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

QuarterWatch: 2009 Quarter 4

Monitoring MedWatch Reports

Reported Patient Deaths Increased by 14% in 2009

June 17, 2010

Executive Summary

In 2009, the U.S. Food and Drug Administration received 19,551 reports of patient deaths associated with drug therapy, a 14% increase compared to the previous year and a 3-fold increase over the past decade.

QuarterWatch ™ monitors all serious, domestic adverse drug event reports received by the FDA through its MedWatch drug safety information program and from manufacturers. The U.S. system for postmarketing safety relies on voluntary reports from consumers, health professionals and others.

We investigated this striking increase in reported patient deaths and found at least three factors contributed:

- **Increased awareness**. Reported deaths increased for some drugs because FDA warnings, product recall notices, new medical studies and media publicity alerted more patients and doctors, who therefore reported the suspect event in increased numbers. We describe this as exposing a greater portion of the iceberg.

- **Known risks continue unabated**. Some high alert drugs—notably the most powerful opioid narcotics and acetaminophen/narcotic combinations—have been associated with patient deaths for many years, and this total has not been reduced. This indicates little or no progress has been made managing the risks of these important but inherently difficult to use drugs.

- **Company direct-to-consumer contacts caused a reporting problem**. Drug companies are in increasingly close contact with their individual patient customers. They enroll them in reminder and information programs; increasingly provide drugs directly to patients rather than through pharmacies; and distribute a growing number of drugs through special restricted programs that collect information from all patients. When treatment is discontinued because the patient dies, many companies report this as an adverse drug event even if no relationship to drug treatment was suspected by anyone.

Specific Drug Examples

- **Rosiglitazone (AVANDIA)** is a prime example of a situation where a growing total of reported patient deaths is the likely result of increased awareness of drug risks. In 2009 this drug for Type 2 diabetes accounted for 1,354 reported patient deaths, more than any other prescription drug. We attribute this large total in part to FDA warnings, medical studies and publicity about rosiglitizone's increasing the risk of cardiac events.

- **Fentanyl (DURAGESIC, FENTORA, ACTIQ, ONSOLIS, SUBLIMAZE)** is a powerful synthetic narcotic that provides an example of continued problems with an important but high alert drug. In 2009 fentanyl products accounted for 397 reported patient deaths, ranked 4th among all drugs. In the main report we also examine non-fatal reports of product problems.

- **Ibandronate (BONIVA),** a once-a-month drug for osteoporosis, is a case where a company consumer outreach program generated numerous reports of patient deaths in which the drug was not identified as a suspect. The company sent monthly reminders to hundreds of thousands of mostly-elderly patients. If a postcard was returned "addressee deceased" the company reported it as an adverse event, accounting for 85-90% of the 250 deaths reported in 2009.

Other Trends Over Time

- **Results for 2009, Q4**. In the final quarter of 2009 the FDA received 29,672 domestic reports of serious, disabling or fatal adverse drug events, an increase of 16% over the same quarter in the previous year and 1.6% higher than the previous quarter.

- **All serious events full year results.** For 2009 the FDA received 116,174 reports of adverse drug events meeting the QuarterWatch criteria. This total was 10% higher than 2008 and 2.8 times higher than for the year 2000.

- **Patient deaths full year results.** The total for 2009 above included 19,551 reports of patient deaths, compared to 17,144 cases in 2008, a 14% increase and 6449 cases in 2000, a 3-fold increase.

Tylenol Product Problems

Johnson & Johnson has recalled at least 120 million packages of Tylenol brand acetaminophen for infants and children after FDA inspections disclosed evidence of bacterial contamination of raw materials. We identified more than 400 reported adverse events for these products, including 64 cases involving hospitalization. These reports were difficult to interpret and the health impact of the company's quality assurance breakdown remains unknown.

FDA Adverse Event Reporting System

The FDA should evaluate and improve the existing guidelines for manufacturer reporting of adverse drug events to reflect the numerous new ways that drug companies acquire information about possible adverse events. The FDA needs more detailed information from manufacturers about the report source—now usually limited to the report source's occupation. Cases obtained from restricted distribution programs, from active surveillance of internet blogs and the news media, or from prescription cancellations because of death could be clearly identified in the report source field. Enriching this source information would enable more accurate and valid comparisons between drugs, and better overall assessment of trends in reported adverse events.

