Institute for Safe Medication Practices
A Nonprofit Organization Educating the Healthcare Community and Consumers About Safe Medication Practices
A federally certified Patient Safety Organization

QuarterWatch: 2010 Quarter 2

Monitoring MedWatch Reports

January 27, 2011

Signals for Varenicline, Levofloxacin and Fentanyl

Executive Summary

The safety signals observed in the second quarter of 2010 included the following: a large number of psychiatric side effects reported for the stop-smoking drug varenicline (CHANTIX); numerous reports of tendon injury or rupture for the antibiotic levofloxacin (LEVAQUIN); and serious injuries resulting from maladministration of fentanyl patches.

Overall in the quarter, the Food and Drug Administration received 33,068 domestic reports of serious injury, disability or death associated with drug therapy. This was an increase of 12% from the same quarter one year ago and little changed from the previous quarter. Trends were different for the two primary sources for adverse event reports. Cases reported directly to the FDA's MedWatch program by consumers and health professionals declined compared to both the previous quarter and the same quarter in 2009. However, this decline was offset by gains in reports originated by drug manufacturers.

Varenicline (CHANTIX) Safety Problems Continue

Despite a prominent boxed warning, a mandatory Medication Guide for every patient and declining use, the stop-smoking drug varenicline (CHANTIX) continued to account for large numbers of reported serious psychiatric side effects. In the second quarter the drug was suspect in more possible cases of hostility-aggression, depression and psychosis than any other monitored drug.

Levofloxacin (LEVAQUIN) Cases Lead Antibiotics

While antibiotics rank among the safest drugs we monitor, levofloxacin (LEVAQUIN) was suspect in more reports of serious injury than any other antibiotic. Most cases involved tendon rupture and other muscle, tendon and ligament injuries. Case reports of this problem substantially outnumbered those for two chemically similar drugs—ciprofloxacin (CIPRO), with greater volume of prescriptions, and moxifloxacin (AVELOX), with somewhat less frequent medical use.

Dronedarone (MULTAQ) Update

Safety signals continued for this relatively new drug for patients with irregular heart rhythms in the atria, or upper pumping chambers of the heart, a condition called atrial fibrillation or flutter. We identified 134 new cases of reported serious injury, including new or worsened heart failure, potentially lethal rhythm disruptions in the main pumping chamber of the heart (ventricular tachycardia), and kidney impairment and failure. In addition, sanofi-aventis, manufacturer of dronedarone, notified doctors and regulatory agencies of a major new reported side effect: severe and potentially life threatening injury to the liver.

With nine different contraindications and numerous interactions with other drugs, we saw additional evidence of serious injury associated with apparent medication errors. Since approval we identified a total of 39 cases (including 4 deaths) in which patients received another antiarrhythmic drug in addition to dronedarone, a practice explicitly not recommended, 16 cases of off-label use, 12 cases of drug interactions, and 15 reports of dosing or administration error. Cases could fall into more than one category.

Johnson & Johnson OTC Recalls

More than a year after Johnson & Johnson's McNeil Consumer Healthcare began a long series of drug recalls of its over-the-counter products, reports of serious injuries associated with the Johnson & Johnson recalls continued to dominate all new case reports indicating a product problem. This quarter's cases primarily involved McNeil ibuprofen and acetaminophen products for infants and children that were recalled starting in May 2010. Evidence available was insufficient either to establish or to rule out a direct connection between more than 700 reported injuries and any identifiable form of product contamination or other defect.

Drug Safety Perspectives

We used new statistical tools to identify and select specific drug safety issues that were reported in large numbers in the quarter and were clinically significant. We describe the new program in the full report. The drugs and issues involved were:

- **Maladministration of Fentanyl Patches (DURAGESIC, generics).** This synthetic opioid is approximately 100 times more potent than morphine and had more than 400 reported cases of problems administering it. This included patches that fell off or failed to adhere, that were applied incorrectly, or that were applied on the wrong schedule. These problems can lead to overdose or opioid withdrawal symptoms.

- **Diabetes and Quetiapine (SEROQUEL).** While most newer antipsychotic drugs carry warnings about diabetes, reports of diabetes associated with quetiapine ranked among the most frequently reported safety issues in the second quarter (191 cases).

- **Skin Cancer and Infliximab (REMICADE).** This immunosuppressant drug for rheumatoid arthritis and other disorders linked to the immune system accounted for

154 reports of non-melanoma skin cancer. The drug carries a boxed warning about increased risk of infection and certain other cancers.

