



# Quarter Watch

Monitoring FDA MedWatch Reports

January 28, 2015 — Data from 2014 Quarter 1 / 2013 Quarter 4

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## A CRITIQUE OF A KEY DRUG SAFETY REPORTING SYSTEM

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### Executive Summary

The Food and Drug Administration's Adverse Event Reporting System (FAERS)—based on MedWatch reports—is the government's primary safety surveillance system designed to identify harms from therapeutic drugs. For the last six years these vital data have formed the core of ISMP's QuarterWatch™ drug safety reports. In this issue we decided to look closely at the system itself. Our conclusion: it seems clear that this drug safety monitoring system is in need of modernization. It suffers from a flood of low quality reports from drug manufacturers and has not yet been updated for the changing environment in which drugs are marketed to health professionals and consumers. We discuss key problems below and offer some recommendations as an organization that relies heavily on data collected through FAERS.

This issue of QuarterWatch includes two recently released calendar quarters of FAERS data, from 2013 Q4, and 2014 Q1. To provide a broader perspective, the main analysis focuses on the 12 months ending with 2014 Q1, and includes all adverse event reports received by the FDA in that one-year period. Previous issues of QuarterWatch have focused on a subset of these case reports, those with a serious outcome and reported by patients in the United States.

### A Vital System

The FDA safety surveillance system for harms from drugs has unusual features. Consumers and health professionals may voluntarily report any injury in which a therapeutic drug was the primary suspect, but they have no obligation to do so. They can make these voluntary reports either directly to the FDA's MedWatch program (<http://www.fda.gov/Safety/MedWatch/default.htm>) or to the drug manufacturer. The companies, in turn, are required to investigate and report only the adverse events they learn about. Manufacturers of all kinds of products need a program to receive and investigate reports or complaints of injuries possibly related to what they sell. In the case of therapeutic drugs, however, the FDA regulations and guidances specify in detail how drug companies must investigate safety complaints and report them to the agency.

The FAERS system is of critical importance for two reasons. Studies by ISMP and the FDA have shown that a majority of new FDA safety warnings about approved drugs come from these adverse drug event reports. Despite its limitations, FAERS is the most reliable system for discovering new drug risks that had not been identified in pre-market drug testing. Also, despite additional perspectives on safety obtained from insurance claims and electronic health records, no other system has comparable international scope, sensitivity to detect rare but catastrophic side adverse events effects, and the capacity to pinpoint potential injuries that were unexpected.

The adjacent Table 1 illustrates adverse event cases reported to the FDA over one year. The total number of cases reported (n = 847,039) is more than double the total reported in calendar 2009 (n = 336,753) with all of the growth occurring in manufacturer reporting. Table 1 illustrates another important feature of FAERS: 96.6% of the case reports are collected and written by drug manufacturers. Thus, the performance of the drug manufacturers, combined with FDA regulations and compliance activity, determines the quality, coverage and completeness of this safety surveillance system. While the current system retains substantial strengths, and the FDA has made improvements (described below), the growing problems outlined in this report need to be addressed.

<b>Table 1. Case reports received for 12 months ending 2014 Q1</b>		
<b>Report type</b>	<b>Cases, (%)</b>	
Total - all categories	847,039	
FDA - direct	29,314	(3.5)
Manufacturer		
Domestic, serious	264,902	(31.3)
Foreign, serious	231,046	(27.3)
Not serious	321,914	(38.0)

## Key Problems Identified

### Incomplete Manufacturer Reports

While drug manufacturers are now reporting adverse drug events in unprecedented numbers from around the world, we judged that the overall completeness of adverse event report was poor. For example, in 36% of cases the age of the patient was not determined; in 44% of cases no event date was indicated. A report was classified as reasonably complete if it contained age, gender, and an event date. While 85% of serious reports sent directly to the FDA were reasonably complete, only 49.4% of the manufacturer serious reports met this basic standard. We also identified thousands of case reports where the adverse event was classified as non-serious and indicated only common health problem such as a cold (n = 1,889), the sniffles (n = 906), or an injection that had been painful (n = 4,331). Manufacturer report quality for serious adverse events varied widely. The weakest performance was seen in four companies that submitted reasonably complete reports in only 15% or fewer cases; not one manufacturer equaled the FDA's 85% record for complete reports; and only 5/74 (7%) manufacturers reported at least age and gender in 90% or more serious reports.

### Was the Drug Responsible?

Central to any kind of customer or health professional safety reporting system is the idea that someone believed the product likely caused the injury. While further investigation might disclose that the product might not have caused the adverse event, the central concept underlying adverse drug event reporting is "an inference of causality."<sup>[1]</sup> Further, as the case count grows describing a specific adverse effect, the inference of causality is strengthened. If hundreds or thousands of health professionals or consumers complain of a specific adverse effect (e.g., weight gain, psychosis), some might be mistaken, but could they all be wrong? However, QuarterWatch has observed steadily increasing number of cases in FAERS where the report did not reflect a complaint, but instead was a byproduct of various programs in which the drug manufacturer initiated contact with patients or health professionals. This includes prescription refill reminders, assistance getting insurance coverage, or patient and health professional education. Additional interactions occur because of restricted distribution and other risk management plans required by the FDA for high-risk drugs. When patients with life-threatening diseases such as metastatic cancer or pulmonary arterial hypertension are contacted by a drug manufacturer, the company will frequently learn the patient has died. By FDA regulation this death must be reported whether or not the drug was suspected by anyone of contributing to the patient death. For patient deaths during the study period, we estimate that in 28.5% of reported deaths, no information was provided about whether the drug was suspected of contributing to the fatality. In thousands of other cases, the reported adverse event was the patient's underlying disease without a determination or suspicion that the drug therapy had exacerbated it.

## Gaps in System Coverage

The FAERS system works best for serious adverse events report in adult patients taking newer brand name drugs, and works worst for patients taking older generic drugs and for events in newborns and children. Both the FDA and QuarterWatch have previously reported that the number of reports in children were too few for effective postmarket surveillance. For birth defects, reporting is even more limited, compounded by poor quality reporting. Even though 86% of outpatient prescriptions are for generic drugs, according to IMS Health Inc., the major brand name manufacturers provide the overwhelming majority of adverse event reports, even when sales of the brand name drug are extremely small. For example, Pfizer accounted for 66.5% of all serious U.S. adverse event reports for the antidepressant sertraline (ZOLOFT), even though its brand name product accounted for less than 1% of sertraline prescriptions in 2013.

