



# Quarter Watch

## Monitoring FDA MedWatch Reports

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### ANNUAL REPORT ISSUE

Two tumor necrosis factor blockers lead overall report totals in 2014  
Novel oral anticoagulant safety profiles diverge, but risks remain high  
Atorvastatin (LIPITOR) accounts for most safety-related lawsuit reports

## Executive Summary

This issue provides an overview of prominent drug safety issues as reflected in 833,076 adverse drug events reported to the U.S. Food and Drug Administration during 2014. For this annual review, we identify the drugs that account for the most reports overall and in key subgroups such as children, cases from legal claims, and reports indicating product problems. For each perspective it is important to consider both the insights revealed and the substantial limitations of the underlying data.

Although drug adverse effects are estimated to account for 100,000 to 200,000 patient deaths and 1 to 2 million hospitalizations each year, neither the FDA nor the Centers for Disease Control and Prevention publishes annual assessments of serious injury and death resulting from drugs in therapeutic use. Despite a world of proliferating digital data, the primary source for identifying injuries from therapeutic drugs remains the voluntary reports to the FDA’s Adverse Event Reporting System (FAERS). The QuarterWatch™ assessment is based on publicly released excerpts of case reports submitted for the first time in 2014.

## The Data Profile

The U.S. system for postmarket surveillance depends primarily on reports prepared by drug manufacturers. The types of reports that the FDA received in 2014 are described in Table 1. In 2014, manufacturers submitted 798,962 (95.9%) of the reports that the FDA received. The remaining 34,114 (4.1%) cases were submitted directly to the agency’s MedWatch drug information program portal by consumers and health professionals. Any individual who desires to report an adverse drug event has the option of either submitting one directly to the FDA or contacting a drug manufacturer. Manufacturers, in turn, are required to report every adverse event they learn of through any channel that could range from a consumer help-line telephone contact to a refill reminder that was returned indicating the patient had died. The strength of the system is that it collects information from a wide array of sources that range from episodes observed by hospital pharmacists to legal claims

**Table 1. Adverse drug event reports received by FDA in 2014**

	Number, %	
Total (initial reports)	833,076	
Manufacturer	798,962	95.9%
Domestic, serious*	284,845	34.2%
Foreign, serious	218,309	26.2%
Domestic, not serious	295,808	35.5%
Direct to FDA	34,114	4.1%
Serious	25,038	3.0%
Not Serious	9,076	1.1%

\*Includes death, disability, hospitalization, life threatening, required intervention, and other serious injury.

for drug-induced injury filed in state and federal courts. Reporting events to the FDA is closed to no one.

## Two Anti-TNF Products Post Most Injury Reports

In 2014, two similar biological products that inhibit a key element in the immune system—tumor necrosis factor (TNF)—accounted for the largest number of reports of injury received by the FDA in several different categories. The two drugs, adalimumab (HUMIRA) and etanercept (ENBREL), are approved to treat various autoimmune disorders, notably rheumatoid arthritis, Crohn’s Disease, and forms of psoriasis. Counting all reports from all sources, adalimumab ranked 1<sup>st</sup> with 46,937 new reports and etanercept 2<sup>nd</sup> with 38,929 cases. For comparison, in 2014 we identified 1,604 therapeutic drugs with reports, with a median of 37 reports per drug. Only 168 drugs accounted for more than 1,000 reports each.

The primary focus of QuarterWatch is the subgroup of serious reports of domestic origin. By this measure etanercept ranked 1<sup>st</sup> (n = 7,752) and adalimumab 2<sup>nd</sup> (n = 6,081). Another category of interest is expedited reports about new, serious adverse events without full warnings in the prescribing information. Again etanercept ranked 1<sup>st</sup> and adalimumab 2<sup>nd</sup>. The two drugs were the primary suspect drugs in 1,809 patient deaths in reports from all sources.

Three factors combine to produce such large totals: 1) Larger patient exposure; 2) substantial toxicity; and 3) marketing and educational programs that increase the manufacturer’s contact with patients and health professionals, causing the company to learn about more cases. In this report, we examine how all three factors contributed to the high event totals for these two anti-TNF products. Most adverse events were linked to the two drugs’ immunosuppressant properties.

## Contrast in Novel Anticoagulants’ Safety Profiles

Rivaroxaban (XARELTO), dabigatran (PRADAXA), and apixaban (ELIQUIS) are “novel” oral anticoagulants approved from 2010-2012, and marketed as easier-to-use replacements for warfarin (COUMADIN), the high-risk standard treatment since the mid-1950s. All are approved to lower the risk of stroke in patients with atrial fibrillation, and most for use after hip and knee replacement surgery. Although rivaroxaban accounted for more direct reports to the FDA (mostly from health professionals) than any other drug, we expanded the focus to examine the safety profiles of all three novel anticoagulants. Key findings:

- Rivaroxaban emerged the winner of the race to replace warfarin, with more dispensed outpatient prescriptions than the other two drugs combined. We examine whether both hemorrhage events (too much anticoagulant) and blood clot related events (not enough anticoagulant) are linked to a disconnect between its once-a-day dosing and a terminal half-life of 5 to 9 hours.
- Dabigatran had the highest overall total of domestic, serious adverse event reports among the three, the largest total of reported severe hemorrhages, and the most patient deaths. The differences persisted after adjusting for patient exposure and other report characteristics. Previously, we have questioned whether a drug with a 5-fold variability of effect among patients getting the same dose was suitable for use in a single primary therapeutic dose. The 2014 data further illustrate our concerns.
- Apixaban was the third new anticoagulant to win FDA approval, but showed the strongest safety profile from several perspectives. Its twice-a-day dosing regimen was consistent with its 12-hour half-life. A lower dose for older and other high risk patients for bleeding was tested and found to reduce bleeding risk without loss of efficacy. And it accounted for the fewest reports and the fewest patient deaths both before and after adjusting for patient exposure.

## Atorvastatin (LIPITOR) and Diabetes Lawsuits

A separate and distinct forum for evaluating drug safety exists in the U.S. court systems, where thousands of patient claims of injury for a drug are litigated at cost of millions of dollars in an elaborate process that may take years to complete. When legal claims reach a drug manufacturer they are also reported to the FDA as adverse events. In 2014, the biggest reported litigation target (n = 4,727) was the cholesterol-lowering drug atorvastatin (LIPITOR), and the issue was whether it causes diabetes in women.

