When the Food and Drug Administration (FDA) approved Merck’s quadrivalent human papillomavirus vaccine (Gardasil) on June 8, 2006, the agency extracted some post-approval commitments from the company, as it frequently does when it “green-lights” an important new drug around which questions still revolve. Those commitments involved additional testing of Gardasil after it went on the market, particularly in girls 11 to 12 years of age. Only a small number of girls in this age group had participated in Merck’s clinical trials, and these trials were submitted as evidence of the drug’s efficacy and safety. That patient population would loom large in the months after the FDA’s approval as Merck mounted a political campaign to convince states to require the vaccination for sixth-grade girls.

However, the post-approval studies that Merck agreed to perform would not start before June 2009, if then. That short-term safety surveillance study is set up to follow 44,000 vaccinated subjects for just 60 days to monitor visits to hospital emergency departments and for six months to monitor chronic problems such as autoimmune disorders, rheumatologic conditions, and thyroiditis. Merck must include a “sufficient” number of children (ages 11 to 12), although no number is specified in the FDA’s charge to the company.

Other companies that have committed to similar post-approval studies have dragged their feet and, in some instances, have simply ignored the FDA. The FDA has no authority to force a company to complete a study. Even when a study is finished and the FDA receives the data, there is no guarantee that the results—if they are in any way disquieting—will prompt a suitable reaction on the part of the agency, such as immediately requiring new labeling or, in more serious instances, pulling the drug from the market.

In the past few years, a number of unfortunate instances, particularly the rofecoxib (Vioxx, Merck) fiasco, have shown that it is easy for the FDA, because of shortcomings in the data, as well as because of bureaucratic malaise and communication gaps, to miss credible warning signs of drugs “gone wild,” producing numerous adverse reactions.

During the past couple of years, these and other potential problems have been highlighted, first by the U.S. Government Accountability Office (GAO) and later by the Institute of Medicine (IOM), whose report was requested by the FDA. Both the IOM and the GAO cite the failure of drug companies to complete post-marketing studies on time; they also cite the FDA’s lack of authority to compel timely completion.

Serious limitations also afflict the FDA’s MedWatch system, which catalogues reports of adverse drug events (ADEs). Moreover, even when troublesome signs appear after a drug is on the market, that evidence might not be available to the FDA’s Office of Surveillance and Epidemiology (OSE), formerly known as the Office of Drug Safety (ODS). The OSE is set up to ensure that post-marketing problems receive quick attention. It is subservient to the FDA’s Office of New Drugs (OND), which has considerably more stature within the Center for Drug Evaluation and Research (CDER) and which has sometimes been criticized for turning a blind eye to emerging evidence of late-blooming safety questions about new drugs.

Sheila Burke, MPA, RN, Chair of the IOM committee whose members wrote its report, says:

“We found an imbalance in the regulatory attention and resources available before and after approval. Staff and resources devoted to pre-approval functions are substantially greater. Regulatory authority that is well defined and robust before approval diminishes after a drug is introduced to the market. Few high-quality studies are conducted after approval, and the data are generally quite limited.

These weaknesses explain why post-marketing surveillance of drugs is the marquee issue as a major FDA reform bill sashays (or, more appropriately, staggers) down the red carpet of the Congress to the White House—because senators tussled over multiple amendments when that bill, the Prescription Drug User Fee Act (PDUFA) Reauthorization (S. 1082), came to the Senate floor this past May. Controversial amendments involving drug importation and the approval of follow-on copies of biotechnology drugs were removed from the PDUFA bill. However, although there were pitched battles over the provisions in another amendment, the FDA Revitalization Act, sponsored by Senator Edward Kennedy (D-Mass.), there was no question that the post-marketing reforms in the Kennedy bill would be included in the final PDUFA bill, and they were. However, those post-marketing changes were not nearly as far-reaching as Senator Charles Grassley (R-Iowa) had wanted; he had also sponsored a competing FDA post-marketing reform bill.

The House of Representatives is likely to adopt the provisions of the Senate’s bill on post-marketing surveillance, and the bill will probably be sent on to President Bush to sign; he says that his signature will be forthcoming. But before we look at these changes in the Senate bill, it is necessary to outline the problems they aim to resolve.

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The FDA’s MedWatch system is the agency’s first line of defense against a newly approved drug whose side effects, whether or not they have been acknowledged in clinical trials, cast a much darker shadow than previously thought. Physicians, pharmacists, patients, and drug companies send in reports of adverse reactions as the drug begins to be used and potential problems become evident. But even the FDA has admitted the system’s shortcomings. In a November 2006 speech, Scott Gottlieb, MD, Deputy Commissioner for Medical and Scientific affairs at the FDA, acknowledged that MedWatch is a valuable tool but “we know that it is not being used as effectively as it ought to be.”

The FDA and other agencies go by this general rule: for every 10 adverse reactions reported, only one report is submitted to the FDA. Of course, even that minimal number of reports can be useful.