## Outdated FDA Regulations

How drug manufacturers collect and report adverse drug events is specified in legally binding FDA regulations, described in substantial detail in guidance documents, and enforced through compliance inspections. However, the major FDA guidance document has not been revised since 2001, when manufacturer reporting was standardized on a global basis. But the world has changed. Since 2001 the FDA has approved a growing number of drugs available with restricted distribution schemes that require intensive manufacturer contact with both patients and prescribing doctors, spurring large volumes of potential reports. The advent of expensive drugs (from \$10,000 to \$100,000 per patient) targeting smaller populations further increases manufacturer interactions with patients. Standard reporting protocols for company-initiated contacts with patients could be designed to collect valuable information about real-world experience with drugs.

## Strengths of the System

For all its defects, the current system has many vital features not seen in alternative approaches to drug safety surveillance. Since 2001, reporting has been standardized on a global basis, with a common terminology for describing adverse events, detailed definitions of what constitutes an event, and since 2014 an all-electronic system. With coverage of hundreds of millions of patients around the world, it successfully identifies rare but catastrophic side effects not clearly evident in small pre-market clinical trials. Statistical tools have been developed to identify signals in large data sets that were not collected systematically. The FDA has modernized its computer infrastructure, solved some internal data quality problems, and developed a consumer-friendly on-line reporting form for direct reports. Finally, the system captures reported events rapidly. Compliance was good with the FDA requirement that serious, unexpected events had to be reported within 15 calendar days. Our study showed 88.5% of these reports reached the FDA within 15 calendar days of the manufacturer learning the event had occurred.

## Case Study: Sofosbuvir (SOVALDI)

The new hepatitis C drug sofosbuvir (SOVALDI) was notable in several ways. It was the first agent to achieve virologic cures at 12 weeks at 90% rates for the most common viral genotype. At \$84,000 for a course of treatment, it was one of the most expensive and profitable drugs ever approved, producing \$2.2 billion in revenue in the first three months after approval. And under the FDA's new "breakthrough drug" rules, it was one of the first non-cancer drugs approved without a controlled efficacy trial for its largest patient population.

We saw no signals for the first available quarter of adverse event reports for sofosbuvir. However, we also had concerns about the report quality from the manufacturer, Gilead Pharmaceuticals. Only 39% of sofosbuvir reports were reasonably complete, compared to 71% for Vertex Pharmaceuticals' competing drug, telaprevir (INCIVEK). With limited pre-approval testing and weak adverse event reporting, the safety

profile of sofosbuvir remains uncertain. Gilead told us that the company adhered to industry standards and noted that the reports the company received from postmarketing sources often lacked detail.

## Conclusions

Modernizing the FDA's manufacturer adverse event reporting requirements would offer a low-cost opportunity to improve safety surveillance and at the same time either reduce the burden on drug manufacturers or focus existing resources in a more productive direction. Some changes are straightforward: We can't think of a good reason why the quality and completeness of serious adverse event reports collected by drug manufacturers is so much worse than those collected online at the FDA. To interact with a consumer or health professional about a serious adverse drug event without getting the patient's age in 36% of the cases signals inadequate quality control and weak systems. And does the system really need thousands of non-serious reports of the sniffles or that an injection was painful? Providing FDA feedback to companies submitting large numbers of reports with missing data is elementary quality assurance in the digital data era.

Other changes may require substantial discussion and debate. Developing clear and usable protocols for manufacturer-initiated contacts with patients or health professionals may require new report data elements, and specific lists of questions to ask. Improving the quality of patient death reports is non-trivial because patient deaths typically involve multiple contributing factors, and assigning cause may be a subjective medical judgment. But there is no point in manufacturers submitting thousands of reports of deaths in which a possible drug role was never alleged, ascertained, or investigated. In all of these situations, much could be gained from requiring a simple critical question in company-initiated contacts that asked: "Was the drug suspected of contributing to the event?"

Gaps in coverage for generic drugs, birth defects, and adverse events in children may require different kinds of solutions or even new or different information sources. But improving FAERS coverage of these areas could still provide an additional perspective.

It makes no sense for drug manufacturers to be required to spend millions collecting and submitting adverse drug event reports promptly when so many reports contribute little to the assessment of drug safety. The FAERS system, for all its flaws, nevertheless remains the primary source for detecting new, serious adverse effects in approved drugs and identifying other risks to patients.

The FDA has invested millions in developing an alternative surveillance program it calls the Sentinel System that is based primarily on insurance claim data from 178 million patients. While this will provide useful new perspectives for some kinds of adverse drug events and types of information unobtainable from FAERS, we agree with Janet Woodcock, director of the Center for Drug Evaluation and Research at the FDA, who noted that "FAERS is an invaluable asset and we're not seeking to replace it." [2] To that view should be added the idea that improving FAERS should be a higher priority.

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## Contents

<b>A critique of A Key Drug Safety Reporting System .....</b>	<b>1</b>
<b>Executive Summary.....</b>	<b>1</b>
A Vital System .....	1
Key Problems Identified.....	2
Case Study: Sofosbuvir (SOVALDI) .....	3
Conclusions .....	4
<b>Methods Summary.....</b>	<b>6</b>
<b>Results .....</b>	<b>6</b>
<b>Completeness of Manufacturer Reports .....</b>	<b>7</b>
<b>Inference of Causality .....</b>	<b>11</b>
<b>Gaps in FAERS Coverage .....</b>	<b>13</b>
<b>Outdated Regulations .....</b>	<b>14</b>
<b>Sofosbuvir Safety Profile .....</b>	<b>16</b>
<b>QuarterWatch Team and Funding Sources.....</b>	<b>19</b>
<b>References.....</b>	<b>20</b>

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This revised edition of QuarterWatch reflects two corrections listed at <http://www.ismp.org/QuarterWatch/clarifications.aspx>

# Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to the FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source. [3] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site. (<http://www.ismp.org/QuarterWatch/detailedMethods.aspx>)

This issue of QuarterWatch is devoted to a special evaluation of the overall FAERS system. As a result, it focuses on all reports received by the FDA in the 12 months ending March 31, 2014. Previous issues focused primarily on a subset of these reports, those with domestic, serious adverse events. This analysis includes reports of injuries that were not classified as serious, cases from the legal departments of drug companies, and foreign reports, all cases that were excluded in our standard analysis.