Atorvastatin was the fourth most widely used therapeutic drug by the last quarter of 2014, accounting for 22 million dispensed outpatient prescriptions, according to IMS Health data, and approximately 11.4 million person-years of exposure. It has a proven clinical benefit established in mostly high-risk men where a large clinical trial showed it reduced the risk of cardiovascular events by 36%. But the chances of it benefiting any single patient were small: It took 33,000 person-years of observation to document the prevention of fewer than 60 cardiovascular events. If a relatively small risk were overlooked in the clinical studies it might tilt the balance of harm versus benefit.

Use of statins had escalated to one of the most widely used treatments in all of medicine when questions emerged about whether these drugs might also cause diabetes. A reexamination of 13 large clinical trials concluded that indeed treatment might increase the risk of diabetes by around 9%. The studies together suggested that all the statins shared roughly similar risks and benefits, although both might be higher for the most potent statins, rosuvastatin (CRESTOR) and atorvastatin. This was a concern but 9% seemed a small number compared to a 36% reduction in risk of cardiovascular events. But then a major gender gap was identified. The statin trials had largely enrolled men. Observational studies in women showed that the risk of diabetes with statin treatment was much higher – 48% in the largest study. And women had a lower risk of cardiovascular disease compared to men.

In the coming months, experts for both sides will dispute the nature and extent of the diabetes risk of atorvastatin in women. In a peculiar feature of mass tort litigation, much of the scientific evidence on which the competing experts rely often remains secret. In this report we examine other unusual characteristics of drug safety litigation cases in 2014. It is common for drug manufacturers to pay hundreds of millions of dollars in legal claims for a drug risk, and then claim the drug is not, in fact, responsible for the safety problem.

## Additional Safety Perspectives

We identified signals of possible drug risks in other subgroups of reports. Among children under 18, somatropin (or recombinant human growth hormone) accounted for the most domestic, serious adverse event reports. In the oldest patients—those 75 years of age and older—denosumab (PROLIA), a twice-yearly injection to reduce the risk of bone fractures, accounted for the most reports and illustrated that it shared many of the safety issues of alendronate (FOSAMAX). A third subgroup was product quality complaints—most not indicating a serious outcome. Spiriva HandiHaler (tiotropium) accounted for the most complaints in 2014. Among estrogen/progestin products for women, the largest number of domestic, serious events reported was for MIRENA, an oral contraceptive intrauterine device (IUD) that releases levonorgestrel.

## 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 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. While the sheer numbers of case reports have scientific weight, because of variation in reporting rates, they reveal little about how frequently the events occur in the broader patient population. More complete disclaimers and descriptions of

our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

## Conclusions

For our 2014 annual report issue the objective was to identify drug safety issues from different perspectives. Measured by sheer numbers of reports, the anti-TNF products place first, in part because of their potent effects on the immune system that increase the risks of invasive fungal and opportunistic bacterial infections, reactivation of hepatitis virus, and cancer. Intensive marketing and extensive patient contact by manufacturers or their agents also contribute to the high volume of reports.

The adverse event reports for oral anticoagulants confirm the evidence that long-term use remains one of the highest-risk drug treatments in older patients, with injury rates of 15-20% per year. As previously noted in this publication, bringing a new generation of oral anticoagulants to market based on ease of use rather than improved safety was a major wrong turn. In addition, two of the three novel anticoagulants have pharmacological profiles that raise questions about their simple, unmonitored dosing regimens. For dabigatran, a 5-fold variability in different patients getting the same dose creates risks in many patients that could be reduced by optimizing the dose for each patient. However, a reduced dose 110 mg dabigatran capsule and the most accurate blood-level test are not approved in the U.S. The short half-life of rivaroxaban means that once-a-day dosing results in higher maximum concentrations and higher bleeding risk on one hand, and an extended period each day when concentrations may be suboptimal for preventing stroke. Neither rivaroxaban nor dabigatran has lower recommended doses for older patients and most others with higher bleeding risks. At this point, apixaban appears to have avoided these drawbacks with a better safety profile. But the risks of bleeding are so high that individualizing the dose—as with warfarin—promises to improve the safety profile of this risky class of drugs.

The legal contest over the diabetes risks of atorvastatin provides new safety perspectives into the problems of drugs that are administered long-term for prevention of cardiovascular events. To discover after 20 years that one of the most widely used drug treatments in medicine might do more harm than good in a huge subgroup—low risk women—underscores the limited data that support the long-term use of this and other treatments for prevention. Also, the issues at stake illustrate that when a drug has a relatively small chance of providing a future benefit, even a small risk of harm can alter the balance of risk and benefit. Finally, drug safety issues that are addressed in the legal system identify problems that may need to be addressed by doctors, the FDA, and medical organizations. Whether cholesterol treatment guidelines for women are appropriate is one of them.

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## QUARTERWATCH PROJECT TEAM

### Thomas J. Moore

Senior Scientist, Drug Safety and Policy, ISMP

### Michael R. Cohen, RPh, MS, ScD (hon)

President, ISMP

### Curt D. Furberg, MD, PhD

Professor Emeritus of Public Health Sciences,  
Wake Forest University School of Medicine

### Donald R. Mattison, MD, MS

Chief Medical Officer  
Risk Sciences International

## MEDIA INQUIRIES

### Renee Brehio

ISMP Public Affairs

[rbrehio@ismp.org](mailto:rbrehio@ismp.org) 704-831-8822

## CORRESPONDENCE AND SCIENTIFIC INQUIRIES

### Thomas J. Moore

*QuarterWatch* Project Director

Institute for Safe Medication Practices

101 N. Columbus Street, Suite 410, Alexandria, VA 22314

[tmoore@ismp.org](mailto:tmoore@ismp.org)

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# Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site. (<http://www.ismp.org/QuarterWatch/detailedMethods.aspx>)

The severity of the adverse event is classified by FDA regulation [2] as serious if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening or had other medically serious consequences. Cases without these outcomes were classified as not serious.

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.[3] 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. [4]

We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs and System Organ Classes combine the terms into 26 categories. The QuarterWatch database was updated in November 2014 to MedDRA version 17.1.