About QuarterWatch Data

Our findings should be interpreted in the context of the known limitations of a voluntary adverse event reporting system. 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, depending on the details of a given report and the number of reports received, adverse event data may have substantial scientific weight in a broader assessment of causality. A substantial fraction of all new warnings, restrictions or other actions to manage the risks are based on these data. The reporting rate for the system is unknown, and published estimates range from around 1% to 15% in most cases, and up to 30% in unusual cases of enhanced reporting. [1] [2] We have observed wide variations among specific drugs, for different kinds of adverse events, and over different time periods.

CONCLUSIONS

The total of 19,551 reported patient deaths in 2009 is large by any measure, even without adjustment for underreporting. For the most recent year available, 2007, the National Center for Health Statistics reported 17,520 deaths by homicide, 33,185 deaths by suicide and 42,031 deaths from motor vehicle accidents.[3] These are only crude comparisons since a reported death associated with drug therapy might officially be classified as a heart attack, cancer, a suicide or some other medical cause.

Other risks of serious injury and death in our society are monitored carefully and in depth. These risks include crime, air travel, railroads, motor vehicle accidents, and workplace safety. But as far as we know, the ISMP QuarterWatch project is the only ongoing assessment of the risks of drug therapy. And our effort is subject to substantial limitations which we take care to disclose fully.

The number of patient deaths associated with drug therapy ought to be declining because of safer drugs and better programs to understand and manage their known risks. That trend seems unlikely to occur until we develop better measures of drug risks and learn more about which drugs are implicated and the types of reactions they most frequently cause. QuarterWatch remains a down payment on a major unfulfilled task ahead.

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METHODOLOGY

The goal of the QuarterWatch project is to improve patient safety through regular monitoring of all serious adverse drug events reported to the FDA. While the agency does not publish a regular analysis of the reports it receives, the FDA releases computer excerpts for research use on a quarterly basis. [4]

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 or a birth defect, required hospitalization, was 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 a standard ingredient name based on the National Library of Medicine RxNorm project. [5] When case reports are revised or updated we use the most recent version while retaining the original report date. We exclude cases identifying drugs that have been previously withdrawn, or that are specifically identified as being associated with a legal claim for damages.

The results include a special category of drugs with reporting requirements or procedures that are more rigorous than those for other drugs, resulting in much higher reporting rate. For example, thalidomide and lenalidomide are restricted use drugs with a special adverse event reporting program. In other cases the manufacturer retains regular contact with all patients to deliver product or monitor care, and therefore maintains surveillance of the entire patient population. Finally, we group together certain drugs—notably estrogen and insulin products—and list the brand names separately. We examine and rank special reporting drugs separately.

While the QuarterWatch criteria do evolve over time, they remain unchanged in this report. However, 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.