When submitted to the FDA, case reports contain a patient narrative that describes the adverse event that was observed. The event is then characterized by one or more adverse event terms selected from the Medical Dictionary for Regulatory Activities (MedDRA).[4] The outcome (or severity) of the event reported is separately coded under FDA regulation as one or more of the following: of death, disability, a birth defect, hospitalization, required intervention to prevent harm, was life threatening or had other medically serious consequences.[5]

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

“The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2014 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.”

## Results

In the 12 months ending with 2014 Q1 the FDA received 847,039 reports of which 615,124 (73%) were domestic. The number of patient deaths reported—45,688 in the United States and 41,884 from foreign sources—is also very large. By comparison, in the United States, the Centers for Disease Control and Prevention recorded 34,677 deaths from motor vehicles, 15,953 homicides, and 575,313 deaths from cancer in 2011.[6] While these figures provide a broad perspective for the importance of minimizing injuries from therapeutic drugs, the totals must be interpreted with care. On one hand, for consumers and health professionals the reporting system is voluntary, and therefore a large majority of adverse drug events that occur are not reported. On the other hand, as this report documents, for a substantial and growing fraction of these cases the drug was not necessarily suspected of contributing to the death or other adverse event. As approximate as these measures are, we know of no other system or accepted methodology for assessing the extent of serious injury and death attributable to prescribed drugs. FAERS continues to account for more new label warnings and restrictions for approved drugs than any other information source. [5]

The second perspective on these data is to focus on how the only system designed to assess injuries from therapeutic drugs actually works, and how it may be improved. The central feature is that it is a system primarily operated by the world's drug manufacturers who must adhere to the regulations and guidances outlined by the FDA. In the 12-month study period, drug manufacturers prepared and submitted 96.65% of all the case reports that reached the FDA for review and analysis. Although only 14% of dispensed outpatient prescriptions are for brand name drugs without generic equivalents, the brand name manufacturers account

for most case reports. Among the ten manufacturers submitting the largest number of case reports, every one was a brand name manufacturer. This means that the quality and value of the safety surveillance depends primarily on how well the manufacturers collect, code, and follow up on adverse drug events of which they become aware. The quality issues outlined in this report are a shared responsibility between the FDA, which establishes and enforces reporting requirements, and the industry, which must fulfill them.

## Completeness of Manufacturer Reports

To assess the completeness of manufacturer and direct-to-FDA reports we used two standards. First, we judged to be “reasonably complete” any case report that included basic information on the patient age, gender, and the event date. A report was considered “minimally complete” if at least age and gender were present.

### Manufacturer and Direct FDA Reports Compared

The best result was for adverse events reported directly to the FDA, rather than through drug manufacturers. For the 12-month study period 81.3% of direct reports to the FDA were reasonably complete, and 87.9% were minimally complete. The results were better when limited to cases with serious outcomes: 85% of direct reports were reasonably complete and 90% were minimally complete. This seemed like an acceptable level of report quality, although in the era of online forms that reject incomplete or invalid entries, a rate near 100% would be possible.

By contrast, only 46% of reports submitted by drug manufacturers were reasonably complete. For minimally complete reports with at least age and gender, 62.3% of the manufacturer reports contained data in these fields.

### Serious, Unexpected Adverse Events

One might hope that the report quality and completeness problems centered on nuisance case reports of minor health problems where submission was nevertheless required by FDA regulations. Therefore our next analysis focused on the main events the system is designed to detect quickly: Serious outcomes (such as hospitalization, disability, or death) that were “unexpected,” which means that adequate warnings about the specific adverse event were not included in the prescribing information for physicians. This group of manufacturer reports is also classified as expedited reports because FDA regulation requires their submission within 15 calendar days of when the manufacturer first learns of the event.

Figure 1 illustrates that the completeness of the most serious and unexpected adverse events was little better. Overall 48.6% of expedited reports were reasonably complete, compared to 43.8% of other lower priority manufacturer reports. The result was better for reporting both age and gender, 66.1% for expedited reports compared to 57.8% for lower priority periodic reports. Among cases indicating some of the most dire health outcomes, an even smaller proportion was reasonably complete, for example with 25.2% of birth defect cases. We concluded that manufacturers overall did a poor job collecting basic patient and event data regardless of the severity of the event.

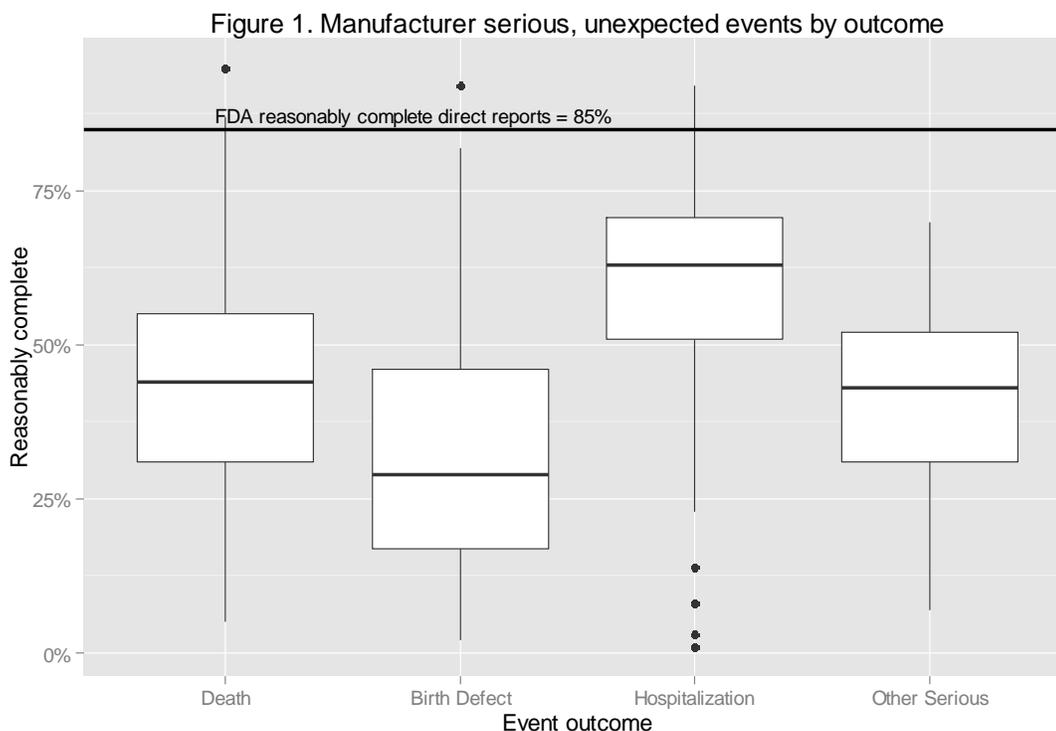


Figure 1 is a boxplot that shows both the industry average and differences between manufacturers. The horizontal line in each box indicates the industry median for each outcome. The box captures 75% of the manufacturer scores. The vertical lines and dots display the more extreme values.

