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ONLINE FIRST

Potential Safety Signals and Their Significance

In 2007, President George W. Bush signed into law the Food and Drug Administration Amendments Act (FDAAA) (121 Stat 962). This Act, by adding subsection (k)(5) to section 505 (21 USC §355), directed the Food and Drug Administration (FDA) to "conduct regular, bi-weekly screening of the Adverse Event Reporting System [AERS] database and post a quarterly report on the AERS Website of any new safety information or potential signal of a serious risk identified by AERS within the last quarter."[1] The AERS contains over 4 million reported adverse events data from 1969 until the present and is aimed to maintain the FDA's postmarketing safety surveillance program for all approved drug and therapeutic biologic products. The content of this database is dependent on the voluntary reporting from both health care professionals and consumers and is mandatory for pharmaceutical manufacturers.[2] For the purpose of this research letter, *potential safety signals* are potential signals of serious risks and new safety information identified by the FDA through the surveillance of the AERS database. The process of posting potential safety signal quarterly reports generated from AERS started in the first quarter of 2008 by the FDA.[3] The FDA indicates that the identified potential safety signals do not denote a causal relationship between the drug and the listed risk. In addition, the FDA emphasizes that prescribers and consumers should not take any action.[3] This creates confusion for both health care providers and consumers because a potential safety signal has been identified on the FDA's Web site, calling into question the meaningfulness of the listed potential safety signal. Should health care professionals and consumers be cautious if a potential safety signal is present on the FDA's Web site?

See Invited Commentaries at end of letter

Methods. On May 3, 2011, the FDA's Web site was used to find quarterly reports of potential safety signals from January of 2008 to December of 2010.[3] The quarterly reports were used to calculate the number of actual label changes resulting from a potential safety signal. The total number of potential safety signals that resulted in labeling changes was calculated as a percentage. Among those potential safety signals that resulted in a label change, subgroups of the different sections of a label were analyzed, and included the following: Adverse Reactions, Warnings and Precautions, Boxed Warning, Drug Interactions, Dosage and Administration, Contraindications, and Use in Specific Populations. The number of safety signals that resulted in either the addition of a Risk Evaluation Mitigation Strategy (REMS) or voluntary withdrawal of a drug from the US market was also evaluated.

Results. After reviewing 153 potential safety signals released between January of 2008 and December of 2010, a total of 74 (48%) label changes had occurred (**Table**), with 4 REMS implemented and 1 drug withdrawn from the market. Among those potential safety signals that resulted in a label alteration, the most common section adjusted was Warnings and Precautions (62%).

Comment. The initial start of many potential safety signals are driven by the FDA's use of the AERS database to assess postmarketing adverse reactions. As of May 3, 2011, close to half of all potential safety signals listed on the FDA's Web site from 2008 to 2010 resulted in labeling changes. Most of these labeling changes resulted in an updated Warnings and Precautions section. This is concerning because the current recommendations to health

Table. Results From Quarterly Reports From January 2008 to December 2010

Result	Quarterly Reports, Year, No. (%)			Total
	2008	2009	2010	
Potential safety signals, No.	60	45	48	**153**
Label changes	30 (50)	28 (62)	16 (33)	**74** (48)[b]
Subgroups[a]				
Warnings and Precautions	16 (53)	19 (68)	11 (69)	**46** (62)
Adverse Reactions	11 (37)	5 (18)	7 (44)	**23** (31)
Drug Interactions	2 (7)	1 (4)	0	**3** (4)
Dosage and Administration	1 (3)	1 (4)	0	**2** (3)
Boxed Warning	6 (20)	2 (7)	1 (6)	**9** (12)
Contraindications	0	1 (4)	1 (6)	**2** (2)
Use in Specific Populations	0	0	1 (6)	**1** (1)
REMS	2 (7)	2 (7)	0	**4** (5)
Withdrawn from market	0	0	1 (6)	**1** (1)

Abbreviation: REMS, Risk Evaluation Mitigation Strategy.
[a] Calculated from the number of actual label changes.
[b] The calculated 48% total label changes includes the 1 drug withdrawn from the market and those drugs with newly implemented REMS.

care professionals and consumers is to not take any action on listed potential safety signals even though each of these signals are of "serious risk" according to the FDA.[3] At best, health care providers should be looking at alternative therapies if serious potential risks are present. First, the FDA should consider changing the statements made on their Web site to better reflect the significance of potential safety signals. This way potential safety signals will not be overlooked by health care professionals and consumers. Second, the FDA needs to consider better dissemination practices with potential safety signals to notify health care professionals and the public.[3] It is currently unclear exactly how the FDA is distributing quarterly reports other than by posting them on the FDA's Web site. The FDA may want to consider updating their guidance on drug safety communication to include wider dissemination practices of these quarterly reports.[4] Future study should consider the impact of these signals on prescribing patterns.

It is important to note that the FDA is not the only group assessing safety signals. The Institute of Safe Medication Practices (ISMP) also screens the AERS database, in which they produce their own quarterly reports of safety signals. Their work, in conjunction with the FDA, has led to many labeling changes, such as with varenicline.[5,6] In addition, publications from others analyzing the AERS database have led to notifications through the medical literature.[7]

Overall, the basis of all health care is to "First, do no harm"; should this process of assessing potential safety signals be any different? It is time we better recognize the importance these signals for the safety of the public even if it they are just a "potential" signal.

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INVITED COMMENTARIES

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Early Signals of Harmful Drugs

The approval of drugs by the Food and Drug Administration (FDA) is appropriately based on the results of phase 3 clinical trials. Unfortunately, most of these trials are underpowered to detect any but the most commonly occurring adverse events. In the postmarketing phase (phase 4), the FDA relies primarily on submission of adverse reaction reports filed by physicians. To provide this information more rapidly to physicians and consumers so that they could use it to change or stop treatment with medications that might be harmful, recent legislation required the FDA to notify the public about "any new safety information or potential signal of a serious risk" based on recently analyzed adverse reaction reports filed with the agency.

An important study[1] in this issue of the *Archives* reveals that the information contained in the reported adverse reactions is of great value. Powers and Cook[1] found that 48% of the signals resulted in label changes within 3 years of public notification.

Given the value of these reports, it is hard to understand why the FDA warns prescribers and patients against taking any action based on this new information. For most, if not all, of these drugs, alternative (usually older) drugs with comparable efficacy and more established safety records can be found. This emphasizes the importance of using the postmarketing Adverse Event Reporting System (AERS) database in updating safety information following approval.

Although the FDA has been advising against using the AERS signals for clinical decisions, they have just announced a new program for "Advancing Regulatory Science at the FDA."[2] There is a discussion in the document about finding new ways for being "better able to identify and accurately predict and reduce the magnitude and likelihood of risks associated with products."[2(p9)] Unfortunately, there is no discussion about using currently available safety information in a much more patient-protective way that reduces risks. The study by Powers and Cook[1] demonstrates the value of signal data. Now the FDA needs to marshal, not discourage, its use.

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