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 2014 (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.”

In this report we also calculated person-years of exposure to provide an additional dimension to assessing the size of the patient population. A patient-year means a sufficient amount of drug dispensed to treat a patient for one year, even though in reality the patient population is larger because many will either start or stop the drug during the period of measurement. In addition, we used 4<sup>th</sup> quarter data to estimate person-years of exposure; it might over- or under-estimate exposure if there were major changes in prescription volume during the four quarters.

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology.[5] When cited in the text, tables, or charts, the brand name of drugs used is the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

# Results

In 2014, the FDA received 833,076 new reports of adverse drug events, an increase of 12.7% from 2013. This total included 293,810 (35%) reports that indicated fatal, disabling or other serious injuries that occurred in the U.S. (excluding legal claims and clinical studies). These domestic reports inform the primary analysis for QuarterWatch. Another large category of reports is for domestic events that were not serious (n = 304,884). This category includes less severe reactions such as nausea, palpitations, and upset stomach, together with medication errors and product problem reports that did not result in a reported serious injury but have implications for drug safety. The non-serious reports increased by 2.1% from 2013 to 2014. The other large category is foreign reports of serious injuries submitted by drug manufacturers who also market the drug in other countries. In 2014 the FDA received 218,309 foreign reports of serious injury. The share of total reports from abroad has increased steadily over the last 10 years and now accounts for 42.7% of all serious injuries reported to the agency.

Serious injuries reported in the U.S. increased by 59,531 cases (25.4%) in 2014, leading all the report categories noted above. However, most of this increase was accounted for by an unusual episode described in a previous issue of QuarterWatch.[6] In spring of 2014 GlaxoSmithKline was required to submit more than 20,000 incomplete case reports for rosiglitazone (AVANDIA), a Type 2 diabetes drug. The cases resulted from a 2012 legal settlement for patients claiming the drug contributed to heart attacks and strokes. Although only a few hundred patients continue to take the drug in the U.S., it accounted for 34,284 reports of serious injury in 2014.

In the next sections of this report we identify the drug products that accounted for the largest number of reports in 2014 in different safety categories. Ranking 1<sup>st</sup> in a category does not immediately demonstrate that the suspect drugs have the highest risks, compared to all other therapeutic drugs. As previously reported, brand name drug manufacturers are the primary source for FAERS data, even though generic drugs accounted for 88% of all dispensed outpatient prescriptions in 2014.[7] Industry marketing and special FDA reporting requirements can increase the number of reports substantially, without necessarily indicating a safety problem. Nevertheless, sheer numbers have scientific weight and thousands of reports of serious injury, large legal actions, or product problems still serve to identify substantial safety problems warranting greater attention to minimize risks.

## Two Anti-TNF Products Lead in 2014 Reports

Tumor necrosis factor (TNF) is a family of signaling proteins created by the immune system. They function primarily to destroy unwanted and abnormal cells in the inflammatory process. Genetically engineered proteins that inactivate TNF have been approved since 1998 to treat autoimmune disorders that include rheumatoid arthritis, severe psoriasis, and Crohn's disease. The two most widely prescribed biological products in this class—adalimumab (HUMIRA) and etanercept (ENBREL)—also account for the largest number of adverse event reports received by the FDA in 2014 in several different categories. Table 2 shows the totals.

Adalimumab ranked 1<sup>st</sup> and etanercept 2<sup>nd</sup> in 2014 in the number of total reports reaching the FDA. In the subset of reports of serious injuries occurring in the U.S. they also ranked at the top, etanercept 1<sup>st</sup> and adalimumab 2<sup>nd</sup>. They accounted for the most expedited reports from drug manufacturers about new, serious adverse events. And they were less prominent in direct reports to the FDA from consumers and health professionals with adalimumab ranking 9<sup>th</sup> and etanercept 11<sup>th</sup>.

To generate an unequalled number of adverse event reports over one year requires a combination of three factors: A substantial patient population, numerous toxic effects, and extensive manufacturer contact with patients and health professionals. In this case, all three factors contributed to the large case totals.

## Exposure

In 2014 Q4, IMS Health data indicates that adalimumab accounted for 558,059 dispensed outpatient prescriptions, or approximately 250,000 person-years of exposure.\* In terms of patient population this was moderate exposure; more than 250 drugs had larger patient populations in 2014. The etanercept patient population was similar, with 438,362 dispensed outpatient prescriptions and a patient exposure of approximately 185,000 person-years.

	<b>ADALIMUMAB</b>		<b>ETANERCEPT</b>	
	Number, %		Number, %	
Total	46,937		38,929	
Outcome				
Death	1,125	2.4%	684	1.8%
Serious	12,270	26.1%	11,818	30.4%
Not serious	33,542	71.5%	26,427	67.9%
Location				
U.S.	39,624	84.4%	34,149	87.7%
Foreign	7,313	15.6%	4,780	12.3%
Source				
Consumer	34,504	73.5%	9,091	23.4%
Health professional	12,303	26.2%	29,780	76.5%
Other/not stated	130	0.3%	58	0.1%
Report Quality*				
Reasonably complete	29,042	61.9%	28,113	72.2%
Minimally complete	30,841	65.7%	36,721	94.3%

\* Reasonably complete = included age, gender and event date. Minimally complete = age, gender

## Harmful Effects

Both drug products are administered with self-injection syringes. Both drugs also accounted for large numbers of injection site reactions, with more than 10,000 reported cases each in 2014. Practically all the injection site reaction cases were classified as not serious. In clinical studies, 20-40% of patients reported injection site reactions or pain. The anti-TNF drugs are also potent immunosuppressants with prominent warnings about the risk of opportunistic and other serious infections. Among serious and fatal injuries reported, 3,298 (24.6%) of the adalimumab cases indicated an infection, and 3,982 (31.9%) of etanercept cases. Anti-TNF products also carry Boxed Warnings about cancer risks, and cancer was frequently reported

\* A person-year means one patient exposed for the entire period. In clinical practice, patient total is larger because some patients start and discontinue during the period.



in 2014. Serious injuries for adalimumab included 1,410 (10.5%) cases of cancer, including 197 reported cancer deaths. Etanercept serious injury cases included 1,253 cancer cases with 90 reported deaths. A third large group of serious adverse events involved hypersensitivity, with 1,438 cases for adalimumab and 1,465 for etanercept.