- **Limb Fractures and Alendronate (FOSAMAX, generics).** While alendronate came into widespread use to preserve bone density in post-menopausal women with osteoporosis, new reports associate the drug with the possibility that leg bones (femur) also might become more brittle and subject to fractures (126 cases). Alendronate was also associated with 53 case reports of osteonecrosis of the jaw.

- **Inflamed Pancreas and Exenatide (BYETTA).**This drug, injected twice daily for the treatment of Type 2 diabetes, accounted for a disproportionate share of a medical disorder called pancreatitis, or inflammation of the pancreas. Symptoms include abdominal pain, nausea and vomiting. All these cases were rated as serious by the reporters or manufacturers (118 cases).

FDA Adverse Event Reporting System

Limited Direct Reporting by Physicians. Despite having more than 800,000 active physicians in the United States and more than 900 million dispensed prescriptions in the second quarter of 2010, the FDA received directly just 425 case reports of serious adverse events from medical doctors. When doctors do report adverse events, 90% of reports are made to drug manufacturers, who collect information and fill out the report. In the full report we discuss why the FDA needs more direct reporting from physicians—many of whom see numerous adverse drug events every day.

Drug Exposure Now Considered

With this issue, QuarterWatch™ is adding a new dimension to its drug safety monitoring program. IMS Health Inc., a global pharmaceutical marketing information company, has agreed to share outpatient prescription volume information for the most widely prescribed drugs. Except for reviewing the accuracy and attribution of prescription data reported, the company does not play any role in our analysis, conclusions or recommendations.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a voluntary adverse event reporting system. The FDA's Adverse Event Reporting System (AERS) data combines 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 substantial fraction of all new warnings, restrictions or other actions to manage the risks of drugs are based on these data. The reporting rate for AERS is unknown, and published estimates range from around 1% to 15% in most cases, and up to 30% in unusual cases of enhanced reporting. We have

observed wide variation among specific drugs, for different kinds of adverse events, and over different time periods. We use the term *signal* to mean evidence that, in our judgment, is substantial enough to warrant publication but requires further investigation to determine frequency of occurrence and establish a causal relationship to the suspect drug. More complete disclaimers and descriptions of our methods are included in the methods section of this report.

Conclusions

We are concerned about the low levels of physician reporting of adverse events directly to the FDA rather than to pharmaceutical companies. A total of just 425 reports among the 33,068 cases in the calendar quarter shows the physician community is essentially not participating in this key element of the postmarket surveillance program. Given the new era of electronically linked computer medical records and information systems, it should be possible to create tools to make physician reporting simple, accurate and timely.

The signal for levofloxacin and tendon and joint disorders illustrates an important, unsolved and recurring problem in drug safety. Identical boxed warnings are required for all three fluoroquinolone antibiotics without any information about how frequently these adverse effects occur, or any indication whether any one of the three drugs might be the safest alternative. A similar problem is seen with the diabetes risk and quetiapine and many newer antipsychotics. A program is badly needed to measure and compare prominent risks among major drug classes to which millions of patients are exposed.

For more than two years we have reported on the adverse effects of varenicline (CHANTIX), and noted substantial responses to our concerns and other data from the FDA and other federal agencies. Nevertheless, despite the safety measures enacted to date, an unacceptable toll continues of reported serious injuries associated with this drug. In the full report we discuss the need for new restrictions or other regulatory action for varenicline.

Finally, we note with thanks to IMS Health the addition of dispensed prescription volume information to our safety monitoring program. Accurate and timely information about the drugs in most widespread medical use informs our safety assessments and permits new kinds of comparisons of drug risks.

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Methods

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

QuarterWatch focuses on domestic case reports of adverse drug events that are classified under federal regulation as "serious," which means events that resulted in death, permanent disability, a birth defect, required hospitalization, were life threatening, required intervention to prevent harm, or had other medically serious consequences. We exclude reports from foreign sources, cases from clinical studies which have different reporting requirements, and events in which the injuries were not serious. We standardize all drug names to an ingredient name based on the National Library of Medicine RxNorm project.[2] We exclude cases identifying drugs that have been previously withdrawn, or that specifically identify a lawyer as the original report source.

We focus on case reports received by the FDA for the first time in the calendar quarter 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 two instances an entire year's adverse events may reach the FDA in one calendar quarter. FDA regulations allow drug companies to submit reports annually for older drugs and types of serious adverse events that already had warnings.[3] Because drug manufacturers are required to monitor the medical literature, annual reports and other published summaries may cover an entire year but be submitted in a single quarter. To compensate, our primary comparison is with the same quarter one year earlier, and we check for periodic spikes that affect individual drugs.

