatitis C, was suspect in 1,926 cases, and vemurafenib (ZELBORAF), a drug for metastatic melanoma, accounted for 633 new cases.

## Perspective: Direct Reports to the FDA

In an important safety signal seen for a second straight year, the anticoagulants dabigatran (PRADAXA) and warfarin (COUMADIN) lead the ranking of direct reports to the FDA. A third anticoagulant, rivaroxaban (XARELTO), ranked tenth in direct reports. Furthermore, the FDA response over the past two years has been disappointing, and focused primarily on statements that dabigatran appears to be no more toxic than warfarin. When both manufacturer and direct reports are included, the three anticoagulants together accounted for 6,234 cases of serious injury, including 789 patient deaths. The report overview is shown in Table 2. The bleeding risks of anticoagulants are substantial and require additional actions to improve patient safety. A study of emergency hospitalizations in the elderly showed that 33% of admissions for adverse effect of all drugs were attributed to warfarin bleeds.[6] A clinical trial comparing dabigatran and to warfarin showed that bleeding had occurred in 34% of the patients, and life-threatening bleeds in 3.6%.[7] Results for rivaroxaban and warfarin were similar.[8] As in our previous analysis, [9] reported dabigatran adverse event cases were more likely to result in death, accounting for 18% of cases, compared to 6.5% deaths for warfarin and 7.2% for rivaroxaban.

**Table 2. Direct and manufacturer reports for 3 anticoagulants, 2012**

| | All cases | Deaths | Direct reports, percent | | Mfr reports, percent | |
|---|---|---|---|---|---|---|
| **Total (n = )** | 6234 | 789 | 1401 | (22) | 4833 | (78) |
| DABIGATRAN | 3292 | 582 | 683 | (21) | 2609 | (79) |
| WARFARIN | 861 | 56 | 492 | (57) | 369 | (43) |
| RIVAROXABAN | 2081 | 151 | 226 | (11) | 1855 | (89) |

### FDA Defends Dabigatran Decisions

The FDA actions since dabigatran was approved in 2010 have been almost entirely supportive of dabigatran and apparently intended to discount safety concerns. In April of 2011 the agency agreed to drop a mandatory Medication Guide required under a Risk Evaluation and Mitigation Strategy (REMS) plan.[9] In May 2012 the agency reversed itself and allowed a claim that dabigatran was superior to warfarin in preventing strokes in its one large trial.[10] In April 2013, the FDA required an unusual Boxed Warning—

normally an alert to a dire drug risk—stating that stopping the drug might increase the risk of stroke, but neglecting to mention that stopping dabigatran would also reduce the risk of severe hemorrhage.[11]

The agency took several additional actions to reassure doctors and patients that growing number of adverse event reports did not signal an important risk. In December 2011 the FDA announced it was beginning a review of dabigatran reports but added, "The FDA continues to believe Pradaxa provides an important health benefit." [12] The agency updated its review a year later, in November 2012, saying that a new study in insurance claims data and electronic health records indicated "bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin." [13] However, the drug safety communication announcement provided few details about the actual study, omitting major facts such as how many cases it had actually examined. The FDA's reassurance about dabigatran was further publicized in April of 2013 when the FDA Office Director who had initially approved dabigatran—Ellis F. Unger—wrote a "Perspective" article [14] in the *New England Journal of Medicine*, discounting the postmarketing reports, summarizing the unpublished study in electronic health records, and concluding, "We believe that dabigatran provides an important health benefit when used as directed." In this unusual editorial the FDA did not reveal how many adverse event reports it had received about dabigatran or warfarin, but nevertheless dismissed them, saying "the large number of reported cases of bleeding provides a salient example of stimulated reporting." However, the health insurance and medical record data on which the FDA had relied proved to be unusually sparse. The FDA study was conducted on data collected so soon after approval that the agency captured only 25 events in dabigatran patients with atrial fibrillation, and the results were not adjusted for age, sex, or clinical differences with the warfarin comparator. Pharmacoepidemiologist Jerry Avorn, MD of Harvard Medical School authored a rebuttal in *Circulation*, a heart journal, noting "the paucity of actual data made the analysis unsuitable for informing the care of patients…."[15]

## Later Developments

For dabigatran, both dispensed outpatient prescriptions and serious adverse event totals declined from 2011 to 2012. Data from IMS Health showed that dispensed prescription volume for dabigatran peaked at 715,740 prescriptions in the first quarter of 2012, but was 7.7% lower in the fourth quarter with 664,335 prescriptions. The 2012 total of 3,292 reported adverse event cases was 12.9% lower than the 2011 total of 3,781.

