



*Producers of Quality  
Nonprescription Medicines and  
Dietary Supplements for Self-Care*

## **CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®**

**October 11, 2001**

### **Scientific Framework for Safety Evaluations of Dietary Supplements**

#### **CHPA Recommendations**

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#### **Introduction and Summary Position**

CFSAN charged IOM as follows: “The charge to IOM is to (a) develop a proposed framework for categorizing and prioritizing dietary supplement ingredients based on safety issues, (b) describe a process for developing a system of scientific reviews with specifications for evaluating the safety of dietary supplement ingredients, and (c) develop at least six scientific reviews as prototypes for the system.”<sup>i</sup>

CHPA supports this activity by IOM and has the following specific recommendations.

1. CHPA recommends a three-part Dietary Supplement Ingredient Safety Review (DSISR) for the safety evaluations of dietary supplements. The three components to this system, parts of which are already in practice to a greater or lesser extent, are:
  - Emergent Post-marketing Safety Reviews: For all currently marketed dietary supplements, (i.e., those marketed “pre-DSHEA,” prior to October 15, 1994, and those recently marketed new, or post-DSHEA, dietary supplement ingredients), this component of DSISR would identify and evaluate emergent safety concerns, such as an interaction between a currently marketed dietary supplement and a new class of Rx products identified as a result of a newly published clinical trial; this component of DSISR would be reactive in nature to emergent science.
  - Prospective Post-marketing Safety Reviews: For all currently marketed dietary supplements, this component of the DSISR would prospectively assess the safety of currently marketed dietary supplements, and would complement the reactive portion of DSISR (i.e., Emergent Post-marketing Safety Reviews).

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<sup>1</sup> The Consumer Healthcare Products Association is the 120-year-old trade organization representing the manufacturers and distributors of dietary supplements and nonprescription medicines. CHPA has over 200 members across the manufacturing, distribution, research, supply, and advertising sectors of the self-care industry.

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- Prospective Pre-marketing Safety Reviews: For new, not previously marketed, dietary supplements (i.e., those marketed “post-DSHEA,” after October 15, 1994), there is a need to ensure an efficient system for the evaluation of 75-day notifications, including articulation of the scope and extent of data needed to support marketing of new ingredients.
2. CHPA recommends a case-by-case, weight-of-the-evidence, data-driven, dialogue-driven approach to evaluating dietary supplement safety.
  3. CHPA recommends that, irrespective of the safety evaluation system that is ultimately described and “beta-tested” by IOM for dietary supplements, the system should include formal opportunity for public comment on the findings of the IOM’s review of six dietary supplements and that of any future review by CFSAN, should the system herein recommended be adopted wholly or in part by CFSAN.

**Detailed Recommendations**

CHPA’s comments are organized according to the following outline.

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**1. DSISR: Emergent Post-marketing Safety Reviews****a. Scope:**

- All dietary supplement products marketed prior to the passage of the Dietary Supplement Health Education Act (DSHEA) on October 15, 1994 (i.e., “grandfathered” dietary supplements); and
- All currently marketed dietary supplement products marketed pursuant to the 75-day notification procedure for new dietary supplements (i.e., “new” dietary supplements).

**b. AER Signal Generators**

The signal generators for potential post-marketing safety issues relating to currently marketed and new dietary supplements include elements of the current multi-tiered post-marketing surveillance system:

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- FDA's Adverse Experience Reporting System, which includes MedWatch
- Published clinical case reports and case series
- Published uncontrolled clinical trials
- Published controlled clinical trials
- Published epidemiological studies
- Published and unpublished animal studies (e.g., reports from the National Toxicology Program relating to carcinogenicity, reproductive toxicity)
- In vitro studies (e.g., mutagenicity studies)
- The Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers (AAPC)
- Special government surveillance studies (e.g., Consumer Products Safety Commission, Centers for Disease Control, etc.)

See section 1.d. (page 6) below for what constitutes an adequate AER signal.

The signal generators for the post-marketing surveillance system for dietary supplements are essentially the same as those for monographed OTC drugs and are reasonably sensitive (e.g., St. John's wort/drug interactions; psyllium choking warning; allergy warning for topical antibiotics; aspirin/Reye syndrome warning).

FDA is seeking additional funding to further build the efficiency of the current AER system for dietary supplements, and CHPA supports this expansion in the context of a system that is similar for OTCs.