## Patient Contacts

Available evidence shows that these two biological products are major revenue producers and are supported by extensive programs involving company contact with patients that could increase adverse event reporting. Adalimumab is the leading product of AbbVie, a spinoff of Abbott in 2011. Adalimumab accounted for \$12 billion in sales in 2014. By some measures,[8] adalimumab ranked 1<sup>st</sup> in worldwide drug revenue. (Etanercept ranked 5<sup>th</sup> worldwide). AbbVie offers patients injection training kits, on-call nurse support, medication reminders, free travel packs, and syringe disposal. Amgen offers similar benefits for etanercept, as well as financial assistance and even a personal visit from an Amgen “Nurse-Partner.” A month’s supply of the drugs costs \$3,000-\$3,500, although patient out-of-pocket costs would likely be lower. Another indication that the two companies are in close contact with their patient populations is the high scores for the quality and completeness of their adverse event reports. Overall 92% of etanercept reports included both age and gender, compared to an industry in which only 62% of reports included that basic information. For AbbVie’s adalimumab reports 63% included the basic information.

## Conclusions

These unequalled totals of adverse event reports are a reminder that the prominent warnings about risks of cancer, infection, hypersensitivity, and other harms are not boilerplate to satisfy legal departments and regulators. These two drugs account for thousands of serious and life-threatening injuries reported each year and many thousands of reports about less severe harm. Because of these risks, the two drugs are intended for autoimmune disorders that are moderate to severe.

Other drugs accounting for very large numbers of total reports included rosiglitazone (n = 35,189), as noted previously, and estrogen/progestin products (n = 29,332), a combined category that includes many different forms of oral contraceptives as well products for other related uses.

## Safety Profiles for 3 Novel Anticoagulants

Our annual review for 2014 revealed that for one key indicator—direct reports to the FDA of serious injury—the anticoagulant rivaroxaban (XARELTO) led all other therapeutic drugs with 525 reports. Reports that health professionals and consumers submit directly to the FDA through the MedWatch portal are only 4% of the total. However, they provide signals of safety issues that are independent of manufacturer marketing and other patient contact programs that can skew results. Direct reports are also of higher quality. As we analyzed the reasons why rivaroxaban accounted for so many direct reports, a larger perspective emerged that illustrated the substantial health risks of anticoagulation therapy with both similarities to and differences from two similar novel anticoagulants—dabigatran (PRADAXA) and apixaban (ELIQUIS). Starting in 2010, the three drugs have been competing to replace the anticoagulant warfarin, first approved in 1956 and currently used by approximately 4 million patients at risk of blood-clot-related disorders after hip/knee replacement surgery or heart attacks or with atrial fibrillation.

## Rivaroxaban Wins the Race to Replace Warfarin

By the close of 2014, rivaroxaban was the run-away winner in the race to replace warfarin. Data from IMS Health reveal that in the 4<sup>th</sup> Quarter of 2014 rivaroxaban accounted for more dispensed outpatient prescriptions than its other two competitors combined. As Table 3 indicates, however, warfarin remained the dominant treatment in this drug class.

## Safety vs. Ease of Use

More than a decade ago, as pharmaceutical company researchers assessed how to develop a new product that would be superior to warfarin, two clear choices were available. It was unlikely that any new product could substantially surpass warfarin for benefit in preventing serious and disabling blood-clot-related events. That is because anticoagulation by any drug lies on the razor's edge. Too much and the result is hemorrhage. Too little, and the drug fails to prevent heart attacks, strokes, pulmonary embolism, and other clot-related disorders. The next choice was safety. Warfarin, by a large margin, was the highest risk outpatient medical treatment in older patients,[9] accounting for one-third of all emergency room visits for the adverse effects of all therapeutic drugs. Most warfarin adverse events were for hemorrhages. A drug that substantially reduced warfarin bleeding events that could injure 16-20% of patients per year would be a major advance in drug safety.

The other possible advantage was ease of use. Administration of warfarin is challenging. It requires blood tests as frequently as every two weeks. Warfarin interacts with dozens of other drugs, even food. The same individual may need different doses over time. All three companies opted for ease of use over improved safety, and designed clinical trials based on the idea that periodic blood tests to establish an optimal dose were not required.

## The Problem of Patient Variability

A high-risk drug where too much or not enough drug can lead to a medical emergency requires that the pharmacology and administration of the drug itself achieve reasonably uniform effects among patients, and over the full duration of the dose period. Although the facts were not fully understood until recently, two of the three new drugs had problems in basic pharmacology that raised questions about their suitability for simple dosing regimens without adjusting for each patient.

## The Dabigatran Problem

As we have previously reported,[10] [11] before dabigatran was marketed, the manufacturer, Boehringer Ingelheim, and regulators had extensive pharmacokinetic/pharmacodynamic (PK-PD) data that raised questions about its suitability for use in a single primary therapeutic dose without blood-level monitoring. Because of problems metabolizing dabigatran, 17% of patients would get a sub-therapeutic dose and therefore minimal protection against stroke or heart attack. Because of 5-fold variability in blood levels among patients receiving the same dose, nearly half would receive more drug than needed, raising the risk of hemorrhage. The highest blood levels and excess anticoagulation were seen in older patients. However, older patients could not be protected by a reduced dose because the FDA rejected the company's request for a smaller dose for older patients.[11] FDA managers justified their decision to ban a lower dose, saying if approved too many doctors would worry about bleeding and use the lower dose.[12] Dose adjustment for older patients and a blood level test are available in most advanced nations, but not in the U.S. Safety concerns about dabigatran likely contributed to its decline in the U.S. market. Although it was the first of the new anticoagulants to be approved, dispensed outpatient prescriptions for dabigatran have declined 22% since mid-2012, according to data from IMS Health.

**Table 3. Dispensed oral anticoagulant prescriptions 2014 Q4\***

	Prescriptions	Person-years
Rivaroxaban	1,758,016	505,560
Dabigatran	560,887	252,780
Apixaban	609,301	231,618
Warfarin	80,266,745	3,944,233

Data from IMS Health National Prescription Audit

## Rivaroxaban Single Daily Dose

For an ease-of-use claim, rivaroxaban had an advantage over the emerging competition. It was the only new anticoagulant with once-a-day dosing for most medical uses, instead of twice a day.[13] Whatever marketing advantage once-a-day dosing might provide, the PK-PD data shown in Table 4 clearly demonstrated that of the three new drugs, rivaroxaban was the poorest choice for a single dose.