In September 2013, a dabigatran clinical trial in patients with recent mechanical heart values was stopped for safety reasons because of excess thromboembolic and bleeding events compared to patients receiving warfarin.[7] The FDA and the manufacturer added a contraindication saying the drug should not be used in patients with mechanical heart valve replacements.[16] That same month, however, the manufacturer, Boehringer Ingelheim, and its investigators published a retrospective study of major bleeding episodes that occurred in five company clinical trials, concluding that dabigatran bleeds did not have worse outcomes than warfarin, and were less severe by some measures. [17]

## Conclusions

Numerous steps can be taken to enhance the safety of anticoagulants. Unlike warfarin, neither dabigatran nor rivaroxaban have antidotes to rapidly reverse the anticoagulant effects of treatment. More and better information for clinicians is needed about how to manage hemorrhages that occur either as a side effect or as a result of accident or trauma. We have previously shown that dabigatran hemorrhage cases are reported in older patients (median age 80) and are more likely to have a fatal outcome. [18] These findings suggest that a lower dose and enhanced monitoring of kidney function would reduce hemorrhages in the older patient group. The FDA's many actions to discount mounting safety concerns about anticoagulant adverse effects remain unexplained.

# Perspective: Manufacturer Reports of New, Serious Side Effects

Some of the oldest and most successful biological products are genetically engineered monoclonal antibodies or fragments of antibodies that inhibit a critical component of the immune system, tumor necrosis factor (TNF). In 2012 three of these anti-TNF products—adalimumab (HUMIRA), etanercept (ENBREL), and infliximab (REMICADE) — dominated the rankings for an important category of reports, expedited reports from drug manufacturers. Expedited reports are the highest priority reports in the FDA system, must be filed in 15 day, and receive early review by the FDA staff in the Office of Surveillance and Epidemiology. Expedited reports describe new, serious adverse events for which warnings in the prescribing information may not be adequate. They are also the largest single overall category of all domestic serious reports, accounting for 157,715/210,648 or 75% of the 2012 total. Three similar drugs leading this category of adverse event reports is an important signal.

TNF is a chemical messenger that performs several different functions in the body. It has a role in the inflammatory process, assists in localized immune response to infection, and can trigger apoptosis or programmed cell death. [19] [20] When discovered nearly 40 years ago, the initial interest was in its capacity to kill tumor cells under certain circumstances, as its name suggests. While its use as a cancer treatment proved limited, an important family of biological products was developed to block the functions of TNF. Etanercept and infliximab were approved in 1998, and adalimumab in 2002. Since then the anti-TNF agents have been approved for a series of autoimmune and inflammation-related disorders, notably rheumatoid arthritis, psoriasis, ulcerative colitis, and Crohn's disease.

The standard that a drug's benefits must outweigh its risks nevertheless allows for the possibility that some drugs may, in fact, have substantial risks. These anti-TNF agents are prime examples of drugs with major risks, most linked directly to its mechanism of blocking normal actions of TNF. Because of TNF's role in infection, blocking it introduces an increased risk of viral, fungal, and bacterial infections. In the 2012 data the three agents were suspect in 3,324 cases of infections, accounting for 38.9% of all serious events for the drugs. TNF also has a role in limiting cancer cells, and blocking it raised fears of increased cancer risk. Although overall cancer rates are only modestly elevated in longer term studies,[21] [22] [23] the 2012 reports showed unexpectedly large numbers of skin cancers reported for all three drugs. All three were also implicated in reports of demyelination of nerve fibers—a disorder that also occurs in Multiple Sclerosis. The results are shown in Table 3.

**Table 3. Expedited and total serious reports for 3 anti-TNF agents**

| | Expedited | All reports | Skin cancers* | Infections** | Demyelination* |
|---|---|---|---|---|---|
| Adalimumab | 2962 | 4110 | 112 | 1288 | 49 |
| Etanercept | 2959 | 4107 | 120 | 1288 | 53 |
| Infliximab | 2623 | 2998 | 110 | 748 | 17 |
| Total | 8544 | 11215 | 342 | 3324 | 119 |

* Standardized MedDRA Query, broad scope. **System Organ Class (SOC)

These data for 2012 continue to emphasize that most drugs that suppress the immune system have substantial risks, and anti-TNF agents rank high in that group. Since approval of infliximab and etanercept in 1998, this class of drugs has accounted for disproportionate numbers of serious adverse event reports.[24] To produce a volume of expedited reports unequalled by other drugs requires a combination of three factors: extensive patient exposure, higher risks of serious side effects, and active manufacturer reporting.

