



**RECOMMENDATIONS FOR  
ADVERSE EVENT MONITORING PROGRAMS  
FOR DIETARY SUPPLEMENTS:**

**EXECUTIVE SUMMARY**

June 2, 2004

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**This is a brief summary of the conclusions reached by LSRO and their Expert Panel. It is not an independent document and should be considered within the context of the full report that can be obtained at [WWW.LSRO.ORG](http://WWW.LSRO.ORG).**

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ISBN: 0975316710

Library of Congress Catalog Number: 2004103755

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## EXECUTIVE SUMMARY

### SETTING

Dietary supplements are used by an estimated one-third of adults in the United States on a daily or routine basis (Commission on Dietary Supplement Labels, 1997). The term “dietary supplements,” as defined in the Dietary Supplement Health and Education Act (DSHEA) (U.S. Congress, 1994), includes vitamins, minerals, amino acids, enzymes, herbs, and other botanicals. Dietary supplements are used to confer health benefits. For example, it is recognized that nutrients such as calcium and folic acid, which are available as supplements, help build strong bones (*i.e.*, calcium) and help reduce the risk of neural tube defects (*i.e.*, folic acid) (U.S. Congress, 1994).

Similar to food additives and medications (prescription and nonprescription), health problems from dietary supplements can arise from improper use, product tampering, and product defects that alter product identity, quality, purity, strength, and/or composition. In addition, safety concerns over certain dietary supplements have been expressed by various sources, *e.g.*, the lay-press, medical journals, the U.S. Food and Drug Administration (FDA). Several studies have reviewed safety and regulatory issues related to dietary supplements (Shekelle *et al.*, 2003; U.S. Food and Drug Administration, 1994; U.S. General Accounting Office, 2003a, 2003b, 2003c).

FDA regulates dietary supplements by enforcing the Federal Food, Drug, and Cosmetic Act as amended by DSHEA, in that dietary supplements are regulated as a subcategory of food (U.S. Congress, 1994). Hence, the regulatory framework for product safety is primarily a “postmarket” program, where there is no requirement for manufacturers to provide evidence of product safety prior to marketing products. However, the manufacturer is required to notify FDA at least 75 days in advance of introducing a product in the market that contains a “new” dietary ingredient that has never been present in the food supply. Most other food products are regulated similarly to dietary supplements, with some exceptions (*e.g.*, infant formulas, new food additives). In contrast, before marketing an infant formula, the manufacturer must provide FDA with assurance of the nutritional quality of the infant formulation. Food additives are also subject to premarket approval by FDA unless their use is generally recognized as safe (GRAS) by qualified experts. Under DSHEA, FDA has the authority to determine that a dietary supplement may not be sold if it “presents a significant or unreasonable risk of injury.”

Because problems in manufacturing of food and medications may lead to adulterated or misbranded products that have the potential to cause adverse health effects, FDA promulgates “current good manufacturing practice” to reduce the risk of adulterated or misbranded products. Recently, FDA proposed “Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements” (U.S. Food and Drug Administration, 2003a). Currently, there is no requirement for a manufacturer to monitor adverse events related to the use of their dietary supplement products. Hence, it is anticipated that dietary supplement manufacturers are unfamiliar with terminology and processes that have been used by other industries to monitor adverse events. An adverse event is any undesirable health-related sign or symptom that is detected in an exposed individual after use of a product.

### STUDY OBJECTIVES AND SCOPE

The Life Sciences Research Office (LSRO) undertook a study of adverse event monitoring programs for dietary supplements. Metabolife International, Inc. (MET) through its counsel, the law firm Patton Boggs, initiated and funded the study.<sup>1</sup> Concerned that the current system of documenting individual data records (IDRs) was not intended as an adverse event reporting system and may not support recognition of product-related effects, MET sought scientific advice on how such a system could be tailored to the task of monitoring the safety of dietary supplements.

The specific objective of the study is to make recommendations for the design and development of adverse event monitoring programs for dietary supplements. Currently there is no federal guidance or mandate for the collection, documentation, or evaluation of health-related consumer complaints associated with the use of dietary supplements.

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<sup>1</sup>Although providing financial resources, MET and its counsel, Patton Boggs, were not responsible for the content of this LSRO report nor were they asked to endorse this report.

