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

QuarterWatch: 2010 Quarter 1

Monitoring MedWatch Reports

November 4, 2010

Signals for Acetaminophen, Dronedarone and Botulinum Toxin Products

Executive Summary

In a review of MedWatch reports received by the Food and Drug Administration in the first quarter of 2010 we identified four signals of potential drug safety problems. These included safety signals for products containing acetaminophen, potential safety concerns about a new heart drug dronedarone (MULTAQ), and increased reports of complications for botulinum toxin products (BOTOX, BOTOX Cosmetic, DYSPORT).

Overall, the FDA received domestic adverse event reports of 33,046 cases of serious injury, disability and death associated with drug therapy in the first quarter of 2010. This is an increase of 11% over the previous quarter and 19% over the same quarter in 2009. Reports have increased at a substantial pace with both serious injuries and deaths reaching new highs. These reports are either originated by drug manufacturers or submitted directly to the FDA's MedWatch Safety Information and Adverse Event Reporting Program, but are better known to the public and health profession as MedWatch reports.

The Johnson & Johnson recall of dozens of over-the-counter (OTC) products spurred 492 reports of serious injury associated with its recalled Tylenol products, including cases involving hospitalization and reported patient deaths. A direct link between these numerous reports and the contaminated Tylenol products could not be established or ruled out from these data alone and require further investigation.

The patient deaths reported to the FDA in the first quarter of 2010 also included an entire year's data for drug overdose deaths investigated and documented by the American Association of Poison Control Centers in the medical journal *Clinical Toxicology*. Drug manufacturers extracted and submitted these same cases as adverse events for the FDA, but we discovered the original source data were more accurate and we analyzed them independently for this report. Acetaminophen products were again prominent, accounting for 26.1% of all fatal overdose cases, with 55% of these cases OTC products and the remainder prescription combinations with narcotics. A large majority of deaths for acetaminophen and the other drugs were classified as intentional overdoses.

Specific Drugs

- **Dronedarone (MULTAQ)** is a recently approved drug for patients with a form of irregular heartbeats called atrial fibrillation and flutter. Since August 2009 the FDA received increasing numbers of reports indicating the drug may cause or worsen heart failure, trigger potentially lethal irregular heartbeats, interact with other drugs, and impair kidney function.

- **Botulinum Nerve Toxins (BOTOX, DYSPORT).** We identified four safety issues with these drugs which are approved to reduce wrinkles on the forehead by paralyzing some of the underlying muscles, and for certain other purposes. First, we observed increasing reports that the nerve toxin was paralyzing muscles distant from the intended sites, causing difficulty swallowing, incontinence and breathing problems. Second, we question potentially misleading safety claims that distant site adverse effects have not been reported for FDA-approved cosmetic uses. Also, these drugs have been given new and difficult to read chemical names, creating additional confusion about their safe use. Finally, evidence mounted of extensive off-label use of Botox products.

FDA Adverse Event Reporting System Issues

- **Alprazolam (XANAX, NIRAVAM, generics),** a generic and brand name benzodiazepine tranquilizer, suddenly escalated to the top with 473 reported patient deaths in the first quarter of 2010. We investigated this signal and determined it was a false alarm. The sudden spike in patient deaths occurred because four different pharmaceutical companies with alprazolam products had each reported more than 100 cases extracted from the poison center journal report noted above. Alprazolam was a primary suspect drug in only 13 deaths listed in the report. In 96 other cases, the four drug companies filed multiple reports of patient deaths because alprazolam was on the list of drugs being taken by an individual who died of a drug overdose but alprazolam was not ranked as the primary cause.

- **Palivizumab (SYNAGIS).** A surge in reported infant deaths and other serious injuries associated with this treatment to reduce the risk of respiratory syncytial virus (RSV) was traced to a reporting issue by the manufacturer, MedImmune. The company began electronically filing reports on behalf of its marketing partners abroad, and erroneously coded the country of origin as the United States because MedImmune, the company that prepared the reports, is located in the United States.

- **Missing Age Data.** The FDA investigated our prior report that patient age data was being omitted from thousands of case reports each quarter. A technical problem was identified in the FDA software that converted the patient's date of birth into calendar years for the public release data.

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 through the 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. This occurs in part because these spontaneous reports are capable of identifying rare but important side effects that were overlooked or not detected in testing prior to FDA approval. 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. While we rely on FDA data, and in this issue also data from the American Association of Poison Control Centers, the analysis and conclusions in this report are entirely our own.