# Perspective: Product Problems and Medication Errors

Administering medication in patches raises possible problems not seen with oral tablets and capsules. Patches can be applied in the wrong place, left on too long, or taken off too soon. Absorption in some body areas (for example the neck) is much greater than others. Heat—or even fever—can increase the uptake. Manufacturing problems might make the patch leak, not stick properly, or it could be difficult to remove the protective layer. Combine these issues with a highly potent opioid and the result is a major drug safety problem in the form of fentanyl (DURAGESIC), one of the most powerful painkillers available. In addition, fentanyl has the usual opioid risks unrelated to the transdermal route of administration, namely tolerance, addiction, overdose and abuse. In 2012 fentanyl was associated with 1,890 reported serious adverse events of which 1,148 (60.7%) indicated a medication error and 802 (42.4%) described product quality problems. Reports frequently involved both categories.

The product problems reflected in the computer excerpts of the FAERS reports were mostly vague. "Product quality issue" was the term in 724 cases and "poor quality drug administered" in 78 more cases. Problems with the patch adhesion accounted for 100 more reports.

Many of the medication errors were more specific. "Drug prescribing error" accounted for 48 cases, with the likely possibilities being not ensuring the patients were opioid tolerant, or selecting an inappropriate dose, which can range from 12 mcg/hour to100 mcg/hour or more. No clear dispensing errors could be identified in these reports, although dispensing the wrong dose package could have fatal consequences. At the patient level, the errors were more specific and numerous. Drug dose omission (130 reports) could lead to unpleasant withdrawal symptoms and loss of pain control. Putting the patch on an inappropriate site accounted for another 115 cases, and keeping the patch on for the wrong duration of time for another 40 cases. Given that the patch is applied for a three-day period, chances of it falling off or incorrect duration of use are increased. Of particular concern were 33 cases of accidental exposure, which can be fatal in children. In September 2013 the FDA reported it had learned of two more accidental exposure deaths in children in the past 18 months, both cases originating from ISMP's National Medication Error Reporting Program.

Another group of fentanyl reactions were those expected of a potent opioid: Withdrawal (158 cases), overdose (83 cases), cardio-respiratory arrest (32 cases), as well as classic opioid side effects, nausea (85 cases), and vomiting (68 cases).

## FDA Initiative Focuses on Prescribers, Abuse

The FDA included fentanyl patches and 11 other long-acting opioids in a major but novel program launched in July 2012 that targets "misprescribing, misuse and abuse." [25] [26] The unusual feature of the program is that it mandates that more than 20 pharmaceutical companies marketing long-acting opioids must jointly educate prescribers on safe use of these drugs—but participation by the prescribing physicians is voluntary. To launch the initiative, the agency used its new powers to mandate drug companies undertake Risk Evaluation and Mitigation Strategies (REMS) to address specific drug risks.

In this instance the FDA required that the companies join together to sponsor Continuing Medical Education (CME) programs for physicians, nurses, and physician assistants with a goal of training 25% of the 320,000 opioid prescribers in the first year, and 60% within four years. However, participation by physicians is voluntary because the agency concluded that monitoring compliance would be unduly burdensome. The program intends that the safety information reach patients through counseling documents (similar to existing Medication Guides). The prescriber education program is currently in operation and has a web site: (http://www.er-la-opioidrems.com/IwgUI/rems/home.action). In addition, in July 2013 the FDA announced it would be changing the prescribing information for opioids to provide improved warnings for this class of drugs, and said it would mandate postmarket studies. [27] In September 2013, the agency sought to reduce the risk of accidental exposure to fentanyl patches by changing the color of the patch labels so they can be seen more clearly. [28]

### Conclusions

The FDA has clearly recognized the safety risks of potent and long-acting opioid drugs such as fentanyl and has developed extensive education programs with the objective of managing their risks. In this case the agency has also moved beyond its traditional role of approving drugs and requiring warnings by mandating an education program targeting prescribers together with assessment tools to measure the program's effect. Among the leading drug safety signals for 2012, the FDA has focused substantial attention on this issue.