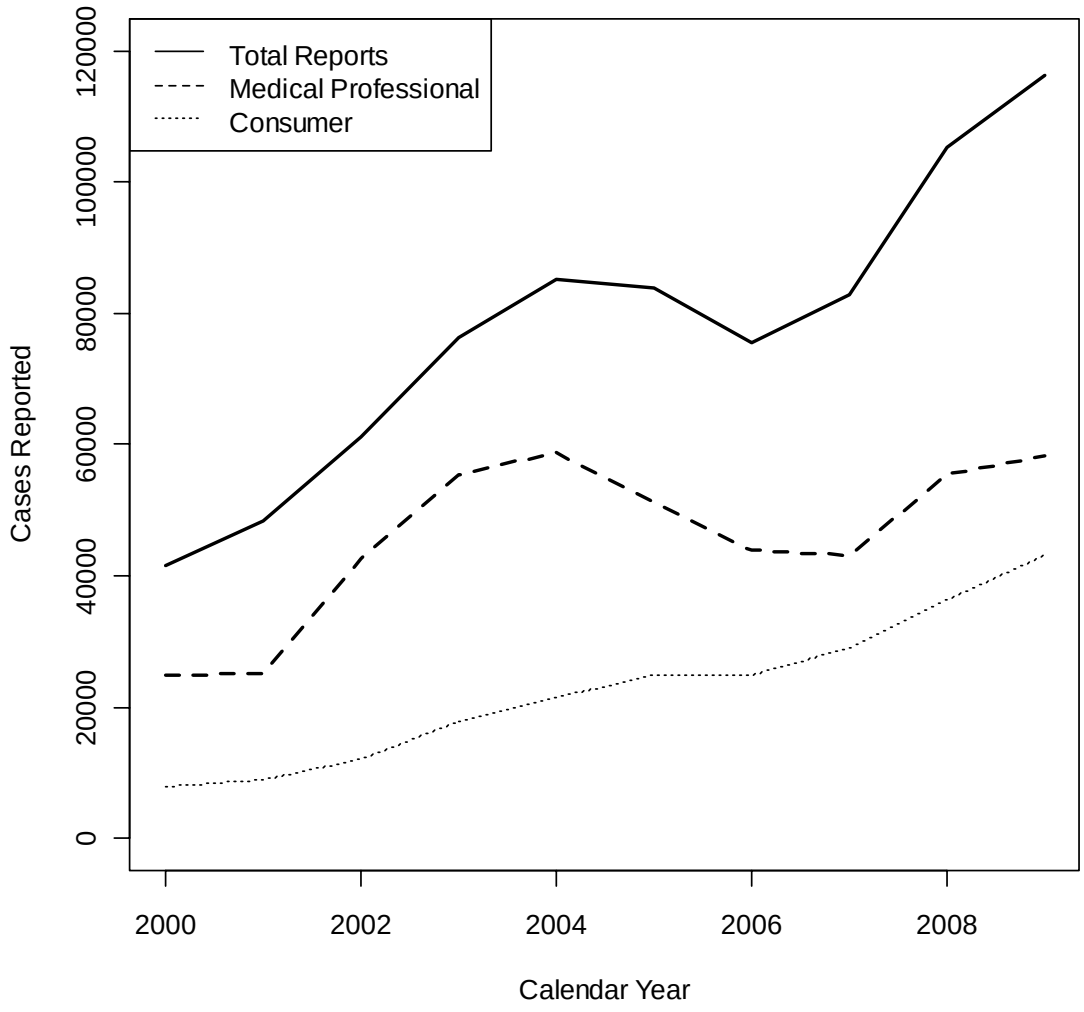
The QuarterWatch master database of all adverse event reports submitted to the FDA is maintained on a MySQL open source database (http://www.mysql.com/) and analyzed with the R Package for Statistical Computing (http://www.r-project.org/).

RESULTS

Changes in 2009

In 2009, the FDA received 116,174 domestic reports of fatal, disabling or serious injury associated with drug therapy, an increase of 10.2% over 2008 and a 2.8-fold increase since 2000. Reports originating from consumers increased more rapidly than those from health professionals during the entire 10-year period. Compared to 2008, reports from consumers increased 18.3% while reports from health professionals increased 5.1%. The results are shown in Figure 1. The figure also illustrates that since 2004 the volume of reports from health professionals has been relatively stable while consumer reports increased steadily.

Figure 1. Total Reported Serious Events: 2000:2009



Changes in 2009 Quarter 4

In the 4th quarter of 2009 the FDA received 29,672 reports meeting the QuarterWatch criteria, little changed from the 29,212 cases reported in the preceding quarter, but 16.3% higher than the 4th quarter of 2008. Compared to the 4th quarter of 2008, the entire increase came in expedited reports submitted by drug manufacturers of new, serious adverse drug events for which adequate warnings did not currently exist. Reports directly to the FDA declined slightly, both from the previous quarter, and from the same quarter one year earlier. In addition, compared to one year earlier, the reports from consumers accounted for 83% of the increase, with health professionals accounting for the rest.

Trends in Reported Deaths

For the full year of 2009, reported patient deaths increased by 14%, from 17,144 in 2008 to 19,551 in 2009. Reported deaths associated with drug treatment have increased 3-fold since 2000, but another peak occurred in 2003, when 18,623 deaths were reported. The drugs most frequently identified as suspect in reported patient deaths are shown in Table 1. As indicated in the section on methodology, we excluded certain drugs with special reporting practices.

Table 1. Most frequent suspect drugs in reported patient deaths 2009.