## Updated Reports

FDA regulations mandate two manufacturer actions that are sometimes in conflict: Prompt reporting (within 15 calendar days) and complete reporting with follow-up if needed. It seemed possible that the requirement for rapid reporting contributed to weak performance on getting basic patient information into expedited reports. Therefore, we compared case reports that were in their initial, 15-day version with those that had been updated at least once. Manufacturer performance improved on revisions: 62.1% were reasonably complete compared to the initial reports, which were 39.6% reasonably complete. But the results still did not get close to the 85% performance seen on direct FDA serious reports.

## Prompt Reports

Identifying new safety issues quickly is another design objective of FAERS, and distinguishes it from other government safety and mortality assessments that often provide quality data but years after the fact. FAERS was getting new cases quickly. In the 12-month study period, manufacturers submitted 88.5% of the initial expedited reports within the required 15 calendar days. Here the likely influence of FDA compliance inspections can be seen, as this is an item routinely examined and non-compliance can result in a warning letter

Reports that are not expedited can be submitted every quarter for the first three years, and annually thereafter. These lower priority reports reached the FDA an average of 138 days after the manufacturer learned of the case.

Although manufacturer reports reach the FDA quickly, this does not mean that the reports are rapidly translated into new restrictions and warnings. Two studies of FDA postmarket label changes in 2009 and 2010 reported that new safety warnings occurred a median of 11 years after drug approval.[7] [8] A majority

of these warnings came from adverse drug event reports. Once a signal is clearly identified, a label change can often take a year or longer and involve extensive interactions with the manufacturer.

## Do Manufacturers Differ?

We investigated differences in manufacturer performance in a subset of the most important safety reports, cases that indicated a serious injury (n = 476,450) and compared them to direct reports to the FDA in the same subset (n = 22,194). To be included, a drug manufacturer also had to have submitted 500 or more case reports in the study period (n = 74). The same completeness criteria were applied; reasonably complete reports included age, gender, and event date; minimally complete at least age and gender. Each manufacturer was counted as a single entity as identified by the FDA, regardless of the number of drugs included in the reports it submitted in the study period.

The reference standard was the FDA performance for events with serious outcomes, with 85% reasonably complete and 90.4% minimally complete. Here are three perspectives on drug manufacturers that help illustrate that better performance can be readily achieved, and improvement is needed. The manufacturer names are as shown on the FDA report excerpts.

## Best Manufacturer Results

Table 2 shows the manufacturers with the highest percentage of reasonably complete reports describing domestic or foreign serious adverse drug events. None of the best performing manufacturers equaled the result for direct FDA reports, with 85% reasonably complete. However, five manufacturers provided age and gender for 90% or more cases, including Actelion, Jazz, and Impact Pharmaceuticals, not shown in this chart.

Rank	Drug manufacturer	Total cases*	Reasonably complete (%)	Minimally complete (%)
1	ARIAD	776	(77.7)	(91.6)
2	GE HEALTHCARE	1440	(77.1)	(79.0)
3	VERTEX	4497	(73.7)	(80.4)
4	UNITED THERAPEUTICS	1139	(73.1)	(96.7)
5	BIOGEN	10413	(72.0)	(75.5)

\*Serious reports in 12 months ending 2014 Q1.

## Biggest Report Volume

Table 3 shows the results for the five drug manufacturers that submitted the largest number of reports of serious injury in the study period. Among the large manufacturers, the biological products company Amgen had the largest percentage of both reasonably and minimally complete reports, and was markedly better than the others shown in the table. These data also show that the burden of creating more than 10,000 reports a year is no obstacle to higher quality reporting. In Table 2 Biogen Idec ranked among the top 5 in quality with 72% reasonably complete. Table 3 shows that Amgen, with 84.9% of reports that were minimally complete approached the FDA's results.

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**Table 3. Manufacturers submitting largest number of reports**

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Rank	Drug manufacturer	Total cases*	Reasonably complete (%)	Minimally complete (%)
1	PFIZER	35419	(47.0)	(67.8)
2	NOVARTIS	35231	(44.3)	(59.3)
3	ROCHE	31905	(44.2)	(57.9)
4	JANSSEN	29522	(49.8)	(61.2)
5	AMGEN	24298	(62.1)	(84.9)

\*Serious reports in 12 months ending 2014 Q1.

## Weakest Performers

Table 4\* shows the manufacturers with the lowest percentages of reasonably complete reports. The lowest ranked, Par Pharmaceuticals, a privately held generic manufacturer, collected event dates in less than 1% of cases, but reported age and gender in 82.5% of cases, a result better than most manufacturers. On the other hand, Cubist Pharmaceuticals and Millennium\* had low-ranking results on both measures of report quality.

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**Table 4. Manufacturers with fewest reasonably complete reports**

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Rank	Drug manufacturer	Total cases*	Reasonably complete (%)	Minimally complete (%)
1	PAR	1232	(0.9)	(82.5)
2	CUBIST	675	(8.1)	(11.3)
3	ROXANE	1331	(10.2)	(77.6)
4	MILLENNIUM	1083	(15.3)	(16.9)
5	WESTWARD	1322	(16.2)	(74.4)

\*Serious reports in 12 months ending 2014 Q1.