In these reports, the adverse event that occurred is described by one or more medical terms selected from the Medical Dictionary for Regulatory Affairs (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and post marketing reports.[4] The MedDRA medical dictionary is updated regularly and this report relies on MedDRA Version 13.1. 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]

To provide a broader perspective on the adverse events reported we assess the patient exposure to drugs on the basis of dispensed prescription data from 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 2010, 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 special category of drugs with reporting requirements or procedures that are more rigorous than for other drugs, resulting in a much higher reporting rate. For example, thalidomide and lenalidomide are restricted-use drugs with more rigorous adverse event reporting programs. In other cases the manufacturer engages in regular direct contact with patients to deliver product or monitor care, and therefore maintains active surveillance of the patient population. In many of these special cases patient deaths, relapses and other adverse events are reported, but the drug was not necessarily suspected of causing a side effect. Finally, we group together certain drugs such as insulins and estrogens because of a large number of similar products, together with incomplete product names in many case reports. These special category drugs are included in the total number of reports but are otherwise excluded from comparisons and rankings. Starting with this report, we added rosiglitazone (AVANDIA) to the special category following its safety withdrawal in Europe and restricted status in the United Sates.

We frequently use the word *signal* to characterize the evidence we see of a safety issue. The term *signal* means evidence of sufficient weight to justify an alert to the public and scientific community and to warrant additional investigation to assess a causal relationship to the drug and determine its incidence.

In this report we also use a term called the Proportional Reporting Ratio or PRR. This is a statistical technique for signal detection as described by Evans et al.[6] and we have used it and described it in greater detail in another published report.[7] The PRR evaluates the possibility that a particular kind of adverse event might have been reported for a drug by chance, and adjusts for the likelihood that a drug that accrued more reports would have greater exposure to chance events. Our comparison group is all serious adverse event reports for all monitored drugs for the previous four quarters.

Because thousands of reports are revised or updated every quarter by manufacturers, the FDA, or QuarterWatch, the event totals change slightly over time. To permit accurate comparisons, the historical tables are revised every quarter.

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/).

Results

Two trends that were previously reported continued in Quarter 2 of 2010, compared to the same quarter in the previous year. Overall, the steady increase in domestic reports continued for another quarter, up 12% compared to 2009 Q2. However, a decline was seen once again in reports sent directly to the FDA, rather than through drug manufacturers. Direct reports to the FDA were 25% fewer than for the same quarter in 2009 and a downward trend has now extended across the last four quarters. Overall, reports from consumers continue to increase more rapidly than those from health professionals. The changes are shown in Table 1.

Table 1. 2010 Quarter 2 changes from previous year.

	2010 Q2	2009 Q2	Change,pct	
All Reports	33068	29486	3582	12%
Report Source				
Consumer	14036	10638	3398	32%
Health Professional	15221	14650	571	4%
Outcome				
Death	4621	4393	228	5%
Disability	1240	1222	18	1%
Other Serious	27207	23871	3336	14%
Originator				
FDA Direct	5496	7312	-1816	-25%
Manufacturer	27572	22174	5398	24%

Limited Direct Reporting by Physicians

Direct physician reporting of serious adverse drug events to the FDA was limited in the second quarter of 2010. Physicians accounted for 425 reported cases in the quarter, or 10.3% of the direct reports for which the reporting source could be identified.

With more than 800,000 active physicians in the United States [8] and more than 900 million prescriptions dispensed in the second quarter,[9] a total of 425 direct reports to the FDA suggests that physicians are essentially not participating. The number of serious adverse drug events occurring has not been reliably estimated, but some studies have shown that adverse drug events account for possibly 4-5% of all hospital admissions[10] and 700,000 emergency room visits each year.[11]

Physicians were much more likely to report adverse events to drug companies than to the FDA, in the current quarter accounting for 6473 expedited reports originated

by manufacturers, or 28.5% of all such reports. Physician reports to drug companies make a valuable contribution to the drug safety system, but they are different from direct reports in several ways. Reports originated by drug manufacturers focus on newer brand name drugs being currently promoted directly to physicians through visits from its sales representatives. In addition report terms and descriptions of the event are written by pharmaceutical company staff following detailed protocols. Finally, physicians who rely on drug companies for adverse event reporting would face difficulty in the case of generic drugs with multiple manufacturers who may be unknown to the physician.

Meanwhile, the nation's 270,000 pharmacists [12] reported 1382 serious adverse events directly to the FDA in the second quarter and another 952 cases that became expedited reports from drug manufacturers. Despite fewer numbers and less direct patient exposure than physicians, pharmacists were much more likely to report adverse events directly to the FDA.