Conclusions

The FDA needs to coordinate an extensive patient education program about the potentially fatal overdose risks of acetaminophen products as well as the importance of immediate medical treatment should an overdose occur. Given the large Tylenol product recall, a newly discovered form of contamination, and so many adverse event reports, we believe the FDA should insure that a complete and objective scientific investigation is conducted, and that the complete results are made public.

Evidence is accumulating that the risks of the new heart drug dronedarone have been underestimated, and its clinical benefits are limited. New adverse event reports that the drug may cause or worsen heart failure, trigger irregular heartbeats, and interact with other drugs frequently taken by heart patients raise serious doubts about its suitability for widespread use.

We also identify two additional cases where the FDA-approved Medication Guides for patients contain risk information that downplays what is known about the risks of the drug. We discuss the examples—the pregnancy risks of dronedarone and the safety claims for Botox Cosmetic—in the full report.

In this quarter we identified two issues involving the reliability of drug-associated fatality information in the FDA's AERS data. In one case, events occurring abroad were coded with the United States as a country of origin because the reports were *prepared* here, rather than because the events *occurred* here. We believe this was not an isolated case, and that reporting guidelines should be clarified. In addition, the FDA system was flooded with duplicated adverse event report deaths extracted from the same annual report in the literature. The agency needs to design and implement a new guideline for handling literature reports that incorporate multiple cases.

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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 are specifically identified as being associated with a legal claim for damages.

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 are 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 12.1.

The QuarterWatch results 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 maintains regular contact with all patients to deliver product or monitor care, and therefore maintains regular surveillance of the entire 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 and list the brand names separately. We group together insulins and estrogens because of a large number of similar products, together with incomplete product names in many case reports.

While the QuarterWatch criteria do evolve over time, this report contains no changes in our study methods. However, based on the previous edition of QuarterWatch we added two drugs to the special reporting category, ibandronate (BONIVA) and deferasirox (EXJADE).[5] Because tens of 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

In the first quarter of 2010 the FDA received 18.7% more serious adverse event reports than it did in the same quarter in 2009. The results are summarized in Table 1. Reports from consumers (up 26.8%) grew more rapidly than reports from health professionals (an increase of 12.8%). Reports originate in two different ways: cases reported directly to the FDA's MedWatch information and reporting program, and from drug manufacturers. In the first quarter of 2010, direct reports to the FDA declined slightly from the preceding year (-2.3%), while reports originated by manufacturers increased by 24.6%. The results also illustrate that drug manufacturers dominate the reporting process, accounting for 27,075/33,046 (81.9%) of all serious cases. In addition, the 33,046 cases reported were 11% higher than in the preceding quarter, the fourth quarter of 2009.

Table 1. 2010 Quarter 1 changes from previous year.

	2010 Q1	2009 Q1	Change number, pct	
All Reports	33046	27836	5210	18.72
Report Source				
Consumer	12175	9605	2570	26.76
Health Professional	17147	15197	1950	12.83
Outcome				
Death	7966	5840	2126	36.40
Disability	1129	1116	13	1.16
Other Serious	23951	20880	3071	14.71
Originator				
FDA Direct	5971	6111	-140	-2.29
Manufacturer	27075	21725	5350	24.63

An increase in patient deaths, primarily reported by health professionals, accounts for the largest share of the increase from the same quarter in the previous year. One substantial reason for that increase is discussed in the next section.

Alprazolam Reports of Patient Deaths

In the first quarter of 2010 alprazolam (XANAX, NIRAVAM, generics) ranked first among all drugs we monitored with 473 reported patient deaths. A benzodiazepine tranquilizer indicated for anxiety and panic disorders, alprazolam is widely available as both a generic and brand name product, and in extended-release formulations. In the last three quarters of 2009 alprazolam had accounted for 15, 8, and 10 reported patient deaths, a marked contrast with 473 cases in the first quarter of 2010.

The sudden spike in patient deaths occurred because four different pharmaceutical companies with alprazolam products had each reported more than 100 cases extracted from one annual report published in the medical literature by the American Association of Poison Control Centers. [6] After evaluating the source document and contacting two of the four reporting companies, we determined that alprazolam was a primary suspect drug in only 13 deaths listed in the literature report. In 96 other cases, the four drug companies filed multiple reports of patient deaths because alprazolam was on the list of drugs being taken by an individual who died of a drug overdose; however, alprazolam was not the first ranked or primary cause. The source document for the alprazolam reports provided valuable insights into a particular class of adverse drug events—intentional or accidental overdoses that lead to death.