As noted in comments by CHPA to CFSAN's 2002 Program Priorities, the development of a "Material Fact" Labeling Guidance is vital to an effective approach to dietary supplement safety since it provides the basis for public health interventions that might result from a safety review by IOM, CFSAN or another body. While this is not a part of CFSAN's charge, CHPA recommends that IOM convey to CFSAN the importance of such a guidance. CHPA provided detailed comments on this point in recent formal comments to CFSAN on the Center's 2002 priorities.

**c. Prioritization: Post-marketing Safety Reviews**

- The charge to IOM is, in part, "to develop a proposed framework for categorizing and prioritizing dietary supplement ingredients based on safety issues." Prioritization is addressed in this section and Section 1.d.; categorization is addressed in Section 1.e.
- Overarching Elements: Prioritization of post-marketing safety reviews of dietary supplement products should be based on the following overarching elements: known toxicity, extent of exposure, severity of the event, intended

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use, and data gaps. (See also below: Section 1.d., page 6: “What Reasonably Constitutes a Higher Priority Potential Safety Issue from Data Derived from a Signal Generator? Case-by-Case Approach.”)

These elements pertain to both intrinsic and extrinsic toxicity of products intended for use as dietary supplements. Whether the safety issue is a result of the inherent toxicity of the dietary supplement ingredient (e.g., an organ specific toxicity) or due to extrinsic factors affecting the safety of the dietary supplement (e.g., quality issues relating to safety, such as: contaminants like heavy metals or pesticides; drug-spiking of botanicals; inadvertent and unwanted intermixing of botanicals), emergent safety issues can be prioritized in importance with respect to: whether the product contains a known toxicant (e.g., a pyrrolizidine alkaloid); how many Americans are potentially exposed to the product; whether the event is “serious” as defined by the MedWatch system<sup>ii</sup>; and whether the product is making outlandish claims of safety in the context of drug-type claims.

Quality issues, however, should be handled as part of CFSAN’s compliance efforts. Here, the signal generators may be FDA field personnel inspecting manufacturing facilities. We do not think that IOM should address these issues as a practical matter, since proposed Good Manufacturing Practices regulations are pending, and it is unlikely IOM would obtain the needed information to “beta-test” the system.

Whether the event is allergenicity, drug-dietary supplement interaction, organ-specific toxicity, etc. is a matter of categorization, not necessarily prioritization. See below.

- In more detail, the overarching elements for prioritizing post-marketing safety reviews of dietary supplement products include a consideration of the following:

- Ingredients with Known Toxicity

For example, CFSAN recently took action to remove comfrey from the dietary supplement market, based on the presence of pyrrolizidine alkaloids (PA’s). CHPA members adopted a voluntary program covering all products with botanical ingredients which contain toxic pyrrolizidine alkaloids, agreeing that such products should not be taken orally and should therefore bear the following cautionary statement on the label: “For external use only. Do not apply to broken or abraded skin. Do not use while nursing.”

CHPA program included, but not limited to: *Alkanna tinctoria* (alkanet), *Anchusa officinalis* (bugloss), \* (*borage*), *Crotalaria* spp., *Cynoglossum* spp., *Erechtites hieraciifolia*, *Eupatorium cannabinum* (hemp agrimony), *Eupatorium purpureum* (Joe Pye), *Heliotropium* spp., *Lithospermum*

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officinale (European gromwell), *Packera candidissima*, *Petasites* spp. (e.g., Butterbur), *Pulmonaria* spp. (e.g., lungwort), *Senecio jacobaea* (European ragwort), *Senecio vulgaris* (groundsel herb), *Symphytum* spp. (**comfrey**), and *Tussilago farfara* (coltsfoot) [ \*note: borage seed oil is specifically exempt from the above label recommendation.]

CFSAN would do a service to ban all dietary supplements listed in CHPA's program, and a IOM recommendation to place this category within the priority hierarchy would facilitate such regulatory action. Other similar categories of known toxicants should be sought, perhaps through a published call for data in the Federal Register by CFSAN.

- Severity of Event

- Only serious adverse experiences should be of high priority concern for a post-marketing surveillance safety system for dietary supplements.
- "Serious" should be defined per FDA's MedWatch program (see endnote<sup>ii</sup>).

- Extent of Exposure

- Based on sales and usage data, the greater the extent of exposure relative to other ingredients with potential safety issues, the more likely a given potential safety issue should be considered a relatively higher priority than other safety issues, assuming other it should be considered as priority safety.