It is clear that once-a-day dosing for a drug with a terminal half-life of only 5-9 hours resulted in substantial peaks and troughs that could be avoided with twice-daily dosing. One head-to-head comparison showed that the peak dose of rivaroxaban was 16.9 times higher than the trough; with apixaban twice a day the peak was 4.7 times higher than the trough. [14] In addition, the problem was clearly identified by the FDA pharmacology staff prior to approval.[15]

## No Worse than Warfarin

Despite these unfavorable characteristics in pharmacology studies, both dabigatran and rivaroxaban were approved for reducing the risk of stroke in atrial fibrillation patients on the basis of large clinical trials at the fixed-dose regimens. The results showed that overall, both drugs were no worse than warfarin.[16] [17] While FDA pharmacologists could and did assert that rivaroxaban 10 mg twice a day had a better profile than 20 mg once a day, they also noted that “the clinical relevance was uncertain.”[15] That was because only the once-a-day regimen had been tested in the pivotal clinical trial. As later safety questions arose about the safety of dabigatran in older patients, the FDA appeared to be satisfied with findings that the safety profile appeared to be no worse than warfarin—likely the highest risk outpatient treatment in older patients.

## Apixaban in Contrast

Although apixaban was not approved until 2012—two years after dabigatran—the development plan appeared to avoid the limitations observed for rivaroxaban and dabigatran. Apixaban was tested in both once- and twice-daily regimens in patients following knee replacement surgery.[18] Twice a day was deemed safer and its advantages over a comparator were confirmed in a larger study.[19] In its longer-term trial in atrial fibrillation, older patients and others at higher risk for bleeding were given reduced dose. In the older patients getting the reduced dose, severe bleeding was reduced compared to warfarin but efficacy was retained.[20] At least partly because of these factors, the apixaban trial in atrial fibrillation was the only one to show a clear safety gain over warfarin, reducing severe hemorrhages by one-third, or 2.1% compared to 3.1%. On the other hand, apixaban approval was delayed because of FDA questions about the quality of the data in the pivotal trial.[21] Also unanswered is whether apixaban safety could be further improved with individualizing the dose for each patient, as is done with warfarin.

## The Adverse Event Comparison

The strengths and weaknesses of the three new anticoagulants are also reflected in their serious adverse event profiles. The comparisons are shown in Table 5. While rivaroxaban led in the largest number of reports directly to the FDA, by most other measures dabigatran had a less favorable safety profile. In overall serious reports in the U.S., dabigatran had the largest number. After adjusting for differences in exposure, the difference with the more widely dispensed rivaroxaban was still greater, 14.1 serious injury reports per 1,000 person-years for dabigatran, compared to 6.6 for rivaroxaban, and 4.4 for apixaban. Examining the severity of the reported cases, the mortality rate for dabigatran events, at 20.9 % was about double that for the other two drugs.

**Table 4. Anticoagulant half-life, dosing**

	Half-life	Dosing
Rivaroxaban	5-9 hr	Once daily
Dabigatran	12-17 hr	Twice daily
Apixaban	12 hr	Twice daily
Warfarin	20-60 hr	Once daily

Drug	Total	Direct to FDA		Death outcome		Embolic-thrombotic*		Hemorrhage*	
		Number, %	Number, %	Number, %	Number, %	Number, %	Number, %		
Rivaroxaban	3,331	525	15.8%	379	11.4%	1129	33.9%	1,647	49.4%
Dabigatran	3,592	188	5.2%	752	20.9%	721	20.1%	2,709	75.4%
Apixaban	1,014	95	9.4%	108	10.7%	224	22.1%	492	48.5%

\*Standardized MedDRA queries (SMQ), broad scope

Rivaroxaban cases were notable in one area that would be expected, given its short half-life and once-a-day dosing. It had an excess of embolic-thrombotic events (or treatment failure) compared to the other two drugs. It had the largest number of these cases (n = 1,129) and the largest percentage of cases, 33.9% compared to 20.1% for dabigatran and 22.1% for apixaban.

Apixaban had the best adverse event safety profile by several measures. It had by far the fewest reports (n = 1,014), and the difference remained but was smaller after adjustment for prescription volume. It had the fewest direct reports to the FDA, the fewest deaths, and the lowest percentage of deaths. However, the differences with rivaroxaban in percentage of deaths and total hemorrhage cases were small.

We also compared the three novel anticoagulants to warfarin as a reference drug, and used logistic regression to adjust for other differences in the drugs' reports. The odds of a death outcome for dabigatran compared to warfarin were nearly 3 times higher (Odds Ratio 2.76, p < 0.001) after adjusting for patient age, the share of direct reports, and concomitant therapy with other blood-clot-inhibiting drugs. For rivaroxaban, embolic-thrombotic events (treatment failure) compared to warfarin were more likely to be reported (OR 2.73 p < 0.001), after adjustment for patient age and other clot-inhibiting medication. The other two novel anticoagulants also had increased odds of embolic-thrombotic events compared to warfarin, but less so: dabigatran (OR 1.45 p < 0.001); and apixaban (OR 1.58 p < 0.01).