Overdose Deaths Examined

Acetaminophen products emerged as an important cause of overdose deaths when we analyzed the poison control center data directly to eliminate the multiple reports of the same data from manufacturers.

The American Association of Poison Control Centers publishes an annual report of data from its 60 centers in the journal *Clinical Toxicology.* [6] Poison control centers are staffed with physicians, nurses and pharmacists to provide information and assistance to consumers and medical professionals about all forms of poisonings. The association also evaluates and reports on all patient deaths from poisonings of which it learns. In its most recent report—covering cases in 2008—the centers evaluated 1,315 poisoning deaths, identifying a first-ranked or primary suspect, and also listing all other substances detected. While fatal poisoning cases included household products such as drain cleaner, hair spray, and antifreeze, identifiable prescription drugs were primary suspects in 972/1,315 (73.9%) of fatal exposures.

For this report we analyzed the poison control centers data using QuarterWatch criteria. The resulting rankings and conclusions do not represent the views of the American Association of Poison Control Centers. Since pharmaceutical products—unlike antifreeze—are intended for human consumption at recommended doses we classified all poisoning deaths as overdoses. We limited our analysis to over-the-counter

and prescription pharmaceutical products, excluding other poisons and street drugs, and classified as primary suspect the first-ranked substance in each case.

Types of Drug Overdoses

Among the 972 fatalities investigated, 774 cases (79.6%) were classified as intentional overdoses; the remaining 198 cases (20.4%) were unknown, a result of therapeutic error, or an adverse drug event. Among the cases classified as intentional, 552/774 (71.3%) were classified as suicide; the remaining cases were associated with drug abuse or uncertain specific motivation. Table 2 lists the 15 most frequently named drug products for all overdose cases.

Table 2. Most frequent primary suspect drugs in overdose deaths

Drug Name	Deaths	Rank
ACETAMINOPHEN	115	1
ACETAMINOPHEN/HYDROCODONE	76	2
METHADONE	75	3
OXYCODONE	61	4
SALICYLATE*	49	5
MORPHINE	34	6
FENTANYL TRANSDERMAL	31	7
ACETAMINOPHEN/DIPHENHYDRAMINE	25	8
QUETIAPINE	24	9
BUPROPION	21	10
VERAPAMIL	20	11
DILTIAZEM	16	12
AMITRIPTYLINE	16	13
ACETAMINOPHEN/OXYCODONE	16	14
CARDIAC GLYCOSIDE**	15	15

* Aspirin and similar drugs.

**Digoxin and similar drugs

The 15 most frequently identified drugs in overdose deaths accounted for 61.1% of all pharmaceutical product cases. This follows a pattern seen in many other categories of adverse drug events, namely that a relatively small number of drugs account for a disproportionate share of reported events.

Acetaminophen products accounted for 254/972 (26.1%) overdose deaths, more than any other drug group. (This includes acetaminophen combinations not shown in Table 2.) This combined total included 140 cases of OTC acetaminophen or OTC combinations (55%) and 114 cases of prescription combinations with opioids (45%). OTC acetaminophen also led every subcategory: first overall (100 cases), first in intentional overdose cases (95 cases), first in accidental or unknown deaths (23 cases) and first in fatal therapeutic errors (5 cases). The principal hazard of acetaminophen is that it is capable of destroying the liver at about 2.5 times the daily dose, and in some cases smaller doses. [7] A published FDA study estimated that acetaminophen causes an

estimated 56,000 emergency room visits, 26,000 hospitalizations and more than 450 deaths each year. [8] Another published FDA/CDC study ranked acetaminophen products first among all painkillers in emergency department visits, after adjusting for the frequency of use. [9]

Methadone, ranked 3rd , is a powerful but slow acting, longer lasting opioid used in the treatment of drug abuse to replace other opioids, and for chronic pain. The slow onset of action—and once-a-day dosing—avoids the altered moods created by heroin and faster acting narcotics. However, methadone shares with other opioids a substantial risk of causing respiratory arrest with overdose, [10(p583)] and it is a leading cause of drug abuse/overdose deaths.[11]

The poison control center data have particular strengths and weaknesses. The data are systematic and of high quality, with each case reviewed by toxicologists and other experts. However, only a small proportion of overdose deaths that occur are represented in these data, with one recent estimate indicating the data captured about 3.5% of all poisoning fatalities, including those caused by non-pharmaceutical products. [12] As with adverse event reports, the reporting rate could differ for different drugs, and the number of people exposed to each drug also varies widely.