Drug Name	Brand Name	Deaths	Rank
ROSIGLITAZONE	AVANDIA	1354	1
DEFERASIROX	EXJADE	1320	2
DIGOXIN		506	3
FENTANYL		397	4
ACETAMINOPHEN		362	5
ACETAMINOPHEN; HYDROCODONE		273	6
IMATINIB	GLEEVEC	261	7
SUNITINIB	SUTENT	252	8
OXYCODONE		251	9
IBANDRONATE	BONIVA	250	10
QUETIAPINE	SEROQUEL	248	11
ALPRAZOLAM		233	12
CAPECITABINE	XELODA	218	13
SILDENAFIL	VIAGRA, REVATIO	190	14
TACROLIMUS	PROGRAF, PROTOPIC	180	15

As in prior quarters, a relatively small number of drugs accounts for a disproportionate share of all patient deaths that are reported as adverse drug events. QuarterWatch monitored 1986 identifiable drugs in the 4th quarter of 2009. For 1604 drugs (80.7%) no patient deaths were reported. Another 191 drugs (9.6%) had 2 or fewer patient deaths reported in the 4th quarter. For drugs with much larger totals, typically the risk of the drug, the number of patients exposed, and the likelihood of reporting all contribute to the report volume. Two examples follow.

Focus of Public Attention

Rosiglitazone (AVANDIA), the drug ranked first with 1,354 reported deaths 2009, is widely used in the treatment of Type 2 diabetes. It was also the focus of a major scientific controversy about its risks and benefits. As we have previously reported, [6] scientific evidence has accumulated that rosiglitazone, rather than having a protective effect, increases the risk of heart failure and may increase the risk of heart attack, stroke and bone fracture. The manufacturer, GlaxoSmithKline, told us earlier that it believed many of the adverse drug event reports for rosiglitazone were associated with possible lawsuits against the company. While we exclude identifiable reports that are associated with legal claims, we cannot rule out this as one reason for increased reporting of cardiovascular events and deaths in 2009.

Digoxin (DIGITEK brand) was the target of large scale drug recalls in 2008 and 2009 leading to a massive increase in reported patient injury and death in both years, as we have previously reported. [7] In 2009 it ranked No. 3 with 506 reported patient deaths. The primary product defect leading to recalls was potentially overstrength tablets. This is a serious defect in a drug in which a small overdose can be potentially fatal even with a normal strength tablet. From the data available in these reports it was not possible to separate cases that might have resulted from defective tablets from events reported because the recall notices heightened awareness of this drug's existing and known risks of overdose.

Pain Medications Prominent Among Known Risks

Acetaminophen (ranked No.5) and the acetaminophen-hydrocodone combination (VICODIN, HYCET, LORTAB, others) (ranked No.6) are among the most widely used pain medications. A modest overdose of acetaminophen can result in severe and fatal liver damage. The acetaminophen-narcotic combination has special hazards because patients develop tolerance to the narcotic over time and seek to increase the dose to retain the pain relief, again leading to potentially toxic acetaminophen overdose. In addition acetaminophen is frequently identified as a suspect drug in intentional overdoses leading to death. [8] While a substantial overdose of many drugs might not prove fatal, in the case of acetaminophen it frequently results in death.

Fentanyl (DURAGESIC, FENTORA, ACTIQ, ONSOLIS, SUBLIMAZE) is a synthetic narcotic that is approximately 80-100 times more potent than morphine, and is used for severe, continuing pain in patients who have developed tolerance to lower-strength narcotics. For many years its use has presented an array of drug safety risks.

These include prescribing error (to patients not opioid tolerant), accidental exposure of children and caregivers, failing to remove older patches, and abuse. Oxycodone (OXYCONTIN, PERCODAN, others), another synthetic narcotic, presents accidental and intentional overdose risks as increasing blood levels lead to respiratory depression and death. Oxycodone is also associated with drug dependency and abuse.

Providing adequate pain relief with safety remains an unsolved problem of pharmaceutical medicine and the adverse effects of these drugs are not well managed.

