Health Affairs | Robert Wood Johnson Foundation

Health Policy Brief

JUNE 4, 2015

The FDA's Sentinel Initiative. The Food and Drug Administration has launched a new system to assess the safety of prescription drugs after they are approved for sale.

WHAT'S THE ISSUE?

Prescription drugs are a mainstay of medical care. In particular, people who have chronic conditions such as high blood pressure, diabetes, high cholesterol, or arthritis may take prescription medicines every day for years or decades. The majority of Medicare beneficiaries take at least one medicine for a chronic condition, and 25 percent take five or more. Generally, these treatments have been shown to manage or improve patients' health. But all drugs carry some risks. Sometimes these risks emerge in studies of the drug before its approval and are known by regulators, drug makers, and health care providers when a drug hits the market. Many risks, however, only become evident after drugs reach the market and begin being used.

For example, the nonsteroidal anti-inflammatory drug rofecoxib (Vioxx) was approved by the Food and Drug Administration (FDA) in 1999 and widely promoted for use as a pain reliever. But studies and analyses done after Vioxx hit the market confirmed that it raised the risk of heart attack. An estimated 40,000 people died as a direct or indirect result of taking the drug before it was taken off the market in 2004. The diet drug fenfluramine-phentermine (Fen-Phen) also was removed from the market after studies found its risks outweighed its benefits and that people had been harmed. Thus, vigilance about the safety of approved drugs is essential.

Until recently, however, the FDA had primarily relied on passive collection of adverse events obtained from manufacturers or through voluntary physician and consumer reporting to track emerging safety issues after drugs received FDA approval. The FDA also learns about potential safety problems from published studies and—on rare occasions—from studies conducted by drug makers to address a specific question posed by the FDA.

There are inherent limitations to relying both on passive collection of adverse event reports and on postmarket studies conducted by drug makers. For example, spontaneous reports may lack complete data and have little power to detect common events such as heart attacks and strokes that might be increased in connection with taking a drug. Prospective trials of safety issues are costly and can take years to conduct.

A confluence of recent developments—electronic health records (EHRs); new software tools; the advent of big-data analytics; and the increased focus on coordination and alignment among health systems, doctors, payers, and government to solve systemic problems in care delivery—now makes it possible to more

> "The Sentinel Initiative has the potential to enhance the FDA's ability to detect emerging safety problems with prescription medicines."

quickly and more efficiently track patient outcomes and treatment results on a larger scale.

One leading example of how these developments are changing the health care system is the FDA's Sentinel Initiative, which aims to use big data and broad networks to proactively and systematically detect and respond to emerging risks associated with prescription medicines.

WHAT'S THE BACKGROUND?

Prescription drugs undergo clinical testing for efficacy and safety before the FDA approves them for marketing. The preapproval testing process takes, on average, about six years. But preapproval clinical trials cannot detect every possible adverse reaction or safety issue that a new drug might cause. This is due to the fact that prescription drugs are almost always tested in limited numbers of patients (sometimes fewer than 500) in controlled settings, and the trials often exclude key populations of patients (such as women or the elderly) who would get the drug after its approval. Rare side effects may not show up at all in a study of a few hundred people, and studies involving a small number of people can lack the statistical power to discern whether common clinical events (such as an elevation in blood pressure) are linked to a drug.

Indeed, pharmaceutical companies often test new medicines in people who don't demographically or medically reflect the population in which the new drug might potentially be used. For example, a chemotherapy drug might be studied in cancer patients ages 40–60, but once approved the drug is used most commonly in cancer patients ages 70–85 with numerous comorbidities who are taking many other potentially interacting drugs. In addition, once a drug is available, doctors can prescribe it for additional indications not formally approved by the FDA (so-called off-label use).

For these reasons, once a drug is on the market and prescribed to hundreds of thousands or millions of people, it's not uncommon for safety problems or side effects to emerge that were never detected in the clinical trials that led to the drug's approval.

The FDA's Legacy Reporting System

The FDA's Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to the FDA by doctors, nurses, pharmacists, hospitals, lawyers, manufacturers, and consumers. Reporting into the system is voluntary, with one exception: If a manufacturer receives an adverse event report, it is required to send the report to the FDA—within fifteen days if it is serious and unexpected (that is, if the nature or severity of the report is not consistent with previous documentation). If it is not serious and unexpected, reports must be made quarterly for the first three years and annually thereafter.

FAERS data, updated four times a year, are available to the public yet not easy to use. However, the FDA's consumer-facing website, MedWatch, http://www.fda.gov/Safety/MedWatch/, now includes basic drug safety information, recent regulatory actions, and the option to sign up for alerts. It is also the platform through which adverse events can be reported.

