

# Enhancing FDA's Post-Market Surveillance of Dietary Supplements: Two Simple Steps to Build Capacity

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**ABSTRACT.** Up to 52% of Americans spend \$20 billion annually on dietary supplements, which rank among the top suspected causes of poisoning among adults. The recent recall by the US Food and Drug Administration (FDA) of a top-selling supplement linked to liver toxicity highlights the need for post-market surveillance. Unfortunately the agency is ill equipped to provide such surveillance, only recording about 1% of all adverse events. Poison control centers may be detecting 10 times more adverse events but are not forwarding them to the FDA. The FDA could increase its post-market surveillance capacity by coordinating with poison control centers and by utilizing external researchers.

**KEYWORDS.** adverse event reporting, post market surveillance, FDA, partnership, risk

## *THE LATEST CHAPTER: HYDROXYCUT*

On May 1, 2009, the US Food and Drug Administration (FDA) announced the recall of Hydroxycut, the top-selling (Lobb, 2009) dietary

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weight-loss supplement in the United States, after the agency had received some six dozen reports of adverse events (AEs) linked to the product, including 23 cases of liver toxicity and at least one death (FDA, 2009). While the FDA's Medwatch AE reporting system did not publicly report any such events until the product's recall (Lobb, 2009), their Center for Food Safety and Applied Nutrition's Adverse Event Monitoring System (CAERS) database had been receiving adverse event reports (AERs) about Hydroxycut since the database's inception in 2002 (FDA, 2009). The only public warning of possible harms associated with this supplement was the case reports of liver toxicity and other AEs that had been growing in the medical literature. In April a review of these case reports was published that called for enhanced FDA post-market surveillance (Lobb, 2009). While it is unlikely that the FDA's recall was influenced by the call for action published the previous month, it illustrates the point that FDA actions or public warnings about product safety frequently lag behind such expressions by researchers. Though FDA reviewers had access to the same data as the review author, not to mention AERs in their own database, FDA's analysis and action were not completed and released until 4 months after the published review was completed and submitted for publication. Moreover, it took a full 2 years for the case report of fatal liver failure that presumably sparked the FDA action to come to the agency's attention (FDA, 2009). Past experience displays a similar trend: the FDA's 2004 ban of ephedra lagged calls for such action by groups such as the American Medical Association and the American Heart Association by a significantly larger margin and was preceded by ephedra bans in several states (US Government Accountability Office, 2003); and besides issuing a consumer advisory about potential liver damage (FDA, 2002), FDA has taken no actions limiting the availability of the herbal supplement kava kava, despite calls to do just that by safety advocates such as the Consumers Union (Consumer Reports, 2003). Regulators in Europe have deemed kava kava risky enough to pull it from that market (Lobb, 2009).

While calls for wholesale reform of the FDA are frequent, enhancing the agency's surveillance of dietary supplement (DS) AEs could likely be achieved without sweeping, politically and financially untenable changes. What follows is a proposal to enhance FDA's post-market surveillance of DSs through the implementation of a surveillance network that utilizes existing information databases and requires few changes to the FDA's current processes and no increase in the agency's legislatively mandated authorities.