Physicians make an essential contribution to a voluntary reporting system because these are the health professionals who will diagnose and treat a specific drug adverse effect. Also, the reporting system is focused on the most serious adverse effects—including those which are life threatening, cause hospitalization, disability or death. In such cases physician involvement is all but certain. Thus physicians are in a pivotal position to observe adverse drug events as they occur.

More Varenicline (CHANTIX) Safety Signals

One year after the FDA required major new warnings about psychiatric side effects, varenicline continued to account for more reports of three different psychiatric side effects than any other monitored prescription drug. In the second quarter, varenicline accounted for 130 possible cases of clinical depression, 112 possible cases of hostility-aggression, and 70 cases of psychosis or losing touch with reality. Case reports of these serious side effects outstripped those from the most powerful antipsychotic and antidepressant drugs which are used more directly in vulnerable patient populations with mental disorders. These categories were developed and tested by the pharmaceutical industry to identify possible specific adverse effects and are called Standardized MedDRA Queries (SMQs). [5] A case could fall into more than one category. Overall, varenicline accounted for 378 serious adverse drug events of all types in the quarter.

We have previously reported extensively on the safety profile of this pharmaceutical alternative to the nicotine patch and cold turkey for smoking cessation. In 2008 we published a special report on varenicline, together with a major update. [13] [14] Follow up analysis in the peer reviewed scientific literature further described the association of varenicline with reports of violence/aggression and suicidal behaviors and compared varenicline with other drugs with powerful effects on the brain. [15] [16] [7] Our studies also confirm and extended two FDA internal studies. [17] [18]

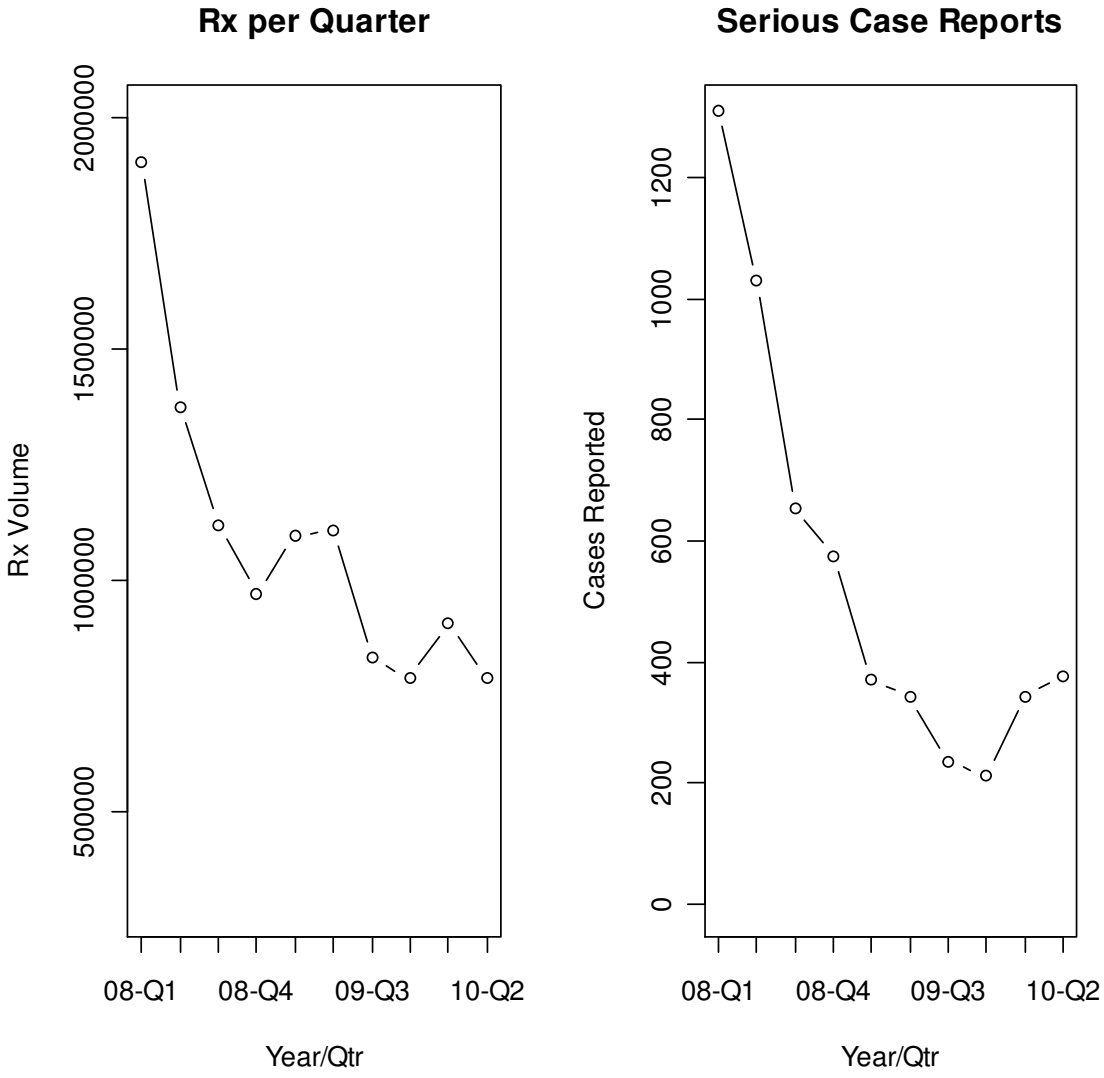
The FDA has deployed most of its regulatory tools short of product withdrawal. This included an Early Communication of possible drug risks, two public health advisories, a requirement for a Risk Evaluation and Mitigation Strategy (REMS) plan, a