## Effect of Platelet Inhibitors

The adverse event data for 2014 raised questions about why no clear guidelines existed about when or even whether patients should take two different kinds of drugs that inhibited the formation of blood clots. The anticoagulants reduce blood clot formation by inhibiting the enzyme that triggers the formation of fibrin threads that help seal the platelets that aggregate to plug bleeding site. Aspirin, clopidogrel, and other non-steroidal anti-inflammatory drugs inhibit the aggregation of platelets. Low-dose aspirin was allowed in the large atrial fibrillation trials for all three drugs—and up to a 2-fold increased bleeding risk was observed among aspirin users.[16] [17][20] An FDA analysis of rivaroxaban showed that in a subgroup of patients with the highest levels of anticoagulation who were also taking aspirin, 13.8% experienced severe bleeding.[15]

In the adverse event data, we found that concomitant therapy with platelet inhibitors increased the odds of a hemorrhage event by threefold (OR 3.01 p < 0.01). The increased risk was found across all three of the novel anticoagulants and warfarin. However, the 17% of patients on combined therapy had no greater risk of a death outcome (p = 0.861) and had a reduced risk of a blood clot/treatment failure event (OR 0.64 p < 0.001)

The prescribing information for all three drugs contains no guidance on the concomitant use of anti-platelet agents other than a warning that an increased risk of bleeding was observed. The unsolved problem of combination therapy was further illustrated by the clinical trials in which lower doses of the three novel anticoagulants were tested in high-risk heart patients with Acute Coronary Syndrome (ACS) but only when added to the established treatments using platelet inhibitors. The apixaban trial was stopped because of excess bleeding and no identifiable benefits.[22] Dabigatran development for ACS was stopped after a pilot study.[23] The FDA twice denied an ACS indication for rivaroxaban for ACS after two advisory committees voted that the evidence was not convincing that benefits outweighed the increased risk of bleeding.

## Limitations

These adverse event report comparisons have limitations. Although all three anticoagulants are newer brand-name drugs, the adverse event reporting rates could be different. There were other differences among the drugs. Notably, rivaroxaban was used in younger patients, had more diverse indications, and had a larger share of reports from health professionals. Dabigatran had a substantially larger share of reports from consumers. However, we conducted sensitivity analyses to test whether these differences had an effect on the key findings and reported the adjusted odds ratios.

## Conclusions

The need for steps to improve the safety of anticoagulant drugs is increasing. Although warfarin remains the most widely used oral anticoagulant drug, the introduction and marketing of three alternatives promising ease of use has increased dispensed prescriptions for these high-risk anticoagulants by 65% since 2010. In calendar quarters after 2010 it appeared that the new anticoagulants were mostly replacing warfarin. However, in the final two quarters of 2014 dispensed warfarin outpatient prescriptions were the highest since 2008.

Actions that could reduce bleeding risks have not been taken. There are limited guidelines for whether to use anticoagulants with platelet inhibitors in long-term use. The FDA has not taken action to reduce the bleeding risks of dabigatran through making a lower dose available for older patients, and blood level tests to identify patients with sub-therapeutic or unusually high blood levels. These risk-reduction tools are available in Europe, Canada, and elsewhere. The safety and efficacy of once-a-day dosing of rivaroxaban compared to twice-a-day dosing needs to be reassessed. It is time to move toward individualizing the dose for all long-term anticoagulant therapy.

## Atorvastatin (LIPITOR) Leads Legal Claims

The FDA's adverse event report data form a crossroads between two systems: drug safety regulation through the FDA, and the legal system where thousands of patients pursue claims that they were injured by therapeutic drugs without adequate warnings. Litigation to resolve legal claims (for example whether varenicline (CHANTIX) caused suicidal behaviors and violence) can involve thousands of claimants and require a drug company to produce tens of millions of pages of scientific studies, emails and other documents. The company can demand medical records and other detailed information from every patient claiming to be injured. Both sides employ scientific experts to write lengthy reports with hundreds of citations. A judge (most often a federal judge) evaluates whether the experts have built their opinions on a solid scientific foundation. The net documentation available is usually more elaborate than the hundreds of thousands of pages of studies in a New Drug Application to the FDA and takes several years. Ultimately most legal claims are negotiated settlements, sometimes after trying a group of test cases, and sometimes without a single trial in open court. When drug manufacturers are sued for safety claims, they are required to file adverse event reports, which signal a safety problem important enough to be pursued in the legal system.

In 2014, the largest number of reported legal claims identified atorvastatin (LIPITOR) as the primary suspect. Atorvastatin, a cholesterol-lowering agent, is one of the most widely prescribed drugs in the world. In the 4<sup>th</sup> quarter of 2014, atorvastatin was the 4<sup>th</sup> most frequently dispensed outpatient drug in the U.S., accounting for an estimated 11.4 million person-years of exposure.

## The Legal Issue: Diabetes

The medical need for atorvastatin is established primarily through a laboratory test of lipids, notably total cholesterol and low-density lipoprotein cholesterol (LDL-C), and the results of treatment are determined through changes in the laboratory test values. Unless adverse effects occur, no changes that a patient could detect are expected. The key medical evidence that this reduced cholesterol is beneficial with atorvastatin came through a long-term clinical trial that established that among patients (mostly men) with hypertension

and high cholesterol, the risks of future cardiovascular events was 36% lower than in a comparable group receiving a placebo.[24] But the chances of any one patient benefiting were small: It took 33,000 person-years of observation to document that treatment with atorvastatin in older high-risk men prevented fewer than 60 cardiovascular events.[24]

Treatment of the adult population with atorvastatin and other statins had been established for a decade when new evidence emerged that while statins lowered the risk of cardiovascular events they apparently increased the risk of diabetes. A trial in low-risk patients with another statin—rosuvastatin (CRESTOR)—showed an increased risk of newly diagnosed Type 2 diabetes.[25] This triggered a wave of research that involved reexamining large previous trials, possible mechanisms of action, and new observational studies. Studies combining 13 previous trials of statins with more than 1,000 patients showed a 9% increased risk of diabetes.[26] But there was an important problem: most earlier large statin trials had a large gender imbalance, enrolling 80% or more men. When investigators re-examined one of the largest clinical studies ever conducted in women, with more than 1 million person-years of follow-up, use of a statin was associated with a 48% adjusted increased risk of diabetes.[27] However, the study was retrospective and designed to monitor the effects of hormone replacement. Higher risk of diabetes for women was confirmed in a re-analysis of results women in cholesterol-lowering clinical trials.[28] While assessments varied, many concluded that the increased risks of diabetes were real, and higher for the more potent statins, rosuvastatin and atorvastatin. Among the results were a new warning from the FDA [29] and major litigation targeting atorvastatin.

## Litigation Reported

In 2014, atorvastatin accounted for 4,727 reported legal cases, far more than any other therapeutic drug. (The contraceptive IUD Mirena (levonorgestrel) ranked 2<sup>nd</sup> with 721 cases.) All of the atorvastatin legal cases indicated the claim was Type 2 diabetes. Notably, 98% of the cases with gender data indicated women. Some cases indicated known complications of diabetes such as damage to the kidneys (n = 49), vision (n = 129) and nerves (n = 185). These cases, however, involve allegations that have yet to be proven through this legal process. However, the underlying safety question is significant. Women have a lower risk of cardiovascular disease than men, and if proven to have a 2-3 times higher risk of diabetes, guidelines for treating women with cholesterol lowering drugs need to be reassessed.