## Trends Over Time

The final question was whether report quality and completeness were improving or getting worse. We compared all the reports the FDA received in 2014 Q1 with the same quarter in 2001, the year the major FDA guidance and international standards for adverse event reporting were adopted. The biggest change was in overall report volume, which had increased 6-fold, from 41,840 cases in 2001 Q1 to 258,262 cases in 2014 Q1. Of this large increase, 98.3% was in reports from manufacturers. The number of foreign reports increased 8-fold, reflecting the globalization of the pharmaceutical industry, and capturing events from a much wider patient population. Generally, increased reporting was judged to be beneficial. However, the other indicators of manufacturer report quality got worse over the period: The percentage of reasonably complete manufacturer reports declined from 59% to 48%, and minimally complete from 70% to 65%. Also, the least valuable cases, domestic reports of non-serious events, increased 15-fold, from 7,072 in 2001 to 106,207 in 2014.

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\* Millennium is a subsidiary of Takeda Pharmaceutical Company and specializes in oncology drugs. Cubist is now a wholly owned subsidiary of Merck, and Roxane is a subsidiary of Boehringer Ingelheim.

# Inference of Causality

At its core, an adverse drug event report is similar to any complaint about an injury or malfunction of a company product. A customer complains that a product caused harm or didn't do what it was expected to do. In the case of drugs, approximately half of such reports to manufacturers come from health professionals, who are assumed to be trained and experienced observers. This is not a guarantee that the target drug caused the adverse effect. But in the words of an international panel of industry experts that considered the issue, there is an "inference of causality."<sup>[1]</sup> FDA adverse event reporting instructions define an event that "is suspected to have resulted in an adverse outcome in a patient."<sup>[9]</sup>

## Spontaneous and Voluntary

The core idea was that the adverse experience had sufficient weight to motivate a patient or health professional to report it voluntarily to the FDA or manufacturer. But the manufacturer has no duty to solicit reports, only to investigate and report complaints. If the company did solicit reports, the FDA regulation defined it as a post-approval safety study and required that it be reported separately.<sup>[10]</sup>

However, both FDA regulation and pharmaceutical marketing practices have changed since 2001, when the requirements were last formalized on a global basis.<sup>[11]</sup> Increasingly, new forms of contact between manufacturers and consumers and health professionals generate adverse event reports that were not based on spontaneous complaints.

## Patient Contacts for Marketing Purposes

Manufacturers contact patients through mail, email, and telephone banks to remind them to renew their prescriptions, or to reinforce the value of the medicine. In the process, the companies may learn of a death or other adverse outcome. For example, the manufacturer of a biological product to reduce the risk of respiratory syncytial virus in premature infants telephoned parents prescribed the product to remind them that their infants needed the injection each month during the infectious disease season. In these monthly calls the manufacturer learned of the deaths of many premature infants and reported them. Similarly, Roche sent reminders via robo calls, mail, and email to elderly patients taking ibandronate (BONIVA), its once-monthly treatment for osteoporosis.<sup>[12]</sup> If the company learned that the patient was deceased, it reported the death as an adverse event. Biogen Idec told us that every quarter it telephoned every multiple sclerosis patient taking its drug interferon beta-1a (AVONEX).<sup>[13]</sup> In the process it learned of and reported many MS relapses, which are expected in a relapsing /remitting disorder. The biological product adalimumab (HUMIRA) web site offers injection training, on-call nurse support, medication reminders, and pen/syringe disposal for patients with rheumatoid arthritis, Crohn's disease, and other treated disorders.<sup>[14]</sup>

## Restricted Distribution Schemes

The FDA has increasingly approved drugs with restricted distribution schemes to manage some of the most serious drug risks, such as birth defects, blood disorders, liver toxicity, cardiac arrest, fatal brain infections, and drug abuse risks. Restricted distribution has also been used as an alternative to drug safety withdrawal to make a drug available to existing patients. As of 2014, we know of at least 35 drugs with some form of restricted distribution. <sup>[15]</sup>

The restriction program requirements vary, but may involve extensive direct contact with patients or physicians. Some require physician training or education programs as for tapentadol (NUCYNTA ER), or signed patient informed consent forms. Others are available only through specialized pharmacies or certified infusion centers, which require regular patient contact for renewal. Because of the risk of birth defects, isotretinoin for severe acne requires patient and physician education and registration, and every patient is required to enter pregnancy test results into a central system every month through the iPLEDGE program shared by six generic manufacturers. <sup>[16]</sup>

## Insurance Authorization

The growth of high-cost biological products and drugs for smaller patient populations has resulted in drug manufacturers providing patient support programs to help consumers navigate insurance approval and locate physicians who will provide treatment (often injections or infusions). For example, the new hepatitis C treatment ledipasvir-sofosbuvir (HARVONI) costs \$94,500 for a 12-week treatment.[17] The Harvoni web site offers five different forms of patient assistance, including insurance verification, financial assistance, co-pay assistance, and 24/7 “live nursing support.” [18]

## Multiple Forms of Contact

Some drugs involve multiple routes of patient contacts. For sodium oxybate (XYREM), a drug for some forms of narcolepsy, Jazz Pharmaceuticals provides a “patient connection mentor,” “admissions specialists” to manage insurance coverage, and a specialized pharmacy team to telephone each patient monthly prior to shipping the drug.[19] Erlotinib (TARCEVA) is approved for two frequently fatal forms of cancer, metastatic/advanced non-small cell lung cancer and advanced-stage pancreatic cancer. Genentech, the manufacturer, offers an oncology nurse hotline and a “Tarceva Access Solutions Specialist” to navigate insurance and arranges contact with the specialty pharmacies that provide the drug. [20] The combination of metastatic and advanced cancers with low survival rates and multiple forms of patient contact means that every year hundreds of patient deaths are identified and reported as adverse events for erlotinib without a determination of whether the drug had contributed.

## Effect on Adverse Event Data

Overall, the effects of the changing nature of drug regulation and marketing are substantial, although difficult to measure precisely. Shown next are three categories where we have detected and measured an impact.

## Questionable Death Reports

The most prominent and readily measured effect can be seen with patient death reports in which the only coded information about the cause of death is the single event term “death.” Not only was the cause of death not coded, there is no indication that a drug role was suspected or investigated. In reported patient deaths in the study period, we found 24,939/87,572 or 28.4% had no useful information about the cause of death or possible drug role. Examining all the cases, we found that overall 67% of patient death reports were of limited value, with either the single event term “death” or the absence of one or more of the following: age, gender, or event date. Another patient death issue is discussed below in the section on generic drugs.