boxed warning on the Chantix prescribing information for doctors, and a mandatory Medication Guide for every patient.[19] [20] [21] [22] In addition, the Federal Aviation Administration has banned varenicline for pilots and air traffic controllers, [23] the Department of Transportation has limited its use among truck drivers [24] and the Department of Defense has banned it for use by some military personnel, including pilots and missile crews.[25]

We have seen possible improvement for one psychiatric side effect—suicidal and self injurious behavior. In the second quarter of 2010, the 45 possible cases of suicidal behaviors were fewer than the other categories and did not outnumber all other monitored drugs. This may reflect some benefit of the FDA warnings which focused primarily on this adverse effect.

Nevertheless, a large volume of serious adverse event reports for varenicline continues despite a decline in dispensed prescriptions. The results are shown in Figure 1. This drug has now triggered reports of more than 8500 serious injuries. Figure 1 also challenges the claims that the numbers of reported injuries were mostly inflated by spurts in media publicity about sensational episodes of violence or suicidal behaviors. These data show that over 2 ½ years the flow of reported serious injuries has largely tracked the number of prescriptions dispensed [9] with a steady stream of reports that exceeds that of most other drugs.

Figure 1. Varenicline (Chantix) changes over time.



The evidence shows that the numerous regulatory actions from the FDA and other restrictions have not succeeded in achieving substantially safer use of varenicline beyond a possible effect in reducing dispensed prescriptions. A major reassessment of this drug's place, if any, in a program of treatment to assist in smoking cessation is needed. Its association with reports of violence makes it unsuitable for use in any occupation in which lethal weapons are routinely available and used and poses risks to other sensitive occupations. Patient monitoring and prominent warnings have apparently not been effective in assuring safe use of this medication.

Signal for Levofloxacin (LEVAQUIN)

In the second quarter of 2010 levofloxacin (LEVAQUIN) was the suspect drug in 246 serious adverse event reports. This exceeded any other antibiotic and was more than

double the 2nd ranked antibiotic, the chemically similar ciprofloxacin (CIPRO) with 105 reports. Levofloxacin was even more prominent in the subgroup of cases reported directly to the FDA—rather than being originated by drug manufacturers. In the second quarter levofloxacin ranked 2nd in direct reports to the FDA; in the first quarter of 2010 it ranked first.

Levofloxacin is a fluoroquinolone antibiotic widely used to treat urinary tract infections, pneumonia and skin infections. Other fluoroquinolones include ciprofloxacin and moxifloxacin (AVELOX).

All three fluoroquinolone drugs carry a prominent boxed warning about the risk of tendon inflammation and rupture. These same adverse effects dominated the cases reported in the second quarter for levofloxacin, including 116 cases of tendon disorders, 119 cases mentioning muscle, tendon and ligament injuries and 54 cases specifying limb injuries. (A single case could include mentions of one or more of these terms). Overall, 2 out of 3 reports for levofloxacin indicated an adverse effect on the musculoskeletal system. A comparison of the three drugs is shown in Table 2.

Table 2. Tendon disorders for fluoroquinolone antibiotics 2010q2.

