

PHARMACEUTICAL GOMMERCE

Business Strategies for
Pharma/Bio Success

Adverse Event Reporting: At the Front Lines of Drug Safety

Industry and regulators are taking steps to revolutionize the basic regulatory function of collecting and analyzing adverse medical events

By Nick Basta

The metaphor of changing an airplane's engine while in flight comes to mind when looking at the current landscape of pharmacovigilance and the adverse event report (AER) process. The system is widely acknowledged to have serious flaws, especially in underreporting events; there is disagreement over how AERs should be analyzed, and difficulties at FDA in simply keeping up with their flow; and there are there are dramatically new approaches in the offing, but adopting them broadly will take some heavy lifting.

Meanwhile, per long-standing regulatory mandate, every manufacturer (and repackagers and distributors as well, to get technical about it) is required to collect and codify AERs as they come in from healthcare providers, patients and caregivers, and report them to FDA on a schedule. The volume of AERs is now approaching 700,000 annually in the US (Fig. 1)—which is somewhat paradoxical because more AERs are generated early in new drug's commercial existence, and the number of new drugs has been flat for several years now. More importantly, the number of serious adverse events—those that cause life-threatening conditions or result in permanent impairment—is rising. (Both the growth of AER volume and the serious AEs, though, could be attributed to better data collection and more energetic reporting.)

The Vioxx debacle from 2004, when a widely used, heavily promoted pain medication was withdrawn from the market after unforeseen cardiac arrests occurred among patients, continues to drive pharmacovigilance structure. FDA has embarked on ambitious plans—Project Sentinel, the Observational Medical Outcomes Partnership, and FAERS, the FDA Adverse Event Reporting System (an update to its existing AER system). MedWatch, the basic intake system for AERs is in the process of becoming MedWatch-Plus. The FDA Amendments Act of 2007 led to the creation of an FDA Office of Surveillance and Epidemiology (OSE), along with directives for the new research efforts.

“Today's system is a mess,” bluntly states Dr. Edward Fotsch, president of PDR Network, a for-profit subsidiary of the iHealth Alliance, which is a united effort among medical societies.

“Everyone [we've talked to] agreed that the AERS [Adverse Event Reporting System, of which MedWatch is part] is seriously flawed,” stated Dr. Stephen Spielberg, head of an FDA advisory panel, in a presentation to the FDA Science Board in

November. “Spontaneous” reports—i.e., the usual reports generated by doctors and patients, not part of a clinical study—“lack critical information” such as the drug manufacturer involved or the gender of the patient. The MedWatch takes too long to fill out, and FDA's internal system



