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Making a difference

If there is one thing that the new team at the US Food and Drug Administration should immediately implement, it is a comprehensive, open database of drug-related adverse events.

Margaret A. Hamburg is US President Barack Obama's nominee as the next leader of the US Food and Drug Administration (FDA), and Joshua Sharfstein, who has been leading the Obama administration's interim team looking at FDA, is slated to become Hamburg's chief deputy. The nominees are seen as an antidote to five years of anemic leadership at the agency, with a mission that might even include a *de facto* split in the duties of the FDA between the very different demands of the food arena on the one hand and the drugs remit on the other.

Whether or not FDA fission takes place, the list of challenges facing the incumbent team is daunting—insufficient funding, understaffing, low morale, a tarnished public image, ballooning drug review times, missed Prescription Drug User Fee Act (PDUFA) dates, a flawed foreign manufacturing inspection system, alleged conflicts of interests on advisory committees and rising calls for tightened oversight of not only drugs but now also food, devices and diagnostics. Of course, not every problem can be a priority, and if Hamburg and Sharfstein really want to make a difference, they should place one task right at the top of their list—the immediate overhaul of the FDA's antiquated Adverse Event Reporting System (AERS).

AERS, also known as MedWatch, has been around since 1998 and is thought to be the world's largest database of its kind, with ~4 million voluntary, spontaneous reports of adverse drug reactions accumulating at a rate of over 300,000 per year. However, AERS has several deficiencies that, if addressed, could greatly enhance the utility of the system in providing early warnings of drug safety issues.

One problem with AERS is it is not set up as a database that is continuously updated and readily queried. Currently, the data are compiled and then released quarterly as ASCII or SGML files. The rather obvious consequence of this is a delay of at least 3 months in analysis of new data. FDA staff members in the Office of Drug Safety review each and every individual case report involving outcomes that are life threatening, result in death or lead to hospitalization, disability or congenital abnormalities. Unusual patterns or striking case reports identified by this mind-numbing analysis become the starting point for agency investigations.

In addition, AERS grossly underestimates the number of serious adverse events. Clinicians are asked, but not required, to report all drug-related adverse events. And the process of reporting can be convoluted, either through drug manufacturers—which are required by law to forward reports of serious and unexpected adverse events within 15 days—or directly to the FDA itself. A report last year from epidemiologists at the FDA's Center for Drug Evaluation and Research (*Pharmacoepidemiol. Drug Saf.* **17**, 229–239, 2008) indicated that across a range of statin drugs, only 5–15% of the kidney failure associated with drug use was reported in AERS. Alerting letters from the FDA increase the level of reporting, but even then only two-thirds of the expected number of adverse events appeared in AERS. So both the passive nature of the reporting requirement and the lack of recognition of any connection between the drug regimen and the observed severe effect are part of the problem.

But perhaps the greatest source of under-reporting in AERS is the unfriendly submission interface. The system was primarily designed to allow drug companies and healthcare professionals to submit adverse event data. AERSs' own data indicate that in 1999, the first full year of the database, twice as many submissions came from healthcare professionals as from patients. Ten years later, patients play a much larger role. In fact, last June, FDA announced that consumers have overtaken physicians as the major source of adverse event reports, with 53,216 more submissions than the latter in 2007.

Thus, there is clearly an increasing willingness on the part of patients to contribute data and yet AERS makes little in the way of concessions to facilitate this wider input. Submission forms (http://www.fda.gov/medwatch/safety/3500.pdf) are long winded and bureaucratic and replete with the jargon of professionals. If AERS is to harness the internet's power for mass input, it must adapt to the electronic realities of the 21st century.

So what is needed is an upgraded version of AERS that would allow submissions to be logged instantaneously and seamlessly via the internet together with a more user-friendly interface. Access to the database should be available to all, enabling FDA staffers as well as experts from outside the agency (e.g., Research on Adverse Drug Events and Reports; http://cancer.northwestern.edu/radar/) to develop data mining tools to identify safety signals independently. Having more eyes scanning the data can only be beneficial. Of course, with over half of the data in AERS originating from patients, there is the issue of data quality and bias. But it should be relatively easy to set up the system so data can be sorted according to source and quality.

FDA's new leaders have an opportunity to undertake a prompt revamping of AERS. Compared with some of the other challenges they face, this is doable with present technology and is in line with the IT ambitions of the Obama administration, which last month appointed Vivek Kundra as US chief information officer. The updated database would be a cost-effective way not only of improving surveillance of serious adverse events associated with newly approved drugs but also of rapidly finding life-threatening contaminants in counterfeit or tainted brand drugs. It might also provide FDA with a model for another database, similar to the existing FoodNet system run by the Centers for Disease Control, that could track serious sickness associated with suspect foods. Most important of all, though, with over 100,000 deaths every year from drug-associated toxicities, it is the simplest way for FDA chiefs to save hundreds, perhaps thousands of lives.