## **SUPPLEMENT USE, HARM, AND THE FDA**

Anywhere from 10% to 52% of the US population spends some \$20 billion each year on some form of DS (Gardiner et al., 2008). The Dietary Supplement Health and Education Act (DSHEA) of 1994 defines DSs as a regulatory category that includes vitamins, minerals, herbs, and amino acids. Under DSHEA rigorous pre-market testing for safety and efficacy is not required, and products introduced after 1994 are only required to submit a relatively low level of evidence suggesting that ingredients are safe (US Government Accountability Office, 2003; Wallace, Gryzlak, Zimmerman, & Nisly, 2008). Once on the market, consumers generally use DSs without medical guidance (Timbo et al., 2006; US Government Accountability Office, 2009), often for recreational purposes such as weight loss and enhanced energy or sexual performance and frequently under the assumption that they are natural and therefore safe (Gryzlak, Wallace, Zimmerman, & Nisly, 2007; US Government Accountability Office, 2009), even though they may harbor potent pharmacological agents (Lobb, 2009). It has been estimated that 4% of DS users experience some form of AE (Timbo et al., 2006), only 1% of which are ever reported to the FDA (Gardiner et al., 2008). This low detection rate contributes to the relative paucity of FDA actions in this area, and a lack of adequate staffing may further hamper review even when there is emerging evidence of harm (US Government Accountability Office, 2009). The vast size of the DS marketplace (US Government Accountability Office, 2009) and the ever-changing nature of evidence about safety also hinder timely responses. Since December 2007 manufacturers have been required to forward all AERs they receive about their products to the FDA, tripling the number of AERs received by the agency (US Government Accountability Office, 2009). But since it is the FDA's responsibility to prove that supplements on the market are unsafe before taking any precautionary actions to safe guard DS users (Gardiner et al., 2008; Wallace et al., 2008), the Government Accountability Office has called on the agency to increase the rigor of its post-market surveillance efforts (US Government Accountability Office, 2009).

### ***AE DETECTION: POISON CONTROL CENTERS (PCCs)***

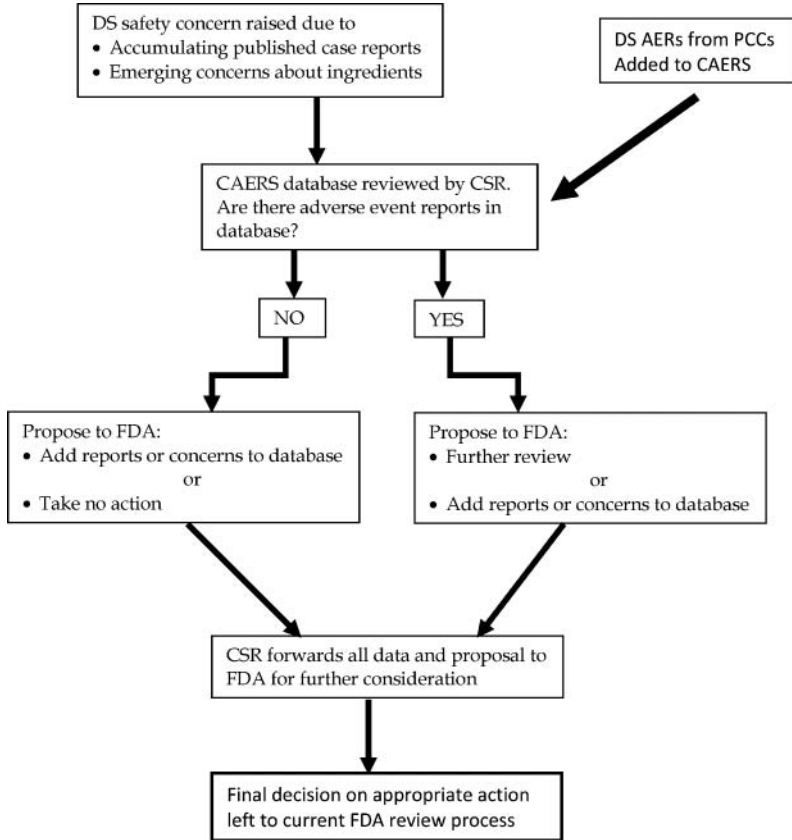
A significantly larger portion of DS AERs are received by the nation's 61 PCCs (Gardiner et al., 2008; Wallace et al., 2008), and the American Association of Poison Control Centers tallies and records the data in its Toxic Exposure Surveillance System (TESS; Gryzlak et al., 2007). PCC