- Intended Use

- For example, if the intended use of the dietary supplement is different than the traditional/historical use of that supplement and is also associated with a series of serious adverse events, then higher priority should be given to the hypothesized safety relationship.
- Note, dietary supplements making disease claims relating to safety are subject to enforcement action by FDA and FTC (e.g., see recent FTC actions) (e.g., disease, as handled in claims enforcement by FTC and FDA; current use different from historical use).

- Data Gaps

- Where data are missing to address putative safety issues, a higher priority should be given to the issues, requesting data development as appropriate from companies, NIH and academic research groups and providing time in the regulatory process for specific research to address the issue.

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**d. What Reasonably Constitutes a Higher Priority Potential Safety Issue from Data Derived from a Signal Generator? Case-by-Case Approach.**

- As stated under comments relating to prioritization (see section above, 1.c.), only serious AERs should be of high priority for review and potential regulatory action. This is consistent with current approaches to post-marketing surveillance of drug products by FDA.
- Given this approach to evaluate serious AERs as high priority, based on the AER signal generators described above (see section 1.b.), the determination of whether a specific AER associated with a dietary supplement rises to the level of priority needing public review and potential regulatory action is a case-specific matter. There is no numerical system/criterion that can be applied in such situations. In general, higher priority AERs would be, for example; one that is serious (as defined by MedWatch) and has a broad exposure of use; one for which the ingredient has known (i.e., well-studied) serious organ-specific toxicity (e.g., known hepatotoxin). Such AERs might be generated from the following:
  - Controlled clinical trial published in peer-reviewed journal;
  - Case reports to peer reviewed journals
  - Safety studies conducted by the National Toxicology Program;
  - Elevated reports of accidental childhood poisonings in the Toxic Exposure Surveillance System (TESS), as was the case for iron-containing dietary supplements several years ago;
  - Compilation of adverse experience reports that have been evaluated using the full set of information accompanying the MedWatch file on each of those reports.
- Once, identified as a signal, an appropriate hypothesis should be developed for controlled testing. In the vast majority of cases, AERs have so many data gaps that they are suitable only for hypothesis-generating, not for hypothesis-testing, nor for serving as the sole basis of public health intervention.

**e. Categorization of Currently Marketed Dietary Supplements Based on Safety Issues**

- The charge to IOM is, in part, “to develop a proposed framework for categorizing and prioritizing dietary supplement ingredients based on safety issues.”
- CHPA recommends that the framework for categorizing dietary supplements *based on safety issues* should be according to the nature of the known or suspected toxicity. There should be a specific stipulation that great care should be given to avoid extrapolating data sets without the appropriate mechanistic studies needed to define human relevance if the data/information stem from in vitro, bacterial or animal studies or define the in-use relevance if the data/information are derived from human experiments:

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- Genotoxicity
  - Carcinogenicity
  - Reproductive toxicity
  - Organ/system toxicity (e.g., liver, GI, cardiovascular system; cerebrovascular system, CNS/behavior, etc.)
  - Allergenicity and sensitization
  - Interactions: drug-dietary supplement; food-dietary supplement
- Ingredients may be placed in more than one categorization.
  - Where appropriate/relevant, explanatory notes should accompany such categorizations, to avoid inappropriate extrapolations from in vitro, bacterial, or animal studies and from human studies where a clinical finding may not translate to in-use relevance. Animal and bacterial systems differ mechanistically from human biological systems. Further, for example, while methylcellulose used for regularity has been shown clinically to delay time to C<sub>max</sub> for digoxin, the fact that this has no bearing on managing patients on steady-state digoxin therapy means no interaction warning is needed on the label.
  - Ingredients with safety issues for which the database is incomplete, the presumption in the system should be that the marketed dietary supplement is safe. Such ingredients should be placed in a defined pending category to permit data development over a reasonable time by companies or other research groups (i.e., NIH, academia, others) prior to any public health interventions.