## SURVEILLANCE PROGRAMS

Over the last 40 years, both voluntary and mandatory postmarketing risk management programs have been established by various industries to gather and integrate product-specific, health related data. These programs, referred to as “postmarketing surveillance,” have proven to be effective and relatively inexpensive to operate. Postmarketing surveillance programs exist for household goods, foods, and products produced by the chemical industry. Products monitored by surveillance programs, such as nonprescription medications, are generally labeled with toll-free numbers to report adverse events. Because voluntary postmarketing surveillance is uncommon in the dietary supplement industry, there are no accepted surveillance terminologies or standards. Hence, for the purposes of this report, LSRO has drawn upon terminology utilized by other industries. A glossary and list of acronyms used in this LSRO report are provided in Appendix H. Some definitions, adopted for the purposes of this report, may differ from definitions presented by others (*e.g.*, the term “serious”).

Postmarketing surveillance programs are similar across diverse product categories because they follow similar information processing principles. An overview of postmarketing surveillance programs is provided in Section II. In general, surveillance programs establish standard operating procedures by which the receipt, collection, analysis, interpretation, and documentation of IDRs can be consistently achieved. In this LSRO report, the term “surveillance program” is used to refer to all personnel, processes, and computer resources that carry out surveillance. The primary purpose of a surveillance program is to identify potential product-related health problems that are appropriate for rapid dissemination of information or other actions. In an operational sense, a surveillance program allows the adverse events that are submitted in connection with a particular product to be scrutinized for disproportions or unusual cases that might represent problems, a process known as signaling. Surveillance systems generate signals that require further quantification and evaluation to determine whether the signals represent coincidence, artifact, or a genuine problem in toxicity that might lead to changes in labeling and/or restrictions in use. Thus, in other industries, such as the pharmaceutical industry, adverse event data are required to be collected and evaluated without a requirement for evidence of causality.

A surveillance system consists of the following functional steps:

1. Recognition and reporting of adverse events in individual product users<sup>2</sup>
2. Creation of IDRs
3. Building an integrated, relational database of IDRs
4. Signaling from databases of IDRs
5. Signaling from other information sources
6. Issues resolution and formulation of risk management interventions

In terms of signaling (Step 4), there are three sequential stages by which product-adverse event signals are generated and assessed: (a) signal detection, (b) signal prioritization, and (c) signal evaluation. These stages provide additional data that assist in evaluating whether further investigation of the product-event association is warranted. Signals that have been identified from an adverse event monitoring program are fully assessed in the issues resolution phase of the process by using all pertinent data that is available.

IDR-based postmarketing surveillance programs are intended to identify adverse events early during the marketing of a health care product and to provide additional information relevant to the adverse event profile of a product. These surveillance activities are particularly valuable when identified problems can be addressed by a targeted risk management program and lead to prevention of similar events in the future.

## STUDY METHODS

LSRO reviewed IDRs and postmarketing surveillance for dietary supplements and other consumer products to meet the objectives of the study in two Phases:

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<sup>2</sup>For the purposes of this LSRO publication, the term “reporting” includes the action of submitting a voluntary complaint/report of a consumer’s adverse event to industry.

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**Phase I.** A case study of Metabolife 356® and other ephedrine alkaloid-containing dietary supplements was used to make conclusions about the usefulness of the data generally as signals for product safety (Section III).<sup>3</sup>

- **Phase II.** Several noteworthy surveillance programs described in the scientific literature (Appendices E and F) were reviewed and input from speakers and agency representatives familiar with approaches to postmarketing surveillance of dietary supplements, food additives, and prescription and nonprescription medication was evaluated to identify procedural problems with these systems, and make recommendations about establishing a useful, practical system to monitor and respond to adverse event reports, including criteria for documenting and reporting health complaints.

In Phase I, LSRO examined sample ephedrine-related IDRs that were collected by FDA through a surveillance program and IDRs collected by MET through a customer service hotline. Although the manufacturer did not intend the collection and documentation of calls to a hotline as “postmarketing surveillance,” this system and the resultant data were reviewed by the Committee<sup>4</sup> to gain insight into the design of possible surveillance systems for dietary supplements.