Tylenol Dominates Product Problems

The FDA received 1,066 reports of serous injury associated with product problems with all drugs in the first quarter of 2010. The biggest group, 492/1,066 (46.1%), identified various Tylenol products sold over the counter, primarily in tablet or caplet form. The company recalled large amounts of liquid Tylenol products for infants and children in September 2009 and then began an even larger recall of tablet and caplet products in January 2010. The FDA traced the tablet/caplet recalls to possible contamination with a pesticide called 2,4,6-Tribromoanisole (TBA) which had gotten into the air in a manufacturing plant from wood pallets on which empty bottles had been delivered. [13]

Previous FDA reports—based on earlier data—suggested that no serious injuries had occurred from the contaminated tablets although an FDA official described "non-serious" reports of nausea, stomach pain, vomiting and diarrhea.

In the first quarter data we identified 209 reported cases for Tylenol products that had an explicitly serious health outcome, as defined by FDA. These included 172 cases with an outcome of hospitalization, 28 reports of deaths, 3 cases indicating disability, and 3 described as life threatening. The medical terms describing these serious events included diarrhea (73 mentions), vomiting (68 mentions), nausea (58 mentions) and abdominal pain (41 mentions).

In seven of the fatal cases an association with Tylenol looked possible or probable and should be the focus of additional investigation. In 11 of 28 cases with an outcome of death, the patients were older—from 75 to 91 years old—and may have had complicating

illnesses. Ten other reported deaths contained so little detail it was difficult to evaluate the role of the drug. One case suggested intentional drug misuse.

We contacted the McNeil Consumer Healthcare division of Johnson & Johnson for an update on what had been learned since the January 2010 recall. The company told us that it had analyzed samples of the returned Tylenol products and had detected small quantities of the TBA contaminant. The company also said it had conducted early animal toxicity studies that persuaded the company that quantities of contaminant detected were too minute to be capable of causing human illness. On this basis, the company concluded that none of the reported events were likely to have been caused by the contamination. Therefore, the company believed that the media publicity about the recall and likely symptoms caused consumers to blame the drug when the gastrointestinal illness might have had other causes. However, the company had not made public the studies it believed supported these conclusions, nor could we learn how the reported cases were investigated.

While a direct causal link between these reports and the contamination cannot be established from these data alone, at least three other plausible explanations might account for these cases. First, some people might be unusually sensitive to the TBA pesticide contaminant. Second, some tablets might have contained unusually large concentrations of the pesticide. Finally, given the known manufacturing quality problems, other contamination beside TBA could also have played a role.

Given such a large product recall, a newly discovered form of contamination, and so many adverse event reports, we believe the FDA should insure that a complete and objective scientific investigation is conducted, and that the complete results are made public.

Signals for Dronedarone (MULTAQ)

We investigated three different potential safety issues for a recently approved heart drug, dronedarone (MULTAQ), marketed by sanofi-aventis.[*] We identified reports suggesting that dronedarone may cause new or worsened heart failure, that it might trigger or worsen existing irregular heart rhythm, and might have adverse effects on the kidneys.

In 2009 the FDA approved dronedarone "to reduce the risk of cardiovascular hospitalization" in patients who have episodes of irregular heart rhythms in the two atria or small upper pumping chambers of the heart.[14] The two atria or upper chambers function as small primer pumps for the two main pumping chambers of the heart, the left and right ventricles. In atrial fibrillation and atrial flutter, the upper pumping chambers become electrically disorganized and fail to contract. Losing the primer pump effect reduces the efficiency of the main pumping chambers. While a significant medical problem, it is markedly less severe than when this occurs in the left ventricle or main

[*] This company does not capitalize its proper name.

pumping chamber. Ventricular fibrillation is immediately life threatening and leads to death unless quickly reversed by medical intervention—typically the familiar shocks administered to the chest by defibrillators. Approximately 3 million people have the less severe rhythm disturbance in the atria.[15] It can occur not only in patients with weakened hearts because of a heart attack or other problem, but also in otherwise healthy patients. Atrial flutter and fibrillation can occur in episodes that resolve spontaneously or with medical intervention, or be persistent.