## When Contradictory Results Occur

In early 2015, lawyers announced the biggest provisional settlement in history for a drug still on the market.[30] The Japanese manufacturer Takeda Pharmaceutical Company offered \$2.4 billion to settle 9,000 cases in which legal claimants alleged that pioglitazone (ACTOS) caused bladder cancer, contingent on the requirement that 95% of patients agreed to accept around \$300,000 each. Eight cases were tried in court prior to the settlement offer, with plaintiffs winning five cases.

Whether pioglitazone causes bladder cancer was a question with conflicting answers among drug regulators and in observational studies. Pioglitazone was removed from the market in France and Germany in 2011 after a French study showed increased risk of bladder cancer.[31] The European Medicines Agency (EMA), which regulates the rest of Europe, let pioglitazone remain in limited use. The FDA required a warning on the label but did not restrict its use. As a result, patient exposure to pioglitazone in the U.S. remained substantial. In the 4<sup>th</sup> quarter of 2014, pioglitazone accounted for 1.4 million prescriptions and approximately 650,000 person-years of exposure.

In recent years drug companies have denied that the safety issue exists even while paying large sums of money in compensation. In the case of the proposed pioglitazone settlement, Takeda specifically stated the company “believes the claims made in this litigation are without merit, and does not admit liability.”[32] Boehringer Ingelheim made a similar statement when it settled 4,000 lawsuits involving hemorrhages linked to dabigatran (PRADAXA) and agreed to pay \$650 million. “We...believed from the outset that the plaintiffs’ claims lacked any merit,” the company said in a statement.[33] In a third example, Pfizer settled approximately 3,000 lawsuits for \$300 million to settle claims that varenicline (CHANTIX) caused suicidal

behaviors, aggression, and other psychiatric side effects. In 2014 Pfizer tried to persuade the FDA to remove the prominent warning about psychiatric side effects, saying the scientific evidence did not support a safety problem for which it had paid damages to all the claimants. An FDA advisory committee rejected Pfizer's request to remove the Boxed Warning in an 18-1 vote.[34]

The final feature of drug safety actions in the legal system is the secrecy that surrounds much of the scientific information—and sometimes all of it—discovered and analyzed in litigation. In the dabigatran litigation the judge released a large group of documents requested by lawyers for the patients. But in the varenicline settlement the judge declined to release any documents. It is unfortunate that most of the scientific information uncovered in these intensive investigations lasting years remain under court seal.

## Somatropin and Adverse Events in Children

From a drug safety perspective, children under 18 years of age have several characteristics that set them apart from other age groups. First, they are markedly healthier than adults, with mortality rates that are a fraction of those of middle-aged adults. For example, a 40-year-old-mother is 13 times more likely to die in the next year than her 10-year-old daughter.[35] As a result of good health and for other reasons, medication use is substantially lower for children under age 18 than for other age groups. Children under 18 make up 24% of the population and 19% of visits to the doctor, but only 7.3% of dispensed medications.

In 2014, somatropin (recombinant human growth hormone) accounted for the most serious adverse events reported in children under age 18 (n = 232). The anti-TNF drug infliximab (REMICADE) ranked next (n = 215), followed by the acne medication isotretinoin (AC CUTANE, others) (n = 164).

Somatropin was first approved in 1987 and is currently marketed under 10 brand names, Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Serostim, Valtropin, Zomacton and Zorbtive. Growth hormone is secreted by the pituitary gland in children, and in smaller amounts in adults. Somatropin was originally approved for a limited patient population of children who were proven to be deficient in growth hormone, or had other rare disorders that resulted in short stature. However, in 2003 the FDA greatly expanded the patient population when it approved somatropin in children who were short in stature for unknown reasons. [36]

At the time it triggered a debate about whether somatropin, which cost \$20,000-\$30,000 a year, should be used as a “lifestyle” drug because taller children might have higher self-esteem or increased social acceptance than shorter children. In addition, body builders and athletes used somatropin inappropriately to increase muscle mass.

Measuring the benefits of somatropin was challenging from the start because it required years of observation, and assessing additional growth beyond that which was occurring anyway. Further, clinical trials were small and many had no control or comparison group.[37] Also, skeptics worried that increased growth for a year or two might have little effect on final adult height. One meta-analysis of 10 clinical trials in children of short stature concluded that somatropin provided an average increase in adult height from 1.5 inches to 2.3 inches and cost \$35,000 per inch of height gained.[38] The reason for various reviewers' concern about the poor quality of the benefit data could be seen in the pivotal clinical trial that won FDA approval for wider use in children who were short but had no identifiable endocrine disorder.[39] It enrolled only 71 patients, divided between somatropin and a placebo, and only 16 receiving somatotropin finished the trial. Because it measured final adult height, it took 12 years to complete. Open label trials were larger, but had no comparison group to assess adverse effects.

### Adverse Events

In 2014, we identified 602 serious adverse events reported in the U.S. identifying somatropin as the primary suspect drug, including 232 with age data indicating age less than 18 years. Among cases indicating patient age, the median was 13 years, with one-quarter 9 years old or younger and one-quarter 17 or older. It

included 103 cases where the event required hospitalization, and 32 cases with an outcome of death. However in 24 of the 32 cases indicating a death, the report did not provide enough information to assess whether or not the drug was suspected of contributing to the death.

The most frequent specific adverse event reported was headache (n = 83), which ordinarily might be considered a non-serious event that occurs frequently in the absence of any drug therapy. However, 94% of cases were reported by health professionals, and headache was only one among a diverse group of symptoms that included joint pain, nausea, constipation, and vomiting. Another group of serious reports alleged that somatropin was apparently not working and were coded in these data as 72 cases of growth retardation. A third group of reports described cases of abnormal bone development including scoliosis (n = 30), limb asymmetry (n = 8) and abnormal bone development (n = 6). We also noted that a substantial share of children with reported serious adverse events were on multiple hormones or steroid drugs, including 24% also taking levothyroxine, a thyroid replacement, 19% taking hydrocortisone, and 6% taking testosterone.