	Levofloxacin	Ciprofloxacin	Moxifloxacin
Total Rx (millions)*	2.1	5.3	1.5
Case Reports	246	105	93
% Direct to FDA	52%	71%	42%
% Health Professionals	53%	59%	76%
Tendon Disorders (HLT)	93	29	10
All Musculoskeletal	156	62	20

*IMS Health National Prescription Audit ™ 2010

These data raise the question of why tendon disorders and joint problems are being reported more frequently for levofloxacin than for moxifloxacin despite approximately similar volumes of dispensed prescriptions. While the FDA required identically worded warnings for all three drugs in information for both doctors and patients, no information was provided about how frequently such events might occur.

These data provide a signal that levofloxacin might have a higher risk of tendon and other musculoskeletal disorders than the two other drugs, or that moxifloxacin may have an advantage as a safer alternative. While we have made as many adjustments as possible to these data, more systematic study is required to further document whether one or more of the fluoroquinolones has significant safety advantages or higher risks.

Johnson & Johnson's Ortho-McNeil subsidiary, which manufactures levofloxacin, noted that caution should be exercised in evaluating spontaneous reports, which can be influenced by multiple factors. The company also noted that levofloxacin has carried a warning about tendonitis and tendon rupture since approval in 1996.

This is another case where a substantial risk of drug treatment is clearly understood to exist, but the magnitude of the risk and differences between chemically similar drugs remains undetermined.

Dronedarone (MULTAQ) Update

The signals for heart failure and rhythm disturbances associated with dronedarone (MULTAQ) continued in the second quarter of 2010. In addition, a new side effect of severe liver injury has been reported and we identified numerous reports of injury in patient groups where the drug was contraindicated. We reported in the November 2010 QuarterWatch on this relatively new drug for patients with irregular heart beats in the atria or small upper pumping chambers of the heart. The FDA approved dronedarone "for the reduction of the risk of cardiovascular hospitalization…" in patients with atrial fibrillation or flutter and additional cardiovascular risk factors. The FDA approved dronedarone in 2009 despite a previous clinical trial in which it had doubled the risk of death in patients with moderate to severe heart failure.

In mid-January 2011 sanofi-aventis and the FDA issued prominent new warnings about reports of severe liver injury, including two cases so severe that liver transplants were required. [26] Since approval, we identified nine reported cases coded as serious and described as hepatocellular damage and injury.

Dronedarone poses clinical challenges to safe use because of numerous drug interactions, risk of birth defects, higher risk of death in patients with moderate or severe heart failure, and effects on electrical conduction in the heart. These risks are codified in a section of the FDA-approved prescribing information called "contraindications." A contraindication describes a patient population, according to FDA regulation, where the drug should not be used because the risks outweigh any potential benefits.[27] Many drugs have either no contraindications, or a single contraindication that the drug should not be given to patients known to be allergic to it. Dronedarone has nine different contraindications. One of the most potentially important of those contraindications was a warning not to use dronedarone with other drugs (or even herbal products) with an effect of slowing electrical conduction in the heart. This prohibition would include most other antiarrhythmic drugs.

Despite this contraindication, we identified 39 cases since approval where patients were seriously injured (including 4 deaths) while taking other contraindicated antiarrhythmic drugs, specifically amiodarone and sotalol. We also found 16 reports of injuries mentioning off label use, 12 cases of drug interactions and 15 cases of dosing or administration error. One case could be listed in more than one category.

In addition, the signal we observed for other effects on the heart continued in the second quarter. For a second quarter dronedarone accounted for more cases of three different heart rhythm disturbances than any other drug we monitor. Those were bradycardia (slow heart beat), ventricular tachycardia (potentially lethal rapid heart beat in the main pumping chamber), and supraventricular tachycardia (rapid, uncontrolled rhythm in the atria or upper pumping chambers). In addition, we identified five new possible cases of kidney failure or impairment. Overall the total number of serious adverse events reported in the quarter declined, 134 cases compared to 155 in the first quarter.

Sanofi-aventis provided us with a statement noting that while a causal relationship between dronedarone and severe liver injury had not been established, the company was urging healthcare providers to inform patients about the symptoms of liver injury and to consider blood tests to detect liver damage.

Johnson & Johnson OTC Products for Infants and Children

We identified 726 case reports of serious injury in infants and children associated with the recall of over-the-counter (OTC) drugs manufactured by Johnson & Johnson's McNeil Consumer Healthcare Division. The products most frequently identified as suspect drug were Children's Motrin (189 cases), Concentrated Tylenol Infant Drops (172 cases), and Children's Tylenol Suspension (121 cases). Overall the McNeil children's product recalls accounted for 726/1323 (55%) of all product quality cases reported in the second quarter.