Dronedarone already had a troubling safety profile when the FDA approved the drug. Development of dronedarone had been halted in 2005 after a clinical trial ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe CHF Evaluating Morbidity) in patients with severe heart failure had to be stopped because the drug doubled the risk of death. Within a 2 month time period, 25 deaths occurred in the dronedarone group (310 patients) compared to 12 deaths in the placebo group (317 participants)—8.1 % vs 3.8 %÷ (P=0.027) [16] There were also excess hospitalizations for cardiovascular reasons in the dronedarone group (71 vs 51 for placebo). The agency concluded that dronedarone could worsen existing heart failure but allowed sanofi-aventis to continue a large clinical trial in healthier patients who did not have heart failure. The second trial in this healthier population (conducted primarily in Russia and the United States) showed treatment reduced cardiovascular hospitalizations by 24% but had no statistically significant effect on mortality. [17]

Dronedarone had numerous other safety problems revealed in testing prior to FDA approval. Animal testing produced a convincing signal of cancer risk, with the agency concluding "dronedarone appears to be a carcinogen in both mice and rats." [18] It caused frequent birth defects in rats and rabbits—in the case of rabbits at only one-half the recommended human dose. [14]

Dronedarone has another major safety issue. It interacts with many, many different drugs, including drugs frequently taken by heart patients and especially patients with atrial flutter or fibrillation. [16] It interacts powerfully with digoxin, another treatment for atrial flutter and fibrillation, and warfarin, a blood thinner frequently prescribed for patients with this condition. Dronedarone also interacts with cholesterol lowering drugs, beta blockers and many antidepressants. It interacts with foods, especially grapefruit juice. The interactions with digoxin and warfarin are of particular importance because these drugs are widely used in this patient population and a relatively small overdose of either drug can be toxic.

The drug has two other safety problems. Dronedarone can slow the time it takes for the electrical impulse to contract to spread across the heart muscle, in medical terms prolong the Q-T interval. [14] In some patients, this effect can trigger ventricular fibrillation, a rapidly fatal electrical breakdown of the main pumping chamber of the heart. The effect of dronedarone on kidney function is more complex. Treatment increased a common laboratory test marker—creatinine—which normally suggests impaired kidney function. The company maintained that dronedarone did affect the kidney's processing of creatinine but did not otherwise reduce kidney function. [19]

Opposite this array of adverse effects, dronedarone showed a modest ability to prevent the recurrence of atrial fibrillation and flutter. The drug prevented the recurrence in 11% patients compared to patients receiving a placebo. In the review of the results from this study, the FDA medical reviewers concluded "there is very little benefit to be gained from this drug." [16(p4)] Dronedarone was also markedly less effective than amiodarone—a chemically similar generic drug with many similar safety drawbacks. [20]

Signals in Adverse Drug Events

Since approval, we identified 387 domestic serious adverse events naming dronedarone as the primary suspect drug. The outcomes included 24 deaths, 2 cases of disability, and 361 other serious adverse events. Health professionals accounted for 295 (76.2%) the reports. Overall 100 cases (25.8%) indicated new or worsened heart failure. This was of concern given that worsened heart failure was identified as the reason for increased mortality in the company's trial in heart failure patients; the current prescribing information cautions doctors to consider discontinuing or suspending the drug if heart failure develops. Heart rhythm disturbances were also reported, including 18 potential case of bradycardia (abnormally slow heartbeat), 47 cases of atrial tachycardia (or rapid heartbeat), and 13 cases of ventricular tachycardia. The original signal for dronedarone was our discovery that, in the first quarter of 2010, dronedarone accounted for more reported cases of these kinds of rhythm disturbances than any other drug we monitor. We also identified 33 case reports suggesting that dronedarone was interacting with warfarin and increasing its effect.

In addition we identified 15 cases of kidney failure or impairment, including 4 cases of acute kidney failure. The computer excerpts did not provide sufficient detail to fully evaluate these cases—which could be complex. Heart failure—which is a clinically significant decline in cardiac output—can trigger kidney failure absent any direct toxic effect of the drug. In addition, dronedarone is capable of significantly increasing the levels of cholesterol lowering drugs, which carry an increased risk of kidney failure, especially in high doses. In addition, an adverse effect on the kidneys could have been underestimated in clinical testing.