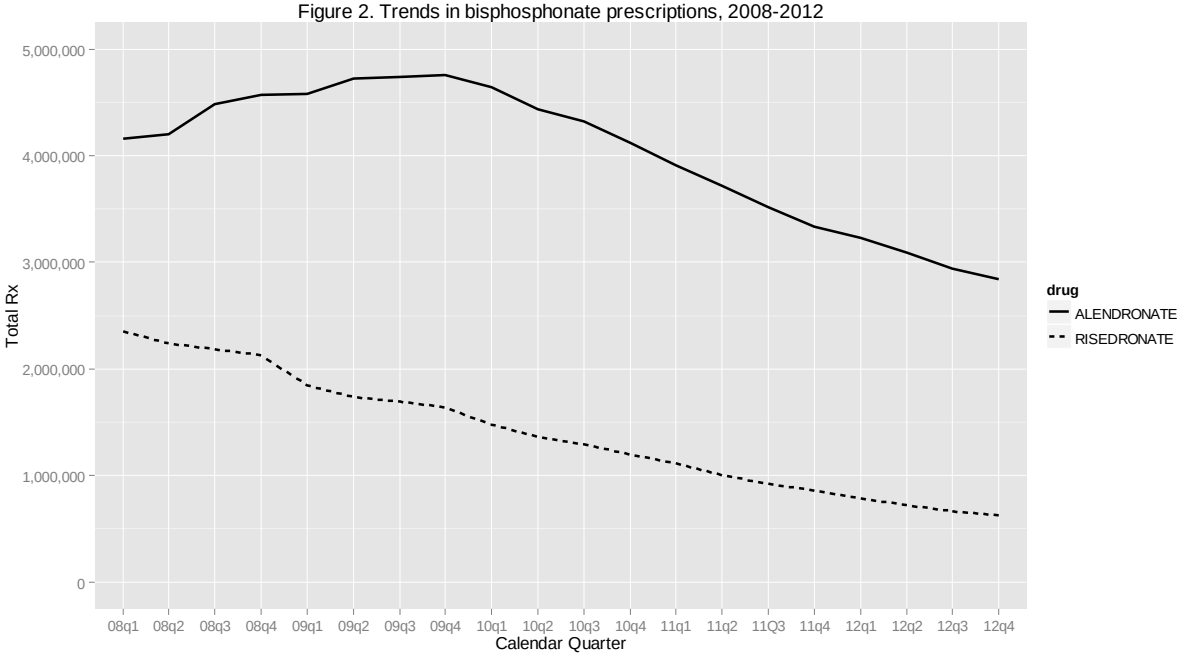
## Perspective: Linking Drugs to Specific Side Effects

The osteoporosis drug alendronate (FOSAMAX) was primary suspect drug in 1,327 reports of bone injuries in 2012, notably 1,201 cases of a femur fracture and an additional 155 reports of osteonecrosis of the jaw. This was one result when we deployed statistical tools to search for associations between specific drugs and particular kinds of adverse drug events. QuarterWatch utilizes a measure called the proportional reporting ratio (PRR), which can identify cases in which a specific drug is disproportionally associated with a particular adverse effect. In this instance, alendronate was 186 times more likely to be associated with bone and joint injuries (PRR = 186, $p < 0.01$), compared to all other drugs after adjusting for the volume of reports. This combination of a high case count and a strong statistical association constituted a signal meriting reporting and additional analysis. Results were similar for risedronate (ACTONEL), an osteoporosis drug with a similar mechanism of action. Reported bone injury cases were many fewer (n = 68) with risedronate, but still disproportionately more than expected (PRR = 27.9, $p < 0.01$).

Alendronate is the most frequently prescribed among the class of drugs called bisphosphonates, which are intended to prevent or treat osteoporosis, a disorder that occurs predominantly in post-menopausal women when the natural cycle of reabsorption and creation of bone cells is unbalanced because not enough new cells are created to keep pace with bone loss. Bisphosphonates, by inhibiting the reabsorption of bone cells, can increase bone density. Alendronate increased bone density over time and in later studies of three and four years duration, both drugs showed they also reduced "vertebral fractures." [29] These largely asymptomatic "fractures" were defined as a 15-20% reduction in vertebral height as determined in a radiological exam.[30] This limited evidence was enough to help propel prescriptions for postmenopausal women into the millions in the years following approval of alendronate in 1995 and risedronate in 1998, and to expand its use to prevent as well as treat osteoporosis. Later analysis combining studies suggested alendronate might also reduce the incidence of hip and wrist fractures in secondary prevention—a more clinically significant endpoint—by an absolute difference of about 1-2%. [31]