An example is Sanofi-Pasteur’s Menactra, a vaccine designed to prevent bacterial meningitis. The FDA approved that vaccine on the basis of clinical trials involving 7,000 children, none of whom had contracted Guillain-Barré syndrome (GBS), a neurological disorder. But lo and behold, when the drug reached the market, reports of GBS developing in the children after inoculation with Menactra began to filter in to the Vaccine Adverse Events Reporting System (VAERS). VAERS is the Center for Biologics Evaluation and Research’s version of MedWatch.

Initially, there were only five reports. The FDA decided not to change Menactra’s labeling, because those five reactions were expected to be the norm with the introduction of a new vaccine. At the time, however, the FDA noted that ADEs associated with the vaccine were not always being reported and that there might be additional cases that the agency might not be aware of.

When Caroline Loew, PhD, Senior Vice President of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA), appeared before a House committee in May 2007, she gave a more expansive analysis of MedWatch’s flaws:

One of the shortcomings of this system is the variable nature of reporting and the quality of reports. Ultimately, any database is only as good as the underlying data, and one of the chief difficulties with adverse event report databases is quality. Precious resources are often expended in contacting health care professionals regarding aspects of a report they have filed. In many instances, the reporter is unable or unwilling to provide sufficient detail for analysis.

The FDA has been moving on its own to address this problem. At the start of 2007, the agency announced steps it would take with the extra $90 million it expects to receive in fiscal 2008 from the higher PDUFA fees that Congress is in the process of authorizing.

One step would be to publish a request for proposals from outside research organizations that would assist in determining the best way to maximize the public health benefits associated with collecting and reporting serious and non-serious ADEs throughout a product’s life cycle.

Central to addressing this question are:

- determining the number and type of safety concerns discovered by collecting the reports of ADEs.
- the age of products at the time safety concerns are detected by the collection of ADEs.
- the types of actions that are taken next to protect patient safety.

In early March, the agency took the next step by sponsoring a public meeting to explore opportunities for linking post-marketing monitoring systems in the private and public sectors to create a virtual integrated, interoperable nationwide product safety network. Such a “sentinel network” could integrate existing and planned private and public sector databases to enable the collection, analysis, and dissemination of safety information about medical products to health care professionals and patients at the point of care; that would be in the clinic, where this information is needed to make informed decisions about safe and effective treatments.

One of the Kennedy provisions in the FDA Revitalization Act essentially seconds the FDA’s motion toward a sentinel network. It authorizes a public and private partnership to establish a routine active monitoring system that would create a “pool” of relevant data assembled from federal and private electronic databases of the health care population. This apparently would be a complement to—or even a rival to—MedWatch. According to the Kennedy bill, the data pool would have to have 25 million patients swimming it by January 1, 2009, and 100 million patients by January 1, 2012.

Although Senator Judd Gregg (R.N.H.) backed a competing bill called the Safer Data bill, he agrees with Senator Kennedy’s challenge to the FDA that it set up an active surveillance system. However, he claims that the Kennedy timetable is too leisurely:

I strongly support this in concept but feel the language needs to be strengthened to ensure that the FDA has the direction it needs to implement a robust system in an expedited timeframe. Information collected must be standardized, and the overall system should be validated.

Despite Senator Gregg’s criticism, it is difficult to see how the FDA could assemble a pool of 25 million electronic health records (EHRs) on Kennedy’s timetable, much less on a faster one. There are 85 million Medicare and Medicaid recipients, but neither of those two federal systems has mandated that physicians produce EHRs. In the private sector, Kaiser Permanente has been the leader in developing EHRs, and it now has them for half of its 8.5 million patients, according to Paul Wallace, MD, Medical Director of Health and Productivity Management Programs at the organization.

The Kennedy proposal, which the House will probably accept, does nothing to correct MedWatch’s debilities. It simply layers a new early warning system based on EHRs on top of MedWatch. However, a second Kennedy proposal promises a better benefit in the near term.

Another element in the Kennedy-sponsored FDA Revitalization Act allows the FDA to order drug companies to prepare Risk Evaluation and Mitigation Strategies (REMSs) for new drugs; this might go a long way toward completing post-marketing studies more quickly.

Vol. 32  No. 6 • June  2007  • P&T • 323
There is no question that drug companies have fiddled with completing these studies, which explains why nearly everyone in Congress is livid. The FDA itself has acknowledged that drug companies decline to perform a significant percentage of the post-marketing studies requested.

The agency’s own statistics for 2006 show that drug companies failed to initiate more than 70% of post-marketing studies that they committed to performing during that year; 899 of the 1,259 post-marketing studies (71%) promised had not begun as of September 30, 2006. This was an increase of 5% over fiscal year 2005. When that report first came out, Representative Rosa DeLauro (D-Conn.), Chairman of the House Appropriations subcommittee, which approves the FDA’s annual budget, said:6

This report clearly demonstrates that drug companies do not intend to keep these promises and that drug companies are taking advantage of FDA’s lack of authority to require these studies.