For three calendar quarters, reports of serious injury linked to product quality problems have been dominated by the massive recall of scores of over-the-counter (OTC) products for infants, children and adults manufactured by the McNeil subsidiary. The first recalls began in September 2009 after an FDA inspection revealed that the raw materials for its liquid products for infants and children might have had bacterial contamination. Recalls were greatly expanded in December 2009 and January 2010 to include Tylenol and other branded OTC products in tablet form. Those recalls were linked to possible contamination of the tablets by a pesticide residue. Then in May 2010 in our current report quarter, McNeil began recalling all liquid Tylenol, Motrin, Zyrtec and Benadryl products. The FDA said the children's products might be contaminated with particles, be overstrength or contain inactive ingredients. [28] The cases we examine here were associated with the May recall.

The 726 McNeil products cases in children included 22 reported deaths, 16 cases classified as life threatening and 213 cases of hospitalization. The average patient was four years old, and 93% of the cases were reported directly by consumers. The medical problems most frequently identified included fevers (170 mentions), nausea and vomiting (113 mentions), and seizures (102 cases). One case could list more than one problem.

Without additional testing of product recovered from those reporting injury it is difficult to interpret these case reports. These data are not detailed enough either to establish or rule out an association of a patient illness with an identifiable contaminant. The illnesses reported do not sound uncommon in young children. The manufacturing quality defects that led to the recall were diverse and not obviously expected to cause a specific form of illness, although particle contamination might trigger nausea, vomiting and possibly seizures. Without independent chemical testing of the specific medicines provided to patients experiencing reported adverse events, it is difficult to assess the role, if any, that the drug played.

Johnson & Johnson's product quality problems have continued. In December 2010 the company announced it was recalling the nation's entire supply of Rolaids, an OTC remedy for heartburn, stomach trouble and gas. The company also suspended

production of Rolaids because of reports of contamination with metal, wood particles and other foreign materials. [29]

Over the past two years we have reported on widespread manufacturing problems that led the FDA to require that entire manufacturing plants be closed; the agency has seized large quantities of substandard products, and hundreds of millions of bottles of medicine have been recalled as defective. In some cases—notably digoxin, propafenone and morphine—the agency classified the quality defects as potentially life threatening. However, we know of no publicly available reports assessing how many—if any—patients were injured or killed by defective medicines in the recent wave of recalls. While we believe that the FDA has increased its enforcement and inspectional programs to improve drug quality, the agency's failure to assess harm among patients reporting injury from recalled drug products remains a major gap in the drug safety system. We have described additional weaknesses in previous reports, notably the failure to disclose the size of product recalls. [30] [31]

Drug Safety Perspectives

This new section of QuarterWatch focuses on medically significant drug safety issues as seen through the adverse drug events being reported to the FDA in the current quarter. In this section we sought to identify what significant drug safety issues were being frequently reported by doctors and patients. Shown in Table 3 are five specific drug safety issues that were reported frequently, were reported disproportionally for the suspect drug, and were unlikely to have occurred by chance. In the table, the Proportional Reporting Ratio (PRR) measures the extent to which the reports of the adverse effect for that drug exceed what might be expected through chance and background noise.

Table 3. Selected drug safety signals 2010 Quarter 2.

Drug Names	Brand Names*	Adverse Effect**	Cases	PRR***	P Value
FENTANYL	DURAGESIC	Maladministrations	447	12.6	< 0.01
QUETIAPINE	SEROQUEL	Diabetes	191	16.5	< 0.01
INFLIXIMAB	REMICADE	Skin cancers	154	101.3	< 0.01
ALENDRONATE	FOSAMAX	Lower limb fracture	126	50.4	< 0.01
EXENATIDE	BYETTA	Inflammation of pancreas	118	32.5	< 0.01

* May have other names **MedDRA high level term

*** Proportional Reporting Ratio

Maladministrations – Fentanyl (DURAGESIC)

Problems with fentanyl patches were one of the most frequently reported drug safety issues in the current quarter, with 447 reports of this problem alone. This potent opioid has long been a high-alert drug. Administering a drug in a fashion that causes serious injury is a safety problem that could potentially occur with almost any drug, and might be a particular problem with a very potent drug administered through a patch. Table 3 shows that maladministration was reported 12.6 times more frequently than expected (PRR), given the total number of reports for the drug. For comparison we could find only 10 case reports indicating maladministration of nicotine products—also widely

used in patch form. A variety of maladministration problems were reported for fentanyl: the product failed to adhere and the patch fell off; it was put at an inappropriate place on the body where absorption could be much greater or less; or was applied on the wrong schedule. These events were classified as serious by the manufacturer or other reporter. With a potent opioid, these seemingly simple patch problems could lead to potentially lethal overdoses or trigger serious withdrawal symptoms in a vulnerable patient population already experiencing moderate to severe persistent pain.