## Conclusions

Even though human growth hormone has been available for more than 25 years, the data about both benefits and risks are limited. The benefit in accelerated growth is hard to measure. The clinical trials were small and had many dropouts. Although treatment typically lasts several years, late onset adverse events are particularly difficult to assess. These data illustrate the need for more and better information about this hormone.

## Other Perspectives

### Reports in Older Patients

Denosumab (PROLIA), a biological product for high-risk women with osteoporosis, leads all other drugs in domestic reports of serious injury and death in patients 75 years age and older. We identified 2,982 reports in 2014 overall. The reports indicated the median age was 78 years; one-quarter of the patients were 86 years or older; and 77% were women. The same product, under the brand name XGEVA, is also approved for treatment with abnormally high calcium levels as a result of cancer. Xgeva reports accounted for 9.6% of the total. Denosumab blocks the effect of the bone cells that cause turnover, thereby increasing bone density, and is administered by health professionals as a twice-a-year injection.

The reports show that denosumab shares with the other major class of drugs for osteoporosis—the bisphosphonates—the risk of osteonecrosis of the jaw (n = 132). We also identified 275 cases of hypersensitivity. Other reports indicated adverse effects on mineral metabolism (hypocalcaemia, n = 74; vitamin D deficiency, n = 45). The denosumab reports also included 1,032 reports of patient deaths without information about whether a drug role was either suspected or investigated.

### Reports of Estrogen Products

Monitoring serious adverse events associated with estrogen products is challenging because of the many different products, combinations, and uses. The largest number of reports of domestic serious injury was for MIRENA, an intrauterine contraceptive device (IUD) that releases levonorgestrel and can be used for up to 5 years.

In 2014 we identified 3,021 domestic reports of serious injury for Mirena, with a large majority indicating an IUD device injury including device dislocation (n = 1,131), uterine perforation (n = 8,790), genital hemorrhage (n = 745), and embedded device (n = 279). A single report could contain more than one of these terms. In addition to these cases, Mirena also ranked second in a separate tally of lawsuit-related cases, with 721 additional cases. Drugs that become litigation targets may also affect report totals outside of litigation because advertising for cases may increase awareness of the putative adverse effect.



## Product Problem Reports

The Spiriva HandiHaler (tiotropium) accounted for the largest number of product problems reported in the U.S. in 2014, a total 843 reports. Product problems are monitored differently from other drug safety issues using the brand name to identify the product and including both serious and non-serious reports (but not foreign reports). The Spiriva report excerpts generally did not identify the specific nature of the product problem, with most indicating an unspecified “product quality issue.” The Spiriva HandiHaler product was also involved in two recalls at the wholesale level, one in late 2013 because of possible foreign particles in the source material, and in spring of 2014 for a possible interaction of the powder with a lubricant on the capsule shell. The company told us that 9.6 million prescriptions were shipped in 2014 in the U.S. with 408 million capsules.

## QuarterWatch Team and Funding Sources

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**Thomas J. Moore** serves as a part-time project director for QuarterWatch. He has developed and maintains the master adverse event database that serves as the primary data source for the publication and conducts the primary analysis for each issue. Mr. Moore receives an honorarium from ISMP for each issue, with the remaining work being on a volunteer basis. He is also a lecturer in the Department of Epidemiology and Biostatistics in The George Washington University School of Public Health and Health Services. Mr. Moore also conducts and publishes other independent studies in the peer-reviewed scientific literature and works as a consultant on drug safety issues, doing business under the name Drug Safety Research. He was a consulting expert to the Attorney General of the State of Texas in a Medicaid fraud lawsuit against Johnson & Johnson regarding the antipsychotic drug Risperdal (risperidone), and was an expert witness for the United States Army in connection with a criminal case involving Chantix (varenicline). He also worked as a consulting expert for plaintiffs in the civil litigation regarding Chantix. In 2013 he was a consulting expert for the plaintiffs in the Celexa and Lexapro Marketing and Sales Practices Litigation. He also conducts confidential assessments for attorneys inquiring about the safety profiles of drugs.

**Curt D. Furberg, MD, PhD** is a Professor Emeritus of Public Health Sciences at Wake Forest University School of Medicine and serves as senior medical adviser to QuarterWatch. He receives no compensation for his work in assessing scientific evidence, defining safety issues, shaping the written report, and communicating with the FDA and others about QuarterWatch findings. He continues to have a research role at Wake Forest and has published more than 450 peer-reviewed scientific articles. An expert on clinical trials of drug treatments, Dr. Furberg is author of a major textbook on that subject, and has worked for the National Institutes of Health and the pharmaceutical industry as an investigator in clinical drug research. In the past five years, has given expert testimony or depositions in cases involving COX-2 inhibitors, Fosamax (alendronate), and Chantix (varenicline). Dr. Furberg is a member of the British Medical Journal Advisory Board.

**Donald R. Mattison, MD, MS** is a retired captain in the United States Public Health Service who has held senior positions at the National Institutes of Health and in graduate public health education. He is currently chief medical officer and senior vice president of Risk Sciences International in Ottawa, Canada, and associate director of the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa. He receives no compensation for his work in assessing scientific evidence, defining safety issues,

shaping the written report, and communicating with the FDA and others about QuarterWatch findings. Dr. Mattison is author of more than 200 peer-reviewed scientific studies and is an elected member of the Institute of Medicine, the Royal Society of Medicine, the New York Academy of Medicine, and the American Association for the Advancement of Science. Risk Sciences International is a consulting company, established in partnership with the University of Ottawa, specializing in the assessment, management, and communication of health and environmental risks. The company has clients in government, industry, and academia, including Health Canada and the FDA.

**Michael R. Cohen, RPh, MS, ScD (hon)** is founder and President of ISMP and guides the overall policies and content of QuarterWatch. He also edits the other ISMP newsletters and is author of the textbook *Medication Errors*. He has served as an advisor and consultant to the FDA, and for his work in medication safety was recognized as a MacArthur Fellow by the John D. and Catherine T. MacArthur Foundation. Dr. Cohen receives a regular salary as president of ISMP and does not engage in outside consulting or legal testimony.

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