Reporting Problems Increase Deaths Totals

Deferasirox (EXJADE) and possible excess morality

We investigated a signal for deferasirox (EXJADE) because of an exceptionally large number of reported patient deaths--1320 deaths for the year 2009 and 903 deaths in the 4th quarter alone. Deferasirox is an orally administered agent that reduces excess levels of iron in patients who have received many blood transfusions to compensate for abnormal red blood cell function. [9] Manufactured by Novartis Pharmaceuticals, it is used in patients with sickle cell anemia and other inherited disorders of red blood cells and certain forms of leukemia. A death total of this size was highly unusual, and even more so given a limited patient population and a drug in restricted distribution.

On the one hand, our inquiry revealed an important safety concern. On the other hand a large share of the deaths was the result of a reporting problem that had occurred at Novartis, and may not have had implications for patient safety. According to the company, in April 2009, the FDA requested that the company investigate previously reported patient deaths, based on the adverse event case reports already received. When Novartis complied it learned that it had not investigated or reported hundreds of patient deaths that had occurred over the preceding five years. The problem, Novartis told us, was that it kept records in two different computer systems. One system monitored reported adverse events. The other system collected data when prescriptions were discontinued as a result of patient deaths. However, these patient deaths were not investigated or reported as adverse events. The large surge in reported patient deaths was a result of updating the company's safety database with the additional cases occurring for several years. However, the new patient death cases—which contained minimal clinical detail—contributed little to understanding the problems that the FDA was studying. In addition, the occurrence of a patient death provides little useful information if no association with the target drug was suspected or reported. That would require further follow up investigation.

When all the data were analyzed by Novartis and the FDA, the result was a new boxed warning for deferasirox about risk of kidney failure, liver failure and gastrointestinal hemorrhage [10] Left unanswered, was the question whether deferasirox, which is available in tablet form for oral use, was more dangerous to these vulnerable patients than a similar agent, deferoxamine, a generic drug which is administered by injection or intravenously. The FDA-approved prescribing information for deferasirox

notes that no clinical benefit has been proven, no increase in survival has been shown, and no advantage was demonstrated over the generic alternative, deferoxamine.[9]

Ibandronate (BONIVA)

We investigated the unexpectedly large volume of reported patient deaths in 2009 for ibandronate (BONIVA) a once-monthly treatment for osteoporosis. Ibandronate ranked No.10 among all drugs we monitor in patient deaths in 2009 with 250 cases. In addition, a chemically related drug for osteoporosis, alendronate (FOSAMAX), accounted for just 27 reported deaths in 2009. It was also of concern because drugs used long-term for prevention in otherwise healthy patients should have low risks.

The large number of patient deaths, we concluded, was another example of patient death reports generated by a manufacturer marketing program, rather than an indication of a new patient safety problem.

Roche, the manufacturer of ibandronate, said it had enrolled hundreds of thousands of primarily elderly patients in a special program to provide monthly reminders to take their medication. The program, called MyBoniva, provided reminders by email, robo-telephone calls and mailed postcards. If the reminder postcards were returned to the company with the notation "addressee deceased," Roche reported this as a patient death in which ibandronate was the suspect drug. According to Roche, 85-90% of all U.S. reported deaths resulted from this program. Our data support Roche's analysis; the mean age of reported deaths since 2005 was 79 years, other details were scant, and 87% came from consumers rather than medical professionals.

Different Medical Use, Higher Risks

Sildenafil (VIAGRA, REVATIO)

Reported patient deaths for sildenafil (VIAGRA, REVATIO) increased sharply compared to the preceding year (190 deaths versus 67) and ranked No. 14 among all drugs on the 2009 list (Table 1). The reported death total appeared unexpectedly high, given a drug whose primary use was in a patient population not seriously ill.

Since 2005 sildenafil has an FDA-approval under the brand name Revatio for an additional medical use in a special patient population with a severe, progressive medical disorder called Group 1 Pulmonary Arterial Hypertension, or primary pulmonary hypertension. [11] It is a poorly understood, potentially fatal progressive form of high blood pressure in the arteries of the lungs.

We determined that 173/190 (91%) of the reported patient deaths for sildenafil occurred in the much smaller group of seriously ill Revatio patients. In addition, reported patient deaths among Revatio patients increased 2.4 fold from the preceding year. While patient deaths are not unexpected in this vulnerable patient population, we recommend that the FDA and the manufacturer, Pfizer Inc., further investigate the reasons for this

change. While Viagra for erectile dysfunction has reported adverse effects that include potential cardiac risks and effects on hearing, these data provided no indication of new or increased risks in this patient group.