The sample IDRs were drawn from the same data sets that were reviewed in other studies, such as the review conducted by the U.S. General Accounting Office (2003b). LSRO did not attempt to examine, describe, or tabulate events for the entire pool of available IDRs related to ephedrine alkaloid-containing dietary supplements available from MET or from FDA (Docket No. 95N-0304), but selected 200 IDRs from each data set. LSRO did not evaluate causality or use aggregate data in any way to assess the probability of a causal link between a product and an adverse event.<sup>5</sup>

LSRO built its analysis of sample FDA and MET IDRs around the specific steps of signal detection, signal prioritization, and signal evaluation. Signal detection is a process of sorting and identifying IDRs in order to find interesting supplement-adverse event relationships that merit further attention. Evidence of causality is not a requirement for signal detection, and the detection of a signal is not equivalent to determining causality (U.S. Food and Drug Administration, 2003d).

The Committee determined that a minimum of five criteria must be met in order for an IDR to support signal detection:

1. An identifier for the product user (*e.g.*, initials, age, gender) was obtained
2. The complaint was health-related
3. A dietary supplement product was consumed prior to the onset of the health-related complaint
4. The IDR was dated (day/month/year)
5. An identifier for the reporter was obtained

For the purpose of the case review, only the first four of these five criteria were used to assess sample sets for signal detection because the identifiable reporter was redacted from all sample IDRs obtained by LSRO.

During the signal prioritization process, weighting factors are applied to select/rank the output from signal detection in preparation for signal evaluation. The Committee determined that two types of data were needed for signal prioritization: (1) data that rank the reliability and accuracy of the record, and (2) data used to rank the seriousness of the health-related event or outcome.

The purpose of signal evaluation is to form and characterize a case series to determine whether further investigation of the product-event relationship is indicated. The Committee identified 11 types of data that are useful for signal evaluation. They are listed below:

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<sup>3</sup>Effective November 18, 2003, MET suspended the sale of their ephedra-containing products. On December 30, 2003, FDA announced plans to prohibit sales of dietary supplements containing ephedra (U.S. Food and Drug Administration, 2003e). The final rule prohibiting the sale of ephedrine-alkaloid containing dietary supplements was issued February 11, 2004 (U.S. Food and Drug Administration, 2004a).

<sup>4</sup>An ad hoc expert Committee was assembled by LSRO to guide the review (Appendix A).

<sup>5</sup>Although LSRO had access to specific databases of IDRs related to ephedrine alkaloid-containing dietary supplements, neither the Committee nor LSRO made any evaluation or conclusion of the safety or efficacy of ephedra products. No attempts were made to identify specific signals. Findings and conclusions on the safety of dietary supplement products are outside the scope of work described in this report. This report does not support any conclusions on the safety of dietary supplement products.

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1. Gender
2. Age at the time of the event
3. Information on pre-existing medical condition
4. Information on concomitant exposure to prescription and/or nonprescription medications
5. Information on concomitant exposure to other dietary supplements
6. Information on why the product was used
7. Batch/lot number
8. Daily dose of bioactive ingredients
9. Time to onset from initial use to the adverse event
10. Rechallenge information
11. Geographic location (e.g., Zip Code)

### FINDINGS

#### *Principal findings of the LSRO Phase I review of individual data records*

It should be noted that the MET records represented information collected, in most cases, during a single telephone contact for the purpose of customer service and these records were not intended to support an adverse event reporting system. In contrast, FDA records represented information collected in an initial contact and in follow up by FDA field representatives for the purpose of surveillance.

Overall, the records collected by MET were qualitatively less informative than those collected by FDA and therefore pose a greater challenge for application in public health-related analyses (Appendix B):

- **Signal detection.** Both MET and FDA sample sets of IDRs had sufficient information to permit signal detection.
- **Signal prioritization.** A substantially greater number of IDRs in the FDA data set had sufficient information to permit signal prioritization because a relatively high percentage of reporters were health care professionals and because most MET IDRs lacked follow up and physician evaluation.
- **Signal evaluation.** Similarly, a greater number of IDRs in the FDA sample set supplied information useful for signal evaluation than did the MET set. This information was likely to have been available at the time of the initial call for many MET cases.

Although FDA records contained more information useful for signal generation than did MET records, the FDA set could have been even more useful had a greater portion of FDA IDRs included important information to calculate exposure, noted batch numbers, and recorded use of concomitant dietary supplements.