After a decade, however, safety questions began to arise about the effects of bisphosphonates on long-term bone health. The drug was associated in some patients with osteonecrosis of the jaw. Another issue was atypical femur fractures, which could occur without any traumatic injury, and sometimes in both legs.[32] And in many cases both problems were associated with the fracture failing to heal normally. These bone disorders were generally not seen in clinical trials. The early warnings came in adverse event reports and case reports in the medical literature. The idea took hold that increasing bone density at the cost of limiting bone cell turnover might not be a good idea over the long term, and likely contributed to the decline in the use of alendronate and risedronate. Prescription trends are shown in Figure 2 based on outpatient dispensed prescription data from IMS Health.

Figure 2. Trends in bisphosphonate prescriptions, 2008-2012




## FDA Warns Optimal Duration of Use Unknown

After studying the matter for two years and consulting with outside bone experts, the agency concluded in 2010 that a causal relationship was not clear, but added “these atypical fractures may be related to long-term bisphosphonate use.” [33] Although declining to judge whether the bisphosphonates were the direct cause of the atypical fractures, the agency did require prominent warnings for doctors and consumers. The FDA also zeroed in on the central question still unanswered: Were the drugs beneficial or harmful in long term use? The FDA required a disclaimer in the prescribing information stating: “Optimal duration of use had not been determined. For patients at low risk for fracture, consider drug discontinuation after 3-5 years use.” [29] A study that compared the effects of discontinuation after 5 years treatment with 5 extra years continued treatment with alendronate detected no higher overall fracture rate. [34] A later meta-analysis concluded there were no clinically meaningful benefits in treatment unless women had experienced a prior fracture or vertebral compression. [35]

## Limitations

The computer excerpts used for this QuarterWatch report do not contain enough information to ascertain whether the femur fractures reported were of the specific atypical, slow healing type judged most likely to be associated with bisphosphonates. However, a more focused adverse event analysis examining all cases reported from 1996 to 2011 to the FDA or in the medical literature reported a disproportion number of non-healing femoral fractures (PRR = 4.5 ) associated with bisphosphonates.[36] While the reports were numerous, and the association convincing in our statistical analysis, these adverse event reports do not allow calculating the incidence, nor can we rule out the possibility that the underlying osteoporosis was an alternative cause.

## Influence of Legal Cases

While identifiable cases from litigation are excluded from regular QuarterWatch monitoring totals, the existence of a large number of legal cases has two implications for drug safety reporting. First, it indicates that patients and attorneys have identified a serious injury for which compensation is sought in the legal system. Also, our statistical analysis has shown that when attorneys advertise on the web and elsewhere for potential cases linked to a drug, it tends to increase the reporting for all cases (beyond those we can identify

as linked to litigation). That process occurred for alendronate in 2012, with an additional 1,883 cases linked to lawsuits. While the underreporting of adverse events likely remains large, this aspect of the legal process does increase reporting rates.

### Conclusion

Our data from 2012 add to the evidence of an association between femur fractures and bisphosphonates. However these data cannot answer the larger health question: Does long-term use of bisphosphonates such as alendronate and risedronate have benefits that outweigh its risks? The signal seen in the 2012 data shows that the issue remains an important drug safety problem affecting millions of women that still needs to be addressed 18 years after alendronate was approved.

## Problems in the FDA Adverse Event Reporting System

The law of unintended consequences loomed large when we investigated an influx of patient death reports (n = 15,192) for three treatments for metastatic or advanced cancers from Roche Oncology, erlotinib (TARCEVA), bevacizumab (AVASTIN), and capecitabine (XELODA). These three oncology drugs accounted for 33% of the 45,421 patient deaths reported for all drugs in 2012. It turned out the company had had direct contact with many treated patients with advanced cancers, and had learned that they subsequently died, but had minimal other information. But because such deaths are required to be reported under FDA regulation, the company had no choice. The details of this episode show the overall effect of FDA policy was to lower the quality of reporting on patient deaths associated with drug treatment.