However, PhRMA’s Dr. Loew has a different take on the numbers:4

While it is true that 71% of open commitments are considered ‘pending,’ these ‘pending’ studies are in the preparatory phase of clinical trial development during which the protocol is drafted and submitted to FDA, IRB approval is obtained and the sponsor begins recruiting clinical investigators. If sponsors simply failed to initiate such studies, the studies would be coded as ‘delayed’ rather than ‘pending.’ However, only 3% of open studies are considered to be ‘delayed.’

No one disputes the value of post-marketing studies. Nothing bears out their worth better than the pediatric studies performed by drug companies in order to get an extra six months of marketing exclusivity, which the Best Pharmaceuticals for Children Act (BPCA) grants them.

For example, a 2007 GAO report about this act showed that about 87% of the drugs that were granted pediatric exclusivity under BPCA required labeling changes—often because the pediatric drug studies found that children might have been exposed to ineffective drugs, ineffective dosing, overdosing, or previously unknown side effects.

And no one disputes the fact that the FDA does not have the authority to compel drug companies to complete studies. The Kennedy bill changes that by allowing the FDA to force companies to accept REMSs when it approves a new drug. A REMS could require that a company conduct post-approval studies, such as a prospective or retrospective observational study, or even a clinical trial, if a study was thought to be an insufficient means of assessing a signal of a serious risk or of identifying an unexpected serious risk. In addition, for the first time, the FDA would be able to issue civil fines of up to $250,000 for not meeting a study deadline, with the amount of the penalty doubling every 30 days, up to a total of $2 million—figures that Senator Grassley insisted be increased from the $10,000 and the $1 million levels in the Kennedy bill. The Senate agreed by a strong majority.

However, by a narrow vote of 46–47, Senator Grassley failed to establish a separate safety office within the CDER that would have equal standing to the OND. Both the IOM and the GAO highlighted the institutional weakness of the OSE, which at the time of the GAO report was called the Office of Drug Safety (ODS).

The GAO report from March 2006 described the OSE as subservient to the OND. When the GAO finished its report, the office had had eight different directors in the previous 10 years. The GAO said that the ODS’s Division of Drug Risk Evaluation was responsible for culling data on adverse drug reactions from MedWatch and for making recommendations to the OND. However, the “new drug folks” did not always listen closely to that advice, and they even barred ODS staff members from appearing before FDA advisory committees when those committees were meeting to recommend the approval of new drugs and handle other matters.

Equally disconcerting was another GAO finding: even when the ODS made recommendations to the OND, no one at the ODS stayed abreast of that particular problem to see how events played out.

Steven Galson, MD, MPH, Director of the CDER, has attempted to at least partially correct those bureaucratic disconnects by elevating the OSE to report directly to him, instead of through the OND. In addition, he established a new position of Associate Center Director for Safety Policy and Communication to focus on developing and implementing broad drug safety and communication policies. Senator Grassley wanted to go further by setting up a separate drug safety office on a par with the OND, but the Senate rejected that approach. The Kennedy bill does not address the OND/OSE imbalance at all.

However, a second Kennedy bill, called the Enhancing Drug Safety and Innovation Act, which was also included in the PDUFA reauthorization, attempts to broaden the flow of clinical trial data into the FDA’s hands. It sets up a new national FDA-administered clinical trials registry and requires that all clinical trials supporting applications for drug approval, as well as all clinical trials conducted with federal funding, be included in that registry. When Senator Kennedy introduced this act on the Senate floor, he explained the need for this new FDA registry by referring to results from clinical trials on selective serotonin reuptake inhibitor (SSRI) antidepressants, which have been linked to suicide in teenagers.

He noted, “Tragically, such information was not adequately available.”

However, all sorts of caveats are in the bill, allowing the Secretary of Health and Human Services (DHHS) to waive reporting requirements. (The FDA is part of the U.S. DHHS.)

Moreover, although it is difficult to argue with the [rationale] for requiring quicker publication of clinical trial data, it is important to keep in mind the limitations of that data. When she appeared before the House Energy and Commerce Committee on May 9, Marcia Crosse, Director of Health Care Issues for the GAO, explained:7

Clinical trials typically have too few enrolled patients to detect serious adverse events associated with a drug that occur relatively infrequently in the population being studied. They are usually carried out on homogen[e]ous populations of patients that will actually take the drugs. For example, they do not often include those who have other medical problems or take other medications. In addition, clinical trials are often too short in duration to identify adverse events that may occur only after long use of the drug. This is particularly impor-
tant for drugs used to treat chronic conditions where patients are taking the medications for the long term.

Given the major problems that the FDA has had in recognizing the initial warning signs of questionable safety and efficacy associated with some new drugs, maybe it is too much to ask that Congress fix those problems in one fell swoop. Certainly, giving the FDA the authority to fine companies who miss deadlines for post-marketing studies gives the agency important new leverage. And the clinical trials registry can’t hurt. But to the extent that the OSE remains a weak cousin within the agency and to the extent that the MedWatch system remains as leaky as a New Orleans levee in the wake of Hurricane Katrina, it is likely that a new Vioxx-type situation will occur, perhaps sooner rather than later.

REFERENCES