We discussed the adverse event cases with sanofi-aventis. The company said it believed that some studies showed that the reporting rate for adverse drug events may be higher during the first two years after introduction. The company also noted that the FDA was itself evaluating at least two signals in the adverse event reports for dronedarone—heart failure and Torsades de Points (a form of potentially lethal heart rhythm disturbance of the left ventricle).

We also identified a serious lapse in the Medication Guide which explains dronedarone risks to patients. Based on animal studies, dronedarone is a teratogen, meaning it caused birth defects. With these findings and other data, the FDA classified the drug as pregnancy Category X, meaning "The risk of this drug in pregnant women clearly outweighs any possible benefit." [21] In addition the drug is contraindicated, meaning that both the FDA and the manufacturer state the drug should not be used in pregnant women. Despite this unequivocal determination, the Medication Guide for patients states:

It is not known if MULTAQ will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.

This statement is misleading and should be immediately revised to reflect the scientific information that is known about the drug's risks to women who might become pregnant. We raised this issue with sanofi-aventis, which told us the company believed the current wording was appropriate.

We have seldom seen a drug with so many issues in so many areas of its safety profile. It caused cancer and birth defects in animals, has potentially serious interactions with other important drugs for atrial fibrillation, may cause or worsen heart failure, causes new heart rhythm disturbances in some patients and doubled mortality in patients with severe heart failure. In the only head-to-head trial with an existing treatment, dronedarone was markedly less effective than amiodarone and did not demonstrate any statistically significant safety advantage.

Botulinum Toxin Products (BOTOX, DYSPORT)

In the first quarter of 2010 we observed a marked increase in serious, disabling and fatal reports associated with this powerful nerve toxin injection. Botulinum products are FDA approved to reduce the furrows in the forehead by paralyzing the facial muscles that control that area, and for dealing with uncontrolled muscle spasms elsewhere. Most reports showed that the nerve toxin had spread to distant sites and were causing difficulty swallowing, incontinence and muscle weakness. These reports also raised questions about safety claims made for Botox products.

Botulinum toxin—normally produced by the bacterium, clostridium botulinum—is one of the most potent paralytic agents known to science. One billionth of a gram is a lethal dose. [22(p1226)] It occupies the junction where nerves join muscles and blocks the signals to contract, an effect that lasts weeks to months. The toxin is packaged and approved in three closely related drugs with a confusing set of similar names. OnabotulinumtoxinA (BOTOX) is approved to relieve certain uncontrollable muscle contractions, and to reduce severe sweating in the armpits. BOTOX Cosmetic (also onabotulinumtoxinA but a different preparation) is approved to improve the appearance of eyebrow furrows or frown lines. Finally abobotulinumtoxinA (DYSPORT) is approved for the same cosmetic use on the face and to relieve persistent muscle spasms in the back. (A third botulinum toxin product, rimabotulinumtoxinB (MYOBLOC), was not evaluated.)

Botulinum toxin products are widely used off label. Allergan, the manufacturer of the Botox products, pleaded guilty in September 2010 to illegal off-label promotion of Botox and agreed to pay $600 million in criminal fines and penalties. The U.S. Justice Department said Allergan illegally promoted Botox for pain and headaches.[23] The department said Allergan held workshops and sponsored dinners to promote off-label use and taught doctors how to obtain reimbursement. In addition, a random survey of websites showed that at least some dermatologists were offering off-label uses of Botox

Cosmetic for other areas of the face, notably crow's feet around the eyes. Physicians are not required to limit the use of drugs to FDA approved medical uses, but companies may not promote drugs for unapproved uses.

In the first quarter of 2010 we identified 6 reported deaths, 18 cases of disability and 100 other reports of serious injury associated with botulinum toxin products. The case total of 124 reports for the quarter was markedly higher than previous quarters, which typically had 30-50 cases and zero or one patient death. For comparison, we monitored 862 drugs in the first quarter with a median of 7 cases per drug. Only 43 other drugs had more reported cases of death, disability or serious injury.