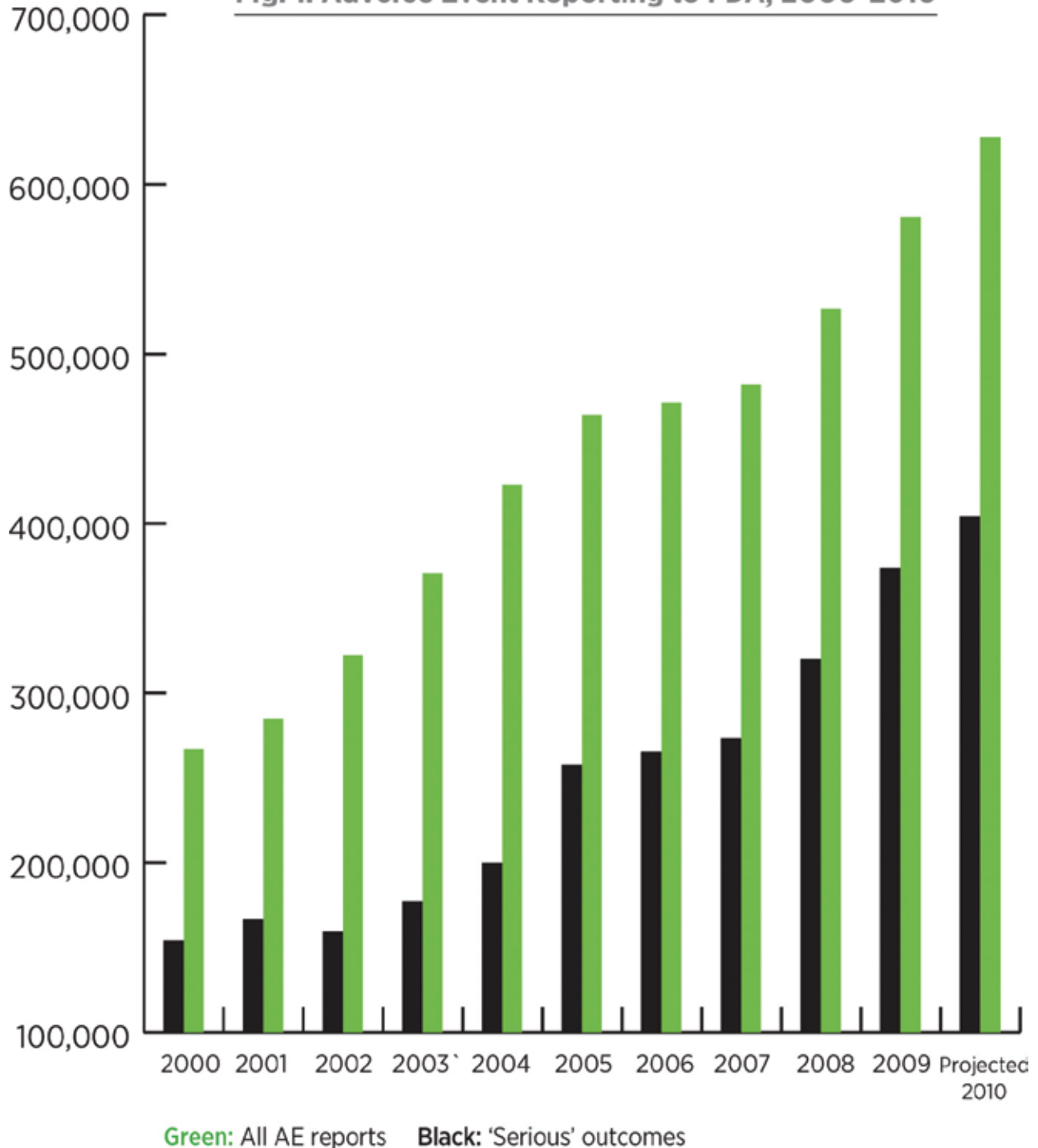
for analyzing data (which often starts with a paper report filing) is cumbersome. Even the procedures by which data are to be analyzed are inconsistent, leading to equally unclear results.

“Recent research has shown that when you look for relationships in healthcare data, the method you use can determine the results you find,” says Wayne Kubick, senior director, product safety, in Oracle’s Life Sciences group. Oracle has made big moves in the past few years in pharmacovigilance, having acquired Argus Safety Systems, a developer of software for adverse event reporting, and Phase Forward, a leading clinical research IT company.

Know the code

Basic AER services are generating healthy business growth for companies that provide outsourced services: call centers staffed with trained health professionals to intake the reports, and IT systems and services to help store and analyze the data. For manufacturers, AER processing is a necessary part of drug commercialization, but it also represents potential insights into new treatments and new therapies. At the clinical research level, AERs are a basic part of the research process; they are what lead to the indications and side effects listed on the label of any approved drug.

Fig. 1. Adverse Event Reporting to FDA, 2000-2010



A 2010 study by Cutting Edge Research (Durham, NC), “Benchmarking Drug Safety and Pharmacovigilance,” found that on a per-product basis, pharma companies spend an average of \$686,000 to manage overall drug safety data collection and analysis (for both clinical and commercial activity). Outsourcing is a growing trend; across all companies surveyed, 28% of their drug-safety budget was spent on outside contractors, but this varies from low ranges among some big pharma companies to essentially 100% at small startups.

“Vendors now offer to perform just about every drug safety task necessitated by regulatory authorities,” says the Cutting Edge report. “This means that companies can outsource virtually all of their drug safety needs.”

“The best system is to have trained medical professionals at the intake call center who can capture the essential information about an adverse event—patient medical data, drug and dosage details, the description of the adverse experience,” says Carole DeRoche, president of DDN Medical Affairs, a Dohmen Co. (Menomonee Falls, WI). “The medical event is then coded, usually according to the MedDRA system, to standardize medical terminology.” (The Medical Dictionary for Regulatory Activities originated in the UK and is now maintained under the auspices of the International Council of Harmonisation, ICH.)

AEs can be “serious” or “nonserious,” and “expected” or “unexpected”—the latter referring to AEs not listed as side effects of a drug. While all AEs ultimately get reported, FDA is most interested in serious, unexpected AEs, because those could be the signal of a new characteristic of a drug. AEs must be filed with FDA within 15 days of being reported, and collated quarterly reports are required for the first three years of a new drug’s entrance, and annually thereafter.