Diabetes and Quetiapine (SEROQUEL)

While all the newer antipsychotic drugs carry a limited warning that that they may cause diabetes, case reports identifying quetiapine (SEROQUEL) as suspect in diabetes greatly outnumbered all other drugs we monitor with 191 cases in the current quarter. This is partly explained by the fact that quetiapine is the most widely used drug in its class by a substantial margin, with 1.5 times more prescriptions dispensed than the second ranked risperidone (RISPERDAL), and three times as many as olanzapine (ZYPREXA). [9] We continue to be concerned that the causal mechanism and incidence rates of diabetes risks for antipsychotic drugs are poorly understood more than 10 years after they were first widely identified, and more widespread glucose monitoring should be recommended for this drug class. AstraZeneca, the manufacturer, has previously told us that it believes diabetes reports may be increased by patients with diabetes filing lawsuits for damages.

Skin Cancer and Infliximab (REMICADE)

This powerful immunosuppressant drug is approved for rheumatoid arthritis, psoriasis, and other disorders linked to the immune system. Many drugs that immobilize important components of the immune system (in this case Tumor Necrosis Factor Alfa) carry an increased risk of infection and cancer. Infliximab (REMICADE) is no exception, and has boxed warnings about increased risks of infection (including tuberculosis) and lymphoma. This cluster of 154 new reports of various non-melanoma skin cancers suggests the possibility of a broader cancer risk and a potential need to monitor patients' skin carefully.

Lower Limb Fracture and Alendronate (FOSAMAX)

In March 2010 scattered reports appeared suggesting a new safety question about alendronate (FOSAMAX) and other bisphosphonate drugs that preserve bone density by slowing the turnover of bone. In postmenopausal women in particular, bone is reabsorbed more quickly than it is created, leading to osteoporosis. The new reports suggested that while bone density was preserved, over time the bones might become more brittle and fracture easily—notably at the hip and upper thigh. The FDA agreed to study the matter while indicating "the data the FDA has reviewed have not shown a clear connection."

In the next three months (the second quarter of 2010 data) the FDA received 126 reports of lower limb fractures associated with alendronate, together with additional but fewer reports for other bisphosphonate drugs.

In October 2010 the FDA announced it was going to require a warning for the possibility of atypical fractures of the thigh. Hedging its bet, the FDA said "Although it is

not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates." [32] In our alendronate data, a lower limb fracture was 50 times more likely to be reported than would be expected for the drug given the total number of reports for all types of possible injury. Alendronate was also associated with 53 possible cases of another bone defect, osteonecrosis of the jaw.

While the FDA announced in October 2010 that new warnings/precautions would be required, as of January 2011 such label changes had yet to be implemented. Merck, manufacturer of the Fosamax brand, told us that lower limb fractures were not a new safety issue, noted that these data did not prove causality, and said the increased reports could be linked to media attention to the issue in 2010.

Inflammation of the Pancreas and Exenatide (BYETTA)

Exenatide (BYETTA) is a twice-daily injected drug for Type 2 diabetes that increases the secretion of insulin by the pancreas. Insulin, in turn, signals the liver, fat cells and muscles to absorb sugar from the bloodstream. In 2007 the FDA issued a public health alert about 30 reported cases of inflamed pancreas, and urged treatment be discontinued if this problem occurred. [33] The FDA updated this warning in August 2008 identifying six additional cases of pancreatitis that could be so severe that cells in the pancreas were destroyed or the organ hemorrhaged. Two of the patients died.

Thus it was a safety concern to observe 118 cases of acute and chronic pancreatitis reported in the second quarter of 2010 alone. Our data showed that this medical disorder was reported for exenatide 32.5 times more frequently that would be expected. We also observed a signal for a second adverse effect of exenatide: 31 cases of renal failure or impairment.

Amylin Pharmaceuticals and Eli Lilly, which manufacture and market Byetta, told us they observed increased numbers of cases reported following the two FDA alerts, but said "Pancreatitis remains a rare event in post market reporting."

It is important that physicians and patients be alert to the symptoms of pancreatitis: nausea, vomiting and abdominal pain. Furthermore, we believe these signals are of sufficient concern to require more systematic study of the incidence of this drug's adverse effects on the pancreas and kidneys. Given that tangible health benefits for all treatments for Type 2 diabetes are poorly documented and would require years of treatment to measure, even relatively low rates of serious adverse effects could outweigh benefits.

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