The FDA has the authority to require manufacturers to conduct additional studies based on FAERS (and other) signals. The agency also has some authority to order a change in the drug's label (the formal guidance to doctors and pharmacists on its use), tell the media and consumers about the problem, or remove the drug or device from the market. FAERS has resulted in many label changes over the years but very few removals of drugs from the market.

FAERS has several serious weaknesses:

• For physicians and patients, reporting is voluntary and thus incomplete. Drug safety experts' best guess is that about 10 percent of adverse events are reported to FAERS.

But no one knows for sure. In 2013 FAERS received a little more than one million adverse event reports—a 30 percent increase over 2012, according to the FDA. FAERS now contains a total of nine million reports.

• Reports to FAERS are not validated because of the sheer volume. Still, the FDA does not believe that the system is widely abused. When a strong signal of a possible problem arises, related reports are scrutinized carefully.

• Many of the reports do not contain enough data to permit a full evaluation of a potential problem such as whether there is a causal relationship between a drug and an event. Use of FAERS reports is also often difficult because there are no related data describing the over-

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all use of the drug, which would serve as the denominator in any prevalence analysis.

The FDA's Limited Authority To Require Postapproval Studies

The FDA has the authority to require a drug company to conduct a safety study on an approved drug if FAERS finds a signal or if other studies signal that there may be a problem. But the authority has limits defined in law. For example, the agency can't order such a study unless there's a perceived "serious risk." The FDA has, in practice, set a high bar on the definition of *serious risk* and has ordered up relatively few postapproval safety studies. In addition, the agency has been criticized for allowing pharmaceutical companies to delay or drag out postmarket safety studies for years, as well as for not sharing full data when such studies are completed.

WHAT'S IN THE LAW?

In the wake of the Vioxx's removal from the market and several other high-profile drug safety problems in the early 2000s, Congress in 2007 mandated that the FDA develop a program and computer-based system to track and analyze the safety of drugs after they hit the market.

In May 2008 the Department of Health and Human Services (HHS) and the FDA launched the Sentinel Initiative. Then-HHS secretary Mike Leavitt pledged "a national, integrated, electronic system for monitoring medical product safety." Ultimately, he said, Sentinel will "help monitor medical products throughout their entire life cycle and thus better ensure the protection and promotion of public health." He pledged the system would be "created through public/private partnerships... [which will] make it possible for the agency to access large, existing electronic databases without compromising patient privacy."

Notably, Leavitt also said that Sentinel would be yoked to another initiative—the Nationwide Health Information Network (NHIN)—which would "connect clinicians across the health care system and enable the sharing of data as necessary with public health agencies."

The NHIN never materialized and eventually morphed into successive efforts—still ongoing and controversial—to create a nationwide interoperable system with EHRs at their core.

As an initial step toward building the FDA's Sentinel system, ten smaller contracts were awarded by the agency to target issues surrounding data infrastructure, privacy, methodological issues, and stakeholder engagement. In 2009 a contract was awarded to Harvard Pilgrim Health Care, a nonprofit health insurer based in Wellesley, Massachusetts. The contract specified that Harvard Pilgrim create a Sentinel coordinating center and evaluate scientific methods to be used in a fully operational Sentinel Initiative. This pilot project came to be called Mini-Sentinel. The FDA also awarded a cooperative agreement to the Brookings Institution to convene workshops and an annual meeting on Sentinel.

In September 2014 the FDA announced the end of Mini-Sentinel and the formal launch of a full-scale system. It awarded up to $150 million to Harvard Pilgrim to continue to develop and lead the system over the next five years.

Sentinel Today

Sentinel is a distributed data network—that is, the data are not collected in a central computer repository but are instead held and owned by participating organizations in a standard format that can be tapped and mined as necessary.

The Sentinel network consists primarily of eighteen organizations that include some of the nation's largest health insurers (Aetna, Anthem, Humana, Kaiser Permanente) and various disease registries. In addition, other institutions have collaborated in establishing the network, and the FDA says that it has access to selected data from eighty-eight hospitals and other inpatient facilities.

Overall, the FDA and Harvard Pilgrim say that they have access to prescription medication data on approximately 178 million people, with the routine accrual of medication data on 48 million currently enrolled or treated at the eighteen core partner organizations. Sentinel, they say, has 358 million person-years of data that include 4.0 billion prescriptions, 4.1 billion doctor or lab visits and hospital stays, and 42.0 million acute inpatient stays.

The data derive primarily from medical bills (claims), but a growing portion comes from EHRs or laboratory results (approximately 10 percent)—a portion expected to grow steadily in coming years. Here's how the system works to proactively assess drug safety:

178
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• Prompted by a signal from FAERS, clinical trials, meta-analyses, case reports, or other regulatory bodies outside the United States showing a potential link between a prescription drug and an adverse event or safety risk, the FDA and Harvard Pilgrim staff and authorized researchers from collaborating institutions send a query via a secure portal to Sentinel's network of data partners.