surveillance data indicates that when combined, substances regulated as DSs are the fifth leading suspected cause of accidental poisoning among adults older than 19, with some 90,000 cases recorded in 2007 (suspected substances included herbs, vitamins, electrolytes, and minerals; Bronstein et al., 2008). While a recent review of the CAERS database for AERs related to the herbs echinacea and St. John's wort located 77 reports received by the FDA between 1999 and 2003 (Wallace et al., 2008), a review of the TESS database for the same botanicals netted over 600 reports for just 1 year, 2001 (most of which were due to accidental ingestion by children, but 195 were of adults more 20 years old; Gryzlak et al., 2007). Assuming an even distribution of events over time and no reporting overlap between the two systems, these findings suggest that PCCs may be detecting 10 times more DS AEs than the FDA (195/year vs. 19/year for the two botanicals studied). Despite such frequent encounters with DS AEs, PCCs are not currently required to forward their reports to the FDA (Gryzlak et al., 2007).

### ***POOLING RESOURCES TO ENHANCE DETECTION***

The FDA's current surveillance capacity could be significantly increased by implementing two relatively simple processes: (a) a system for receiving DS AERs from the nations PCCs and (b) contracting with independent, non-FDA surveillance researchers familiar with DS safety issues (referred to here as contracted surveillance researchers or CSRs). Gathering AERs from PCCs and adding them to the CAERS database would significantly augment the FDA's reception rate for these reports and paint a more robust and timely picture of the true nature and scale of emerging problems. CSRs could contribute additional staffing resources to help analyze the increased data flowing into CAERS. CSRs alerted to a potentially worrisome DS, due to a growing number of case reports in the medical literature or emerging evidence of the potential toxicity of an active ingredient, could also access the CAERS database to check for existing AERs on file. Currently, researchers outside the FDA must submit Freedom of Information Act requests to access the database (Wallace et al., 2008). Figure 1 outlines the process by which emergent data would flow into the current FDA decision and analysis process. In all cases final decisions, and public disclosure of information, would be at the discretion of the FDA, as they currently are. The only role of the CSRs would be to highlight DSs of potential concern that might warrant FDA attention.

FIGURE 1. Proposed enhancements to the FDA's DS surveillance system: FDA, Food and Drug Administration; DS, dietary supplement; AERs, adverse event reports; PCCs, poison control centers; CAERS, FDA's CFSAN Adverse Event Reporting System; CSR, contract surveillance researcher.



### ***THE PROFITS OF PARTNERSHIP***

This system offers several advantages to the FDA's existing systems and is characterized by attributes amenable to timely and relatively simple and low-cost implementation in that it

- (a) provides the FDA with additional analytical assets to assist in the identification of potentially harmful DSs;

- (b) utilizes existing information systems and databases;
- (c) swiftly adds an additional layer of oversight to help protect DS users;
- (d) could be pilot tested and then expanded incrementally; and
- (e) acknowledges the evolutionary nature of scientific knowledge.

Moreover, it

- (a) does not interfere with the FDA's jurisdiction or enforcement or call into question current decision analysis processes for assessing when to call for warnings or recalls;
- (b) does not require expansion of FDA staffing or enforcement powers; and
- (c) does not require significant budgetary increase.

Private–public partnerships such as those being proposed here can offer pragmatic solutions to advance public health goals, as has been discussed elsewhere (McDonnell et al., 2009). Such relationships can be cost-effective and harness private technical expertise for the public interest, enhancing the fulfillment of essential government roles and responsibilities without swelling the size and budgets of government agencies themselves. The relationship between CSRs and the FDA outlined above would loosely formalize and streamline a relationship that already exists, wherein independent reports in the medical literature may assist the FDA in its post-market surveillance efforts. The FDA relied heavily on published case reports in its decision to recall Hydroxycut, though only one of four published reports of liver toxicity was also on file in the CAERS database (FDA, 2009). The coordinated partnership with the poison control community provides the potential for PCCs to enhance their protection of the public by contributing to a regulatory process that can limit access to or provide warnings about possibly harmful supplements; for the FDA it allows for the capture of a larger portion of DS AERs, using an existing data collection network. Coupled with the establishment of the more direct link between independent researchers and the agency, the end result would be more timely and effective detection, review, and enforcement actions to ensure the safety of the DS-using public.

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