Johnson & Johnson's Massive OTC Product Recalls

Since September 2009, Johnson & Johnson's McNeil Consumer Products subsidiary has been conducting what is surely the largest drug recall in history. In September 2009 the company began recalling some of its Tylenol brand acetaminophen liquid products for infants and children, citing possible bacterial contamination of raw materials. [12] In December 2009 and January 2010 the company recalled most of its tablet-form Tylenol, Motrin, Benadryl, Rolaids and St. Joseph's Aspirin products because of possible contamination with a chemical called 2,4,6-tribromoanisole or TBA.[13] In May 2010 Johnson & Johnson expanded its recall to include all Tylenol, Motrin, Zyrtec and Benadryl products that were in liquid form for use in infants and children because of quality assurance problems identified by the FDA in an inspection. [14] The childrens' product recall further expanded to include PediaCare products for children manufactured by Johnson & Johnson but sold under the name Blacksmith Brands. [15] The FDA has ordered closed the Johnson & Johnson plant in Fort Washington PA that manufactured the liquid products for children until its quality assurance practices were judged acceptable. [16]

For the 4th quarter of 2009 we examined all serious adverse event reports to the FDA with standardized medical term (or MedDRA term) indicating a product quality problem. This period of time began just before the first recall notice appeared in September 2009, but ended in December 2009 just as more extensive recalls were announced.

The FDA received a total of 890 serious adverse event reports indicating possible product problems in the 4th quarter, or 3% of all adverse event of all type. Among these cases 602/890 (68%) were submitted by Johnson & Johnson. The 2nd ranked company was GlaxoSmithKline with 27 cases.

Tylenol brand products accounted for 449/890 (50%) of all the reported cases with quality problems, and all but seven of these cases the company assigned the medical term "Transmission of an infectious agent by a medicinal product." All but three of the reported cases occurred in children or infants.

Nevertheless, we suspect that the majority of these reported cases may involve a low likelihood that a child was in fact injured through bacterial contamination in a Tylenol product. In some cases the reported event was an earache, vomiting, or malaise—the sort of ailments that might lead a parent to administer Tylenol. In addition these cases were reported after news media publicity about the first Tylenol recall. On the other hand, we also identified 66 cases involving hospitalization, 1 case of a life threatening condition, 1 case that required intervention to prevent harm and 4 patient deaths.

We sought to discuss our findings with Johnson & Johnson but the company declined. It has stated that no injuries have been linked to the recalled products. FDA Deputy Commissioner Joshua M. Sharfstein recently testified that the FDA (which had the same case reports) had not identified any "significant" patient injuries but was still investigating some reports. [16]

We conclude that the health consequences of the largest drug recall ever have not been properly studied. Claims to have seen "no evidence of injuries" could be technically correct but primarily result from the lack of an adequate investigation. While many reports indeed might prove erroneous, other infants or children could have been injured without the problem being detected or reported.

Johnson & Johnson Fentanyl Patches (DURAGESIC)

Product quality questions also arose over a second important Johnson & Johnson product, fentanyl patches (DURAGESIC) for persistent, moderate to severe pain. This powerful painkiller—approximately 80-100 times more potent than morphine—has been a high alert drug for many years and can be used only in patients who have already developed tolerance for other opioid narcotics.

In the 4th quarter of 2009 Johnson and Johnson reported 144 cases of complaints about product quality for its fentanyl patches, primarily Duragesic-100 mcg/hour transdermal system. The primary problem appeared to be that the patches either did not adhere properly or were falling off. Because of the critical role of this powerful narcotic, this problem could lead to health consequences, notably drug withdrawal syndrome (34 mentions), drug ineffective (28), and pain (18 mentions).

The company's coding of these potentially complex cases was not detailed enough to allow further analysis of the problem. When a patch comes off it could be a result of a manufacturing problem, a weakness in the specific product design, a patient error in how it was applied, or something else (such as moisture). From the information available, no determination could be made.

We recommend that the FDA and the company investigate the reasons why so many product problem cases have been reported for this fentanyl product, but not for others.

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