The adverse event reports were dominated by cases indicating that the nerve toxin was paralyzing distant sites. We identified 41 mentions of unspecified muscle weakness, 36 cases with terms indicating difficulty swallowing, and 11 mentions of difficulty breathing. Because the drug effect is persistent, these side effects may continue for weeks or months. The FDA mandated warning notes that swallowing and breathing difficulties may be life-threatening. [24]

Among the reported cases, 79 cases (63.7%) were for Botox, 26 (21%) were for Botox Cosmetic, 17 (13.7%) cases involved Dysport and, in 2 cases, the brand name product could not be determined.

A Potentially Misleading Safety Claim

These data suggest that the FDA may have allowed an inappropriate and potentially misleading safety claim for Botox Cosmetic products.

The Medication Guide for patients states: [25]

> *There has not been a confirmed serious case of spread toxin effect away from the injection site when…Botox Cosmetic has been used at the recommended dose to treat frown lines.*

The prescribing information for doctors states: [25]

> *No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of Botox/Botox Cosmetic at the labeled dose of 20 units (for glabellar lines)...have been reported…*

These statements raise multiple safety issues. First, they might lead doctors and patients to ignore or discount the dire safety warnings that appear elsewhere in the Medication Guide or prescribing information. The information for doctors has the most severe warning the agency uses, a boxed warning, to caution doctors about potentially fatal distant spread of toxin effects. A prominent warning in the Medication Guide informs patients of "problems swallowing, speaking or breathing" that can be fatal.

Yet the agency allowed the claim (which can be used in advertising) that no "confirmed" or "definitive" cases have been "reported." This undermines and neutralizes

the FDA warnings. Why is the agency requiring these dire safety warnings if no cases have been reported when the drug is used according to its approved indication?

This safety claim can be overtaken by new reports at any time. Also, in a voluntary reporting system these events could be occurring but not reported. The unusual term "definitive" was not defined and no information was provided about whether less than definitive reports were further investigated or merely excluded.

In addition, the FDA should not join manufacturers in a blanket claim of this type stating that certain kinds of cases have never been reported. If the company has conducted a scientifically sound safety study, the FDA should evaluate it and allow its findings to be summarized with proper qualifications, as it does for practically all other claims.

Another problem occurs because the safety claim appears to be carefully qualified to cover only "definitive" reports when Botox Cosmetic was used at the recommended dose for the fairly narrow approved purpose: furrows or frown lines on the forehead. Yet Allergan recently paid $600 million in criminal fines and damages for promoting Botox for off-label use. If the company had "definitive" cases of distant toxin spread that were from off-label use, then the company should have warned that off-label use could lead to this adverse effect, rather than illegally promoting it.

Finally, we are not convinced the safety claim for Botox products is accurate. We identified numerous cases of difficulty breathing, difficulty swallowing and muscle weakness in case reports identifying the Botox Cosmetic product as the primary suspect drug. We don't know what a "definitive" report is, and it is conceivable that all of the cases were off-label use. It is likely that risks of distant spread of toxin effect are lower when injected into the eyebrows than when used elsewhere in the body. If there is valid scientific evidence of that fact, it would be appropriate to summarize it.

We shared our findings and concerns with Allergan, manufacturer of the two Botox products. Allergan told us it was the FDA that made the statement that no definitive cases of distant spread of toxin had been reported when the product was used for furrow lines on the forehead at the recommended dose. In addition, the company said it had reviewed adverse event reports received since April 2009 and found "no new information that would indicate a safety signal."

Names Confusion Made Worse

The FDA, in its August 2009 safety review of botulinum toxin products, appears to have made a bad matter worse in a new scheme for renaming them. The products were previously named Botulinum Toxin Type A (Botox, Botox Cosmetic, Dysport) and Botulinum Toxin Type B (Myobloc). Their new names are shown in Table 4. None of the products are interchangeable in terms of dosages and administration. Myobloc is approved only for cervical dystonia, a rare condition in which muscle spasms hold the head and neck in painful abnormal positions.

Table 4. Botulinum toxin product names

New Name	Old Name	Brand Name
OnabotulinumtoxinA	Botulinum Toxin Type A	Botox, Botox Cosmetic
AbobotulinumtoxinA	Botulinum Toxin Type A	Dysport
RimabotulinumtoxinB	Botulinum Toxin Type B	Myobloc

We believe these 18 and 19 character new names are unreadable in their current form and may utilize more character spaces than are currently available in computer databases used for prescribing medications. This could lead to even more confusion than previously existed. We recommend the FDA and the manufacturers develop better drug name terminology for these products.

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