The limitations in signal generation for these sample sets (e.g., lack of batch numbers) stemmed in part from systematic problems in the methods used for initial data collection. For the MET set, which as previously noted, was not intended to be a postmarketing surveillance system, this was coupled with a lack of follow up to obtain outcome information. Despite these limitations, it is likely that signals worthy of further investigation would arise from such data sets if they were developed in the context of a continuing surveillance program that has the requisite functional components detailed in Section II.

#### *Principal findings of the LSRO Phase II review of existing postmarketing surveillance programs:*

- Although there is no statutory regulation requiring postmarketing surveillance for dietary supplements, a properly designed and implemented surveillance program could be an important component of a proactive risk management plan.
- An adverse event monitoring program for dietary supplements will share many of the challenges of other such surveillance systems in terms of specificity, amount of data, completeness, limitations with analysis, and interpretation of findings.
- Current technologies make it feasible to implement quality systems, but manufacturers may need qualified operators and further guidance to ensure they are using the best possible techniques for analysis.
- When signals arise, especially if at-risk populations have not been adequately studied, additional information beyond routine postmarket reporting may be needed to determine if the signal is real and to determine the appropriate actions to be taken.
- LSRO concludes that it is not appropriate to recommend adoption of the methods of surveillance developed for medications (prescription and nonprescription) for surveillance of dietary supplements. A surveillance

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system for dietary supplements must take into consideration (1) the absence of a statutory requirement to collect and report these data, and (2) less reliance on reporting by medical professionals.

- Surveillance programs in the private sector will complement federal efforts to monitor adverse events associated with dietary supplements. No one system will suffice for postmarketing surveillance of dietary supplements. All likely avenues that product users and health care professionals use to request or convey information should be viewed as complementary. All should be cultivated and combined for maximal detection and analysis of product-event relationships with the goal of preventing future problems and protecting the public health.

### *Summary of principal findings*

The Committee found that properly designed and implemented postmarketing surveillance programs for dietary supplements could contribute to public health through the detection and evaluation of potential supplement-event relationships. A postmarketing surveillance program can complement quality control in manufacturing and extend the tools available for effective risk management. Potential product problems, such as a defective product lot, that are detected through a postmarketing surveillance program can be rapidly investigated and addressed. In this way, product quality is controlled. Postmarketing surveillance programs can increase the confidence of the public that health-related problems associated with the use of these products will be identified quickly and addressed effectively. Consumer awareness of the manufacturer's commitment to product quality is thus enhanced. In addition, such a system can help protect reputable products from false allegations.

## SUMMARY OF RECOMMENDATIONS

LSRO's recommendations are intended to be broadly applicable to dietary supplements and are not tailored to any one particular type of supplement or manufacturer.

### *General recommendation for postmarketing surveillance programs*

In general, LSRO recommends that surveillance programs for dietary supplements should be:

- **Practical.** To be practical, the postmarketing surveillance program should be manageable, professional, efficient, and cost effective.
- **Active.** To be active, the program should be utilized by those with unexpected and/or serious adverse events, have the capacity to produce timely signals, and be responsive to product users and issues in need of resolution.
- **Auditable.** To be auditable, the program should have adequate standard operating procedures, retain documented accounts, and have measures of performance that are examined and verified through quality assurance and oversight.
- **Connectable.** To be connectable, the surveillance program should be able to move confidential IDR information securely between designated databases.

### *Minimal elements for a postmarketing surveillance program*

The following are intended as minimal elements in the design of a postmarketing surveillance program tailored to the dietary supplement industry. Should an individual company or the industry as a whole decide to voluntarily implement such a program, LSRO recommends these minimal elements for an effective program.

### **Reporting and intake**

In postmarketing surveillance systems, the term "adverse event" is used whether or not the reported event can be attributed to the use of a product. Hence a causal relationship does not have to be established between the product and the event for the reported data to be useful for signal detection and analysis. The surveillance program should have the flexibility to collect incoming data from different input mechanisms. Processes for submission of adverse event experiences should be user-friendly, simple, and concise. The individual submitting an adverse event should be directed to an appropriate resource that is available 24 hours a day, 365 days a year. Company representatives should be trained to ensure that they collect consistent and complete information during each encounter and maintain the confidentiality of the reporter and product user.