“Analyzing the AE details is a critical part of the process,” says DeRoche. “Medical doctors assist in the determination, and some AEs require additional followup such as gathering medical records.”

What drives the outsourcing decision, of course, is economics. Swantek says that a medium-sized AER program handling around 1000 AEs annually can cost \$750,000-1 million for staff, IT resources and overhead; employing a service provider that handles multiple clients can cut that in half or more.

Other companies in the outsourced AER business include Drug Safety Alliance (Durham, NC); Sentrax Safety Solutions (Little Falls, NJ); WRB Communications (Chantilly, VA); Proherent Health (Cordova, TN), a business unit of Medco Health Solutions; and the ICS unit of AmerisourceBergen Specialty Group (Frisco, TX). Clinical research organizations (CROs) have extensive capabilities in dealing with patient outcomes; those that put an emphasis on Phase IV or post-marketing compliance studies also handle AER processes. These include Parexel (Waltham, MA); PPD Inc. (Wilmington, NC); Quintiles (Durham, NC); among others.

PDR Network, which is now comprised of an online communications platform linked to by medical societies, and the publishing operations surrounding the Physicians Desk Reference, is developing an AER service to complement its services for transmitting label information and safety alerts to medical professionals. “Analysts have found that it takes a doctor up to 45 minutes to fill out an AER for MedWatch, and then even more time to provide follow-up information when desired,” says Fotsch. “Our goal will be to integrate AERs with electronic health records for a fast, easy-to-use, Web-based system.” The project is due to come online in the next couple months.

Active surveillance

Mention of EHRs highlights one of the most dynamic parts of pharmacovigilance: using already-collected and digitized medical files to provide the source material for ongoing safety reviews. This is the goal of the FDA Sentinel project, which kicked off in May 2008 with a goal (that