## Reports of Minimal Value

While the system is intended to focus on serious, unexpected injuries in which the drug is a suspect, FDA regulation also requires manufacturers to report adverse events it learns about where the injuries are not serious, and expected. As a result we identified thousands of non-serious reports with a single adverse event term describing a commonplace health problem with little or no value to drug safety assessment. The total included injection site pain (n = 4,331), an “injury” not otherwise specified (n = 917), an unspecified “adverse event” (n = 963), a common cold (nasopharyngitis) (n = 1889) or stuffed up nose (sinusitis) (n = 906). A large group of reports (n = 4,417) contained the report term “no adverse event” indicating an affirmative conclusion that the health problem described was not related to a suspect drug.

## Event Was the Underlying Disease

Manufacturers with extensive patient contact programs also submit case reports where the “adverse event” is in fact the underlying disease. For the restricted distribution cancer drug lenalidomide (REVLIMID), the most frequent terms were “plasma cell myeloma” (n = 814), one cancer for which the drug is indicated,

and “death” (n = 764). For the AVONEX brand of interferon beta-1a for relapsing/remitting multiple sclerosis, the most frequently reported adverse event term was “multiple sclerosis relapse” (n = 497), followed by “death.” (n = 411). For the anti-tumor necrosis factor drug adalimumab, three major indications were prominent reported adverse events: Crohn’s disease (n = 575), psoriasis (n = 282), and rheumatoid arthritis (n = 210). Given that a report has separate sections for patient history and drug indication, it is not clear why manufacturers are including the underlying disease as an adverse drug event. It is possible, however, that drug treatments aggravate the underlying condition, but that is not clear.

## Gaps in FAERS Coverage

The primary strengths and weaknesses of FAERS flow from its historical purpose: to identify serious and unexpected adverse drug events in brand name drugs. Although regulations cover expected events, non-serious events, and generic drug manufacturers, the primary surveillance takes place among the brand name manufacturers. Among the top five generic and brand name drug manufacturers accounting for the largest number of submitted reports (n = 156,375), all were brand name drug manufacturers. The most important gaps in postmarket surveillance are adverse events in children, birth defects, and coverage of generic drugs.

### Adverse Events in Children

Two studies—one by QuarterWatch and the other by the FDA—have documented that FAERS collects too few reports to provide adequate coverage of drug risks to children under age 18.[21] [22] While this age group accounts for 24% of the population and 7.3% of dispensed outpatient prescriptions, it accounted for only 3% of the adverse event reports. A majority of these reports occur at the extremes of the age distribution—during the first year of life and after puberty. Data for drug effects in children is limited overall, although more systematic drug testing in children began with a 1997 regulation and was expanded with patent extension incentives in 2002 and 2007.[23] However, many of the most frequently used drugs in children, notably antibiotics and amphetamine-like stimulants, are primarily generic drugs.

### Birth Defects

A review of the 20 new drugs approved in 2008 [24] found that animal testing of 14/20 indicated birth defects or affected fertility. However, it is not clear that the animal studies predict the risk in pregnant women, especially for the dose and duration they take the medication. [25] Furthermore, the CDC estimates 3% of approximately 4 million live births every year include a birth defect.[26] We know of no credible estimates of drug-related birth defects, but could not rule out that they number in many thousands.

In our 12-month study data, reports of congenital anomaly worldwide were few (n = 3,248) and data quality the poorest of any serious event outcome, with only 25.2% reasonably complete. A medical journal review of postmarket surveillance of teratogenic effects pronounced adverse event reporting “a complete failure.” [27] The FDA’s main approach to improving information about pregnancy risks has been to expand the prescribing information and to promote the use of pregnancy registries. [28] However, an expert review group on teratology noted numerous problems in pregnancy registries, including the inability to detect low to moderate increased risk, selection bias, and high rates of loss to follow up.[29]

### Generic Drugs

Generic drugs accounted for 86% of outpatient prescriptions in 2013, according to the most recent IMS Health Inc. assessment. [30] The same reporting requirements that apply to brand name drug manufacturers also apply to generic drug manufacturers. The FDA also conducts compliance inspections of generic manufacturers and has noted violations. [31] [32]

However, a convenience sample of five widely used generic drugs (Table 5) shows that the original brand name manufacturers are providing the overwhelming majority of adverse event reports, despite accounting for a small minority of case reports for these products.

**Table 5. Brand name drug manufacturer share of prescriptions and serious case reports, 2013**

Generic drug name	Original brand name	Brand name manufacturer	Dispensed prescriptions*			FAERS US Serious		
			Total 2013	Brand name, pct	Total	Brand , pct	Total	Brand , pct
SERTRALINE	ZOLOFT	Pfizer	37,373,747	244,283 0.7%	427	284 66.5%		
OMEPRAZOLE	PRILOSEC	AstraZeneca	64,304,631	57,991 0.1%	252	103 40.9%		
LOSARTAN	COZAAR	Merck	31,697,368	150,206 0.5%	104	24 23.1%		
ATORVASTATIN	LIPITOR	Pfizer	63,069,788	1,615,774 2.6%	1097	881 80.3%		
RISPERIDONE	RISPERDAL	Janssen	9,122,331	78,169 0.9%	417	264 63.3%		
Total			205,567,865	2,146,423 1.0%	2,297	1,556 67.7%		

\* Dispensed outpatient prescriptions, IMS Health Inc.

For this sample of some of the most widely used generic drugs, brand name manufacturers accounted for 1% of dispensed outpatient prescriptions but submitted 67.7% of all serious adverse event reports. There are multiple reasons why generic drug manufacturers submit so few reports. Physicians may not be able to identify the generic drug manufacturer without contacting the pharmacy. The generic manufacturers are not as visible as the manufacturers of heavily marketed brand name drugs. Finally, brand name manufacturers have clear legal obligations to update their prescribing information to include newly discovered drug harms. The responsibility of generic drug manufacturers is in transition following a Supreme Court decision that exempted most generic drug manufacturers from liability for drug-induced injury.[33]

### Literature Reports Duplicated

The FDA requires that both generic and brand name drug manufacturers actively monitor the medical literature for new case reports and other studies potentially revealing new drug risks, and submit every case described as an expedited report. The unintended consequence of this requirement is that the same literature cases are submitted multiple times for generic drugs. As previously reported in QuarterWatch, the most conspicuous effect is the annual journal publication[34] of more than 1000 fatal overdose cases treated at one of the facilities affiliated with the American Association of Poison Control Centers. This annual publication results in duplicate death reports not only of the primary suspect drug, but often for any other drug detected in post-mortem toxicology.