**Table 4. Total reports and deaths for 3 Roche Oncology drugs, 2012**

| Drug name | Total reports | Deaths | Uninformative* |
|---|---|---|---|
| **Total (n =)** | 17424 | 15192 | 12028 |
| Erlotinib | 10092 | 9138 | 7122 |
| Bevacizumab | 5085 | 4294 | 3440 |
| Capecitabine | 2247 | 1760 | 1466 |

* Event term of "death" only

The FDA's postmarket surveillance system places the primary burden of reporting on drug manufacturers, who do not have to search for cases (e.g., active surveillance) but are required to report cases of which they become aware. The FDA's regulations and guidances, along with international consensus guidelines, contain extensive technical detail about what constitutes an adverse drug event and when a company can be said to learn about it. As in most safety surveillance systems, a death is an outcome of particular interest, and FDA regulations require reporting patient deaths "whether or not considered drug related." [2] The presumed intention was useful: the agency did not want drug companies making unilateral decisions about whether a patient death was drug related or not; the agency should get complete reporting. However, such regulations might have made sense before email and internet communication that allows drug companies to operate programs with extensive direct patient contact—in some cases with all patients taking the drug. The current policy on death reporting in the present day makes the entire system less reliable and useful. The results for erlotinib are a prime example.

Erlotinib is a kinase inhibitor intended to target growth factor receptors on tumor cells, thus retarding cellular proliferation. It is FDA-approved for two locally advanced or metastatic cancers with high mortality rates, non-small cell lung cancer (NSCLC) and pancreatic cancer. In a pivotal open label trial for NSCLC, 64% of the patients had died after a median of 22 months of treatment. In pancreatic cancer, 50% had died in six months, and 76% by one year. [37] Unless a drug role was suspected, patient deaths in this dire setting would not provide useful drug safety surveillance information.

The setting in which most of the 9,138 erlotinib patient deaths were uncovered further eliminated any positive value, and were so numerous they had a major effect on overall reported death totals. Genentech

told us that in late 2011 the company discovered that its patient assistance program records contained notes when the patients with metastatic cancer had died and no longer required services from the program. The purpose of the program was to help some patients obtain insurance reimbursement for the cancer treatment, provide financial assistance to others, and help a third group get assistance for part of the cost from foundations. The company searched its data and uncovered patient deaths extending back several years. Such records, the company noted, "contained minimal information in most cases." In the QuarterWatch assessment, 7,122 / 9,138 (77.9%) of the erlotinib death reports contained only the event term "death."

The two other cancer treatments were similar but the numbers smaller, with 4,294 patient deaths reported for bevacizumab and 1,760 for capecitabine. QuarterWatch has previously identified other examples where complying with regulations produced uninformative and undesirable death reports. Notably, in another Roche case, the company reported 250 patient deaths for the bisphosphonate ibandronate (BONIVA) in part because reminder postcards to patients to take their monthly tablets had been returned marked "deceased."[38].

## Conclusions

Unintended consequences of the FDA adverse event reporting regulations have seriously undermined the value of the postmarket surveillance of deaths in which a drug involvement was suspected. The reporting criteria need to be substantially revised to focus on valid case reports. One possible solution would be a program similar to the existing waiver program for another class of unwanted reports-–non-serious reports for drugs on the market three years or more. Under the waiver the companies do not submit the reports, but retain them on file subject to inspection or later FDA request. Another solution would be to create a special purpose event term to identify such cases so they could be segregated or otherwise disregarded. But this flaw in the only federal health surveillance system currently monitoring patient deaths associated with prescription drug therapy underlines the need for making reform a priority at the FDA. Among all drugs in 2012, 47% or 21,467 death cases were of minimal value because they contained the single event term "death."

# QuarterWatch Team and Funding Sources

QuarterWatch is published by the Institute for Safe Medication Practices as a public service. It has no regular income, foundation grant, or other dedicated financial support and is provided to the public and health professions without charge. We seek outside peer reviewers for each issue but their identities are not disclosed. QuarterWatch's essential costs are funded from the general budget of ISMP, a non-profit organization dedicated solely to promoting the safe use of medication. ISMP, in turn, is supported by charitable donations, volunteer efforts, foundation grants, and subscription income from its four other medication safety newsletters, for pharmacists in the acute care and ambulatory care settings, for nurses, and for consumers.

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academia, including Health Canada and the FDA. RSI is a consulting expert on pharmacokinetics to the plaintiffs in litigation regarding cholesterol lowering drugs (statins) and the risk of diabetes.

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