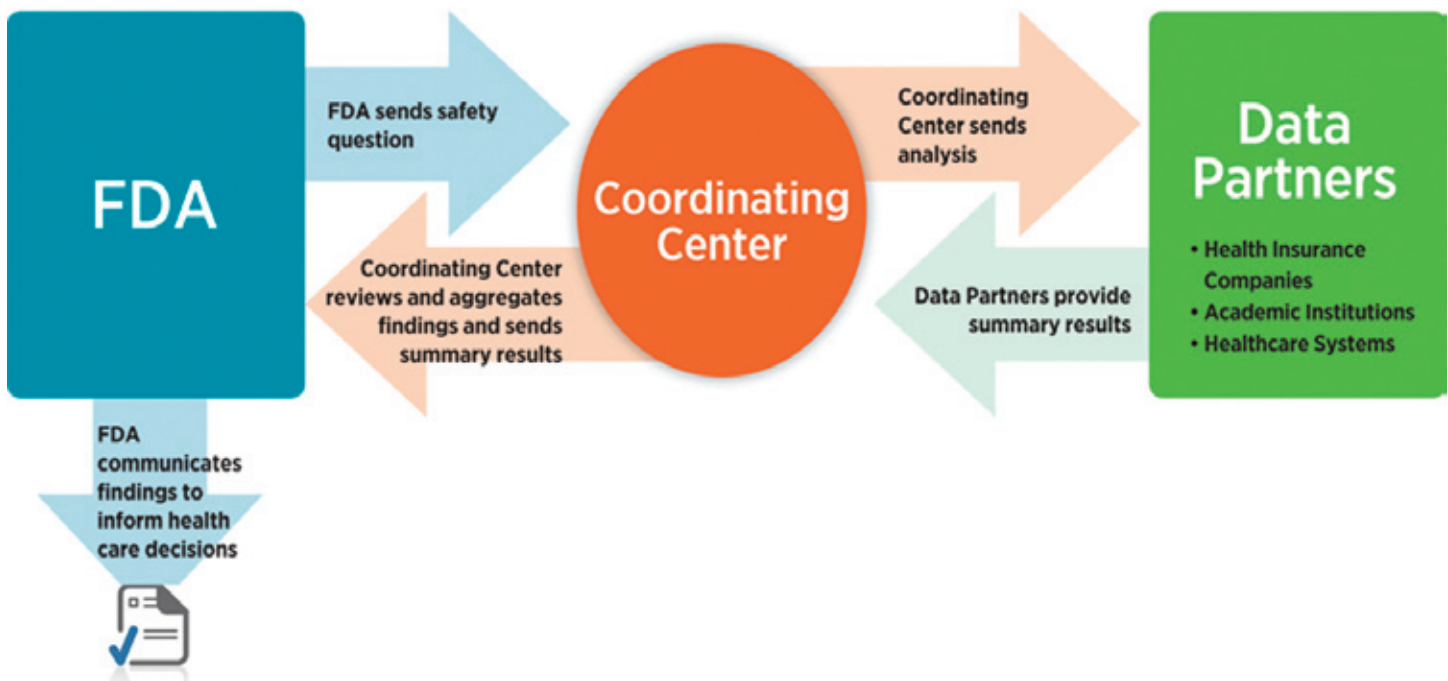
The Pharmacovigilance Process



“Outsourcing doesn’t have to be an all-or-nothing decision in a pharmacovigilance program,” says Steve Swantek, president of Prozar Corp. (St. Paul, MN), another service provider. He says that many of the companies in this business are able to segment their services to specific parts of the overall program, allowing client pharma manufacturers to allocate resources for best fit. “A client might need expanded capabilities during a product launch, but not indefinitely into the future. Or a client might want to outsource basic call center activity, but retain the data analysis.”

has been met) of having 25 million medical records available for analysis by July 2010. The Sentinel Project is part of FDA’s Critical Path Initiative, a longrange effort to move FDA’s overall regulatory processes to a more modern, data-intensive mode.

Fig. 2. Overview of the Mini-Sentinel Safety Question Evaluation Process



Since the 2008 startup, the Sentinel Project has spawned a “Mini-Sentinel Project”—essentially a proof-of-concept pilot that involves a handful of healthcare centers and academics, including Harvard Pilgrim Health Care, the Kaiser Foundation Research Institute, Humana and others (minisentinel.org). At the Third Annual Sentinel Initiative Workshop, held by Brookings Institution in Washington, Mark McClellan, director of the Engelberg Center for Health Care Reform at Brookings (and former CMS Commissioner) noted that Mini-Sentinel, while still “a work in progress” is already a “remarkable resource for gathering evidence and for learning more from the practice of medicine ... in this country.” McClellan also focused on one of the key attributes of Mini-Sentinel (as is intended to be the model of the overall project): it is a “distributed database network,” where “there is not some central database or repository somewhere where everyone’s information, increasingly complex information, gets dumped and held. Instead, the underlying data used in the project stay with the data owners, the people who are actually using these data in the delivery of healthcare, the payment of healthcare, for actual healthcare activities in some way.” A New England Journal of Medicine article on Mini-Sentinel was published simultaneously with the Brookings event (10.1056/NEJMp1014427, Jan. 12, 2011).

Multiple studies are either under way or about to start with Mini-Sentinel, but one in particular will be a dramatic test of the entire undertaking: monitoring the cardiac effects of use of Bristol-Myers Squibb’s Onglyza (saxagliptin) diabetes control product, recently approved (2008), and one that has parallel clinical trials going on. Other diabetes products, pioglitazone, sulfonylurea and long-acting insulin

will be comparators. The study will run across 1.3 million patients with Type 2 diabetes, and run until 2013. Unlike a conventional clinical trial, however, the data will come out of EHRs from Kaiser Permanente and others; these EHRs are structured primarily for hospital billing purposes.

Running somewhat in parallel with the Sentinel initiative is a public-private collaboration, the Observational Medical Outcomes Partnership (OMOP; omop-fnih.org) between the Foundation for the National Institutes of Health, PhRMA and FDA. OMOP is focused more on the scientific and statistical tools to conduct safety analysis; its literature is speckled with phrases like “disproportionality analysis,” “maximized sequential probability ratio test” and the like. A “library” of analytical methods will be developed and compared, and then their value in working with observational datasets will be studied. The overall goal is to improve the science underlying signal detection in outcomes datasets as well as AERs.

“The advantage of active surveillance of medical data over passive, individual-initiated spontaneous reporting, is to get signals much earlier and from a much broader patient population than conventional methods,” says Oracle’s Kubick. “The problem, though, will be the ability to take what is essentially a health-record or claims-processing database and make it suitable for secondary research—can the data be translated and compared, can you adjust for bias and confounding, will the data structures be interoperable? It’s a complex problem.” **PC**