## Outdated Regulations

The most recent authoritative FDA regulatory document for reporting adverse drug events is a draft—never finalized—Guidance for Industry dated March 2001.[11] The 14-year-old text reflects the dawn of the modern digital era, with instructions for preparing paper reports, and describes as optional the MedDRA terminology to describe adverse events now used globally for adverse drug event reports and clinical trials. In June 2014, a new guidance made electronic submission of adverse drug event reports mandatory, but the guidance made no changes in what manufacturers should report.[35]

However, the central problem is that the basic regulatory scheme has not been adapted to the current marketing and regulatory environment. Since 2001, the FDA has approved dozens of restricted distribution drugs; the restriction plans vary, and there are no provisions to establish protocols for this form of close patient and physician contact. Since 2001 the FDA has required Risk Evaluation and Mitigation Strategy (REMS) plans for scores of drugs; some involve patient or physician education or some other form of contact. Also, since 2001, manufacturers have increasingly operated nurse hotlines, assistance in applying

for insurance reimbursement, and/or on-line and personal instruction in using products that involve inhalers, injections, or special preparations.

## Patient Death Reporting

The existing regulations, guidance, and FDA compliance inspections cover many settings where a manufacturer might learn of a patient death. The regulatory environment has been complicated by the increased number of newly approved drugs for life-threatening and frequently fatal medical conditions. In the last 5 years the FDA has approved 53 orphan drugs and 35 new cancer treatments.[30] As noted above, one result is the system being flooded with reports about patients who died, but a drug role was not investigated or determined.

An illustrative case from FDA enforcement records involves two orphan drugs for the frequently fatal disorder of pulmonary arterial hypertension. In 2009 the FDA inspected Actelion Pharmaceuticals and cited it for failure to report 3,500 patient deaths for its specialty products bosentan (TRACLEER) and iloprost (VENTAVIS).[36] The company policy had been not to report as expedited, unexpected serious adverse events those patient deaths it learned about through its patient support programs when it had no information indicating the drug was responsible. But the information was included as an appendix to its quarterly periodic update reports. The company did seek confirmation from the healthcare provider, but response rates were low and only 3% indicated a possible drug role. At the insistence of the FDA, Actelion began submitting expedited reports within 15 days for every patient death it learned about through its patient support program. The result was that in this report study period Actelion reported 1,325 patient deaths for bosentan, including 566 containing no descriptive terms except the adverse event term “Death.” FDA inspectors were applying an outdated regulation to a situation not contemplated in current regulations and guidance.

## Top Priorities for Reform

The FDA’s Adverse Event Reporting System badly needs a thorough overhaul, if not a comprehensive redesign. It is possible to achieve substantial improvements in postmarket surveillance and better data quality with modest and low-cost improvements. Three priority areas include quality improvement, manufacturer-initiated contacts, and coverage of generic drugs.

## Quality Improvement

When a majority of manufacturer reports are not reasonably complete, quality improvement should be a priority. That some manufacturers and the FDA’s voluntary site routinely collect 85% or more reasonably complete reports shows this objective is realistic. Simple computer-driven assessment for each manufacturer’s submissions could provide more extensive feedback than much rarer on-site company inspections. Birth defects and adverse events in children should be priorities for increasing reporting rates and improving the quality of the reports.

## Manufacturer-Initiated Contacts

The system was designed to receive spontaneous reports about suspected drug injury from health professionals and consumers, worldwide. It was not designed to communicate miscellaneous safety information derived from patient support lines, restricted distribution pharmacies, and on-call nursing support.

With a series of pre-approved protocols for manufacturer-initiated contacts, it is possible to provide enhanced safety surveillance with a much higher reporting rate than expected from spontaneous reports. But these data are different from spontaneous reports and need protocols for the transactions and clear identification of the reports obtained through these channels.

## Generic Drugs

With generic drugs now accounting for 86% of dispensed prescriptions, improving coverage of these drugs should be a priority. A solution, however, is not as immediately evident as the topics addressed above. However, it is likely that the current regulations, which simply apply a system designed around brand name manufacturers to low-cost generics, are unlikely to provide satisfactory results. The only easy improvement is eliminating duplicate reporting from the medical literature by exempting generic drug manufacturers from the requirement to monitor scientific publications for case reports.

Programs to publicize and expand the FDA's direct, on-line reporting system could be one answer. Another possibility is selecting some healthcare practices to be sentinels for generic drug adverse event reporting, modeled on the CDC's sentinel system for monitoring influenza-like illnesses during the flu season.

## Future Opportunities

The digital tools and marketing practices that now enable extensive contacts between manufacturers, health professionals, and consumers can be extended to provide enhanced postmarket surveillance. A pilot program is needed to learn how to make physician adverse event reporting easily accessible from the now-required electronic health records. Research is needed to validate methods to collect automatically most of the relevant data. With standardized data systems to collect adverse event responses from manufacturer-patient contacts, these interactions could provide better intensive postmarket surveillance for high-risk drugs rather than the present situation, which produces large numbers of reports of dubious quality and value.

# Sofosbuvir Safety Profile

Sofosbuvir (SOVALDI) was the first of a series of new antiviral drugs that appeared to eliminate common hepatitis C genotypes 1 in 90% or more of patients after 12 weeks of treatment in various drug combinations. The drug was notable for its high cost--\$84,000 for a course of treatment—and the speed with which it was accepted in the medical community, generating \$2.2 billion in sales for Gilead Pharmaceuticals in the first 3 months after approval in December 2013.[37] Hepatitis C is an unusual viral disease, affecting about 3.5 million people, but with such mild symptoms that at least half of patients are unaware they are infected. Over 20-30 years, chronic infection progresses to cirrhosis in approximately 2-20% of patients.[38] In this subset, 1-2% a year develop liver cancer. The other unusual feature of this disease is that the infection and the benefits of the drug are measured solely with a laboratory assay to detect one of the hepatitis C viruses. If the virus could not be detected after 12 weeks of treatment, the FDA approval guidance deemed it a virologic cure.[39]

## Treatment Toxicity

Another major drawback to previous treatments for hepatitis C—in addition to limited efficacy— was the toxicity of the standard treatment regimen of ribavirin and pegylated interferon. An FDA safety review noted they are “associated with a panoply of toxicities affecting almost every organ system.”[40] One major problem was suppression of the bone marrow, causing anemia in 20% or more of patients; skin rashes and psychiatric side effects also occur. Given that sofosbuvir was going to be given in combination with these two antiviral agents for the most common form of hepatitis C, genotype 1, the safety question was what new or additional toxicities might occur by adding sofosbuvir to the combination therapy regime. The answer to that question can't be determined, because sofosbuvir for this virus genotype became among the first non-cancer drugs to be tested in an open label clinical study without a control group.