• The data partners then conduct the query within their systems. All use the same analytical program. The partners are required to update their data sets periodically, with the largest data partners doing this quarterly and less frequent updates coming from smaller partners.

• The findings are returned from each data partner through a secure portal. A team of data experts ensures the data quality before giving the FDA the findings.

Achievements

Sentinel today is one of the largest distributed-network medical data projects in the United States. Indeed, its development has helped inform other similar projects. In practice, because it is unique, the network is being used to do more than probe links between drugs and adverse events. For example, increasingly sophisticated statistical methods are being applied to Sentinel data with the aim of detecting disease trends and patterns.

But drug safety is still Sentinel's main purpose. And there the achievements are less impressive. As of February 2015, queries that occurred under the Mini-Sentinel phase of the initiative have led to assessments of 137 drugs. Of those, the FDA has probed eighteen (several are ongoing) and has issued a drug safety communication in just four cases. Two examples:

• A Sentinel probe confirmed FAERS reports and anecdotal accounts from doctors and patients that patients who took the antihypertensive drug olmesartan for long periods of time developed intestinal problems. As a result, the FDA added a warning to the drug's label.

• A Sentinel study of the relationship between the new anticoagulant drug dabigatran (used to treat atrial fibrillation, a heartbeat irregularity) and a purported dangerous risk of bleeding found the drug carried the same risk as other anticoagulants drugs. The finding—still somewhat controversial, with disagree-

ment among experts and additional studies producing conflicting results—contributed to an FDA message to doctors that a reported higher risk associated with the highly prescribed new drug had not been verified.

A list of Sentinel queries and results can be found here: http://mini-sentinel.org/Reports/.

WHAT'S THE DEBATE?

The FDA and Sentinel's managers at Harvard Pilgrim continue to tackle unresolved issues about data integrity, validity, and reliability; the reproducibility of results; how the FDA plans to integrate FAERS and Sentinel data with manufacturer data and other input to wield its regulatory club; and whether Sentinel can be expanded to be used for medical devices.

Some critics allege that the FDA overstates the usefulness of Sentinel in its current state. They assert, for example, that most of the data still come from claims (medical bills) that poorly relate to actual patient outcomes.

Most important, Sentinel has not yet become a tool for the rapid assessment of potential drug safety problems, which was one initial vision for the system. That's in large part because of persistent technical and methodological challenges. It's also because the complexity of drug usage in humans often conspires against easy answers. And conflicting findings from different databases and studies can still lead to confusion and slow action, despite the power of Sentinel's database.

One recent study in the *American Journal of Epidemiology* by David Madigan and colleagues, for example, examined ten large drug and medical databases focused on the adverse risks associated with ten specific drugs or types of drugs. They found that the databases did not always agree on the risk profile of a drug or class of drug. The authors concluded that simply pooling data or performing a large-scale meta-analysis doesn't necessarily yield the truth about a drug's risk. However, the authors also observed that the more databases that researchers could draw on, the better the analysis would likely be. Thus the study offers an implicit critique of Sentinel but also a boost, since Sentinel queries are structured to receive input from multiple databases.

Another major critique of Sentinel is that the FDA has taken only a handful of regulatory actions with input from Sentinel probes. This

may be consistent with the agency's reputation for caution. The paucity of regulatory actions may be because the FDA has not yet devised a clear path to regulatory action based on the combined results of FAERS, Sentinel, and post-market studies done by manufacturers and others. As discussed above, the FDA has authority to require companies to do postapproval studies when potential safety signals arise. Sentinel should, in theory, make such studies more precise and perhaps more common.

Consumer advocates would like to see the FDA ramp up an "early warning" system to alert physicians and the public about potential problems with drugs and devices if warranted by the signals from FAERS and Sentinel. This, however, raises another question: If FAERS and Sentinel do reveal a possible, but not yet definitive, problem, what should the FDA tell doctors and the public? The FDA needs to address that issue.

WHAT'S NEXT?

The FDA and Harvard Pilgrim plan to increase the number and types of Sentinel data part-ners over the next few years. At the same time, FDA officials have pledged to collaborate on the creation of a national data infrastructure that would "enable other users (for example, other governmental agencies, researchers from academia or industry) to access the Sentinel infrastructure for medical product research and quality improvement."

To achieve that goal, the FDA says it will partner with other data initiatives. Those include the Innovation in Medical Evidence Development and Surveillance program, now housed at the Reagan-Udall Foundation, an organization established by the FDA Amendments Act of 2007; the National Patient-Centered Clinical Research Network housed at the Patient-Centered Outcomes Research Institute; and the National Institutes of Health Collaboratory Distributed Research Network.

Sentinel is at the cutting edge of the big-data revolution. It has tremendous promise. But the FDA has yet to prove that it can use this new tool to its full potential. That may now change as Sentinel transitions from a pilot project to a full-scale program. ∎

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