### **Creation of individual data records and databases**

A standardized questionnaire should be developed that facilitates the collection of data that are useful for detecting, prioritizing, and evaluating adverse event signals. The data collection procedures should be designed to collect as much information as possible during the first encounter. Follow up is conducted to obtain additional information relevant for signal generation. Qualified medical professionals should supervise the medical evaluation of IDRs. A standardized data dictionary should be used to facilitate consistent and accurate coding and data entry. The system should process incoming data and IDRs in a consistent and accurate manner.

The status of the IDR with regard to its completeness during processing and ongoing activities should be readily evident (*e.g.*, physician to return call and supply diagnosis). Source materials (*e.g.*, paper materials, computer files) should be securely stored and readily retrieved as needed. Information imported and exported between databases of IDRs should be accurate and kept confidential.

### **Signaling**

Signaling procedures should be designed and managed by professionals possessing the requisite technical knowledge and experience to effectively perform the operational tasks and provide intelligent analysis. The review and analysis of IDRs should be timely so that notices of potential signals are rapidly disseminated to those who can minimize product risk, especially when serious risks are identified. Only those IDRs with product-events or outcomes that are judged to be serious and/or unexpected should be considered in signal evaluation.

Appropriate statistical methods should be applied that include analysis of changes in the pattern of reporting rates. Once a potential signal surfaces from disproportional type analyses, the product-event combination should be examined in the context of the quality, quantity, and dispersion of previous IDRs (*i.e.*, case series). The need for additional studies to investigate potential signals should be determined, and sufficient resources should be allocated to ensure adequate investigation.

### **Issues resolution and risk management**

Issues resolution requires that a company have a forum whereby professionals (*e.g.*, experts in toxicology, product development, and surveillance) can come together to integrate and discuss all existing relevant information that pertain to a safety signal. Hence, companies should provide an organizational procedure by which signals as well as other relevant information (*e.g.*, studies, medical literature) can be formulated into specific issues. Each issue that is identified should then be formally assessed in terms of its potential public health impact.

We recommend in systems that are developed that company executives responsible for safety oversight be informed of new, serious adverse events related to their product and take appropriate action to protect public health. Although there is no legal requirement for industry to notify FDA, in a system going forward, LSRO advises that FDA should also be informed of new, serious adverse events related to the product. Outreach should be adequate to inform product users and others about new health-related findings associated with product use.

### **Quality assurance**

A quality assurance program should be developed to ensure that the surveillance program is functioning to obtain high quality data and that data are processed in a timely manner and without error, distortion, or disclosure of confidential data. Objective performance measures should accompany the surveillance program.

### ***Recommended enhancements***

In addition to the minimal elements, the evidence suggests an optimal postmarketing surveillance program for dietary supplements will have some or all of the following enhancements:

- **Technological infrastructure.** Surveillance programs will benefit from direct, immediate, and electronic data entry with built-in logic and automated signal generation. To implement this enhancement, the dietary supplement industry should collaborate with experts in key emerging technologies and statistics related to automated surveillance systems.
- **Inter-product databases of IDRs.** A voluntary, industry-wide, and multi-product system would strengthen statistical power to detect adverse events, especially those associated with a specific ingredient

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or involving at-risk populations. This type of system would be particularly beneficial for manufacturers that produce products that are marketed under several different labels. An inter-product system can be constructed to ensure the protection of proprietary information and provide an individual company with autonomy over their customer service and resolution of issues.

- **Reference databases.** Product identification and coding will be improved by establishing a product label database containing up-to-date, accurate, and complete dietary supplement information. This could be made even more effective if employed in conjunction with ingredient reference databases (*i.e.*, contact information for sources, monographs on pharmacologically active substances, methods for chemical analysis).
- **Oversight.** Postmarketing surveillance programs that are monitored by an independent body of experts will have greater credibility than programs that do not have such oversight. An independent body of experts can ensure quality, review outcome measures of success, and identify areas for improvement.

**Research.** An effective program will identify and minimize the barriers to submitting an account of an adverse event associated with use of dietary supplements. A thorough review of the literature should be conducted to help investigate potential signals.