In a new policy of promoting innovation, “breakthrough drugs” may be exempted from the decades-old basic requirement for controlled clinical trials. The agency allowed Gilead to assess the drug for a key indication based on “historical controls.” In addition, it turned out that no actual historical controls were used to set the benchmark for proving benefit, but rather the FDA negotiated with the manufacturer a sustained

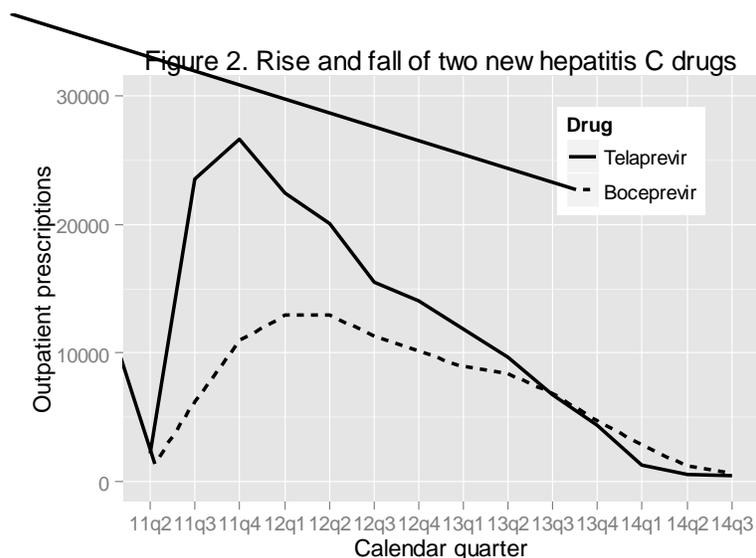
virologic response rate of 60%. In the event, sofosbuvir greatly outperformed the historical control target of 60%, achieving a sustained virologic response at 12 weeks of 90%.[41] At the time, this was the best laboratory test response achieved by any hepatitis C drug treatment. However, with 327 patients in an open label trial, it provided little information about what additional adverse effects sofosbuvir added to an already toxic pair of antiviral drugs. (For another group of patients—those with viral genotypes 2, 3, and 4—a comparison arm had been included.) From an efficacy perspective, sofosbuvir was an acceptable choice for the shortcut of an uncontrolled study. From a safety perspective, however, it meant that tens of thousands of patients were going to be quickly exposed to a new drug whose adverse effects had been poorly studied. The question was non-trivial, since another hepatitis C treatment—telaprevir (INCIVEK)—had been found to increase both the severity and number of adverse effects already known from the other two antiviral agents.

## Adverse Event Profile

With this uncertainty in mind, we examined the first quarter of all adverse drug event reports for sofosbuvir, locating 271 cases, including 8 patient deaths, but no signals of toxicity. The leading adverse event terms were headache (n = 42), fatigue (n = 32), and nausea (n = 29). Of these cases, 93% were submitted by the manufacturer, Gilead. However, the quality of these reports was well below average, even given the weak manufacturer performance noted elsewhere in this report. Only 38% of the Gilead cases were reasonably complete, and 53% did not even capture a patient age. We were also surprised that although anemia was reported in 21% of patients in the clinical trial of the genotype 1 patients, Gilead reported only 5 cases in the adverse event data. We also examined Gilead’s overall report quality, and it ranked near the bottom of all drug manufacturers in our study period, with 30% of reports being reasonably complete. We provided a summary of these results to Gilead, which attributed the problem to the individuals reporting the adverse events. “Adverse event reports received by Gilead from postmarketing sources are often scant and lack detail,” the company said in a statement provided to ISMP. However, Vertex, the manufacturer of a different new hepatitis C drug, telaprevir, ranked among the best in the industry, providing 71% reasonably complete reports for telaprevir compared to Gilead’s 38% for sofosbuvir, assessed separately. From a review of the adverse event report data and the clinical trial results, we did not detect any safety concerns for sofosbuvir. However, below average quality manufacturer reporting and an uncontrolled key pivotal clinical trial impair signal detection and make cases that are identified difficult to evaluate.

## Rapid Changes in Treatment

The rapidly evolving treatment landscape for hepatitis C drugs had many other notable elements. Telaprevir, the first of the direct acting antivirals approved in 2010, was rapidly accepted into medical practice despite the marked toxicity noted in QuarterWatch [42], and then abruptly declined as the more effective sofosbuvir became available. It was discontinued in October, 2014. Boceprevir (VICTRELIS), another direct acting agent approved at the same time as telaprevir, had limited success (Figure 2). The FDA has now approved a new generation of orally administered antiviral drugs that do not require combination therapy with ribavirin and weekly injections of pegylated interferon. The FDA approved ledipasvir-sofosbuvir oral combination therapy on the basis of an open-label study; it approved simeprevir (OLYSIO) for limited use in



Data from IMS Health, Inc.

specific viral subtypes; in December 2014 it approved VIEKIRA PAK, a combination of four antiviral drugs administered with and without ribavirin. A recent report indicated that 11 more direct acting antivirals for hepatitis C were in development. [43]

In the modern world of drug development and approval, an impressive new drug for a largely asymptomatic disorder can generate billions of dollars in revenue within weeks of approval, expose tens of thousands of patients to a new drug in a disorder where toxicity has been the rule rather than the exception, all with a minimum of preapproval testing capable of providing an adequate safety profile. This further underlines the need for an effective, modernized adverse event reporting system.

# QuarterWatch Team and Funding Sources

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