**f. Filling Data Gaps: Post-marketing Surveillance**

- Post-marketing safety evaluations are based on signals generated about a specific potential toxicity. Data gaps may likely exist, since such post-marketing signal generators are generally hypothesis-generating tools, requiring a more rigorous development of an understanding of the potential causal relationship of the signal to the dietary supplement through appropriate controlled hypothesis testing studies. Further, in filling the data gaps there may be a need to understand consumer attitudes and reported use practices as well as agricultural practices, sourcing, manufacturing practices, among other possible data. The scope and extent of filling data gaps is dependent on the specific issue at hand.
- The potential data sources to help address post-marketing safety signals include those identified above under *Section b*: published clinical case reports and case series; published uncontrolled clinical trials; published controlled clinical trials; published epidemiological studies; published and unpublished animal studies (e.g., reports from the National Toxicology Program relating to carcinogenicity, reproductive toxicity); in vitro studies (e.g., mutagenicity studies); the Toxic Exposure Surveillance System of the American

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Association of Poison Control Centers; special government surveillance studies (e.g., Consumer Products Safety Commission, Centers for Disease Control, etc.).

In addition, additional information may be sought from manufacturers relating to, for example, extraction processes, quality control and stability procedures under Good Manufacturing Practices or validated in-process control procedures<sup>2</sup>, agricultural practices (e.g., pesticide use), etc.

- Where a data gap may exist for a marketed product with established history of use (e.g., absence of a two carcinogenicity study) but where there is no clear signal of potential toxicity (e.g., genotoxicity studies provide no evidence to suspect toxicity), there should be no call for additional data development.

**g. DSISR: Public Review and Comment Procedures**

- Regulations establishing the DSISR should include certain components that helped ensure the acceptance and rigor of the OTC Review for nonprescription medicines. These include especially provisions for mandatory public review and comment of advisory committee reviews, deliberations and reports, as well as agency resulting proposed actions, recognizing FDA's statutory authority to declare a particular dietary supplement represents an imminent hazard to public health or safety.
- In the Congressional Finding's supporting the passage of DSHEA, Congress stated: "although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers." Hence, the incorporation of specific review-and-comment procedures as an integral part of the DSISR is vital to ensuring Congress' intent in passing DSHEA is met.

**2. DSISR: Prospective Post-marketing Safety Reviews**

**a. Scope:** Potentially, any currently marketed dietary supplement product.

**b. Prospective vs. Reactive Components of the DSISR**

- The reactive component of the DSISR (see above) addresses the need to identify, review and potentially take action on the unpredictable emergence of new safety information about a currently marketed dietary supplement. The prospective component of the DSISR would evaluate selected dietary supplements for their safety based on the same elements of the post-marketing

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<sup>2</sup> CHPA members use either the industry proposed GMPs or other validated procedures for in-process controls of manufacturing procedures and practices, including official or validated analytical methods for product ingredients.



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safety surveillance system used for emergent issues.

**c. Framework, Prioritization and Categorization, Filling Data Gaps**

- The same basic framework for collecting and evaluating adverse experience signals as well as prioritizing and categorizing safety issues and filling data gaps would be used for the reactive and prospective components of the DSISR, with the exception that the FDA advisory committee(s) charged with the safety review would establish a prospective agenda of ingredients, constituting at least a two-year work plan.
- The prospective safety review activities of the FDA advisory committee(s) chosen to conduct the DSISR would logically be interrupted to evaluate emergent safety concerns, as needed.

**d. DSISR: Public Review and Comment Procedures**

- As stated above, regulations establishing the DSISR should include certain components that helped ensure the acceptance and rigor of the OTC Review for nonprescription medicines. These include especially provisions for mandatory public review and comment of advisory committee reviews, deliberations and reports, as well as agency resulting proposed actions, recognizing FDA's statutory authority to declare a particular dietary supplement represents an imminent hazard to public health or safety. In the Congressional Finding's supporting the passage of DSHEA, Congress stated: "although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers." Hence, the incorporation of specific review-and-comment procedures as an integral part of the DSISR is vital to ensuring Congress' intent in passing DSHEA is met.

**3. DSISR Prospective Pre-marketing Safety Reviews:**

- a. Scope:** All products not yet marketed for which a 75-day notification must be sent to FDA prior to marketing, pursuant to DSHEA
- b. Potential Data Requirements for Pre-market Notifications:** It is likely that pre-market notifications for new dietary supplement ingredients will fall into two general groups: those with prior market experience perhaps in Europe or Asia; and those with no or very limited market experience. Flexibility should be built into the system in order to account for overseas market experience as a part of the basis for safety of new ingredients.

Data requirements for 75-day notifications might include some or all of the following information:

Product Information

- Statement of intended use and claim(s)
- Serving amount/dose and recommended interval of use
- Copy of the Label

Safety Information

- In vitro safety information, if relevant
- Genotoxicity studies
  - NOTE: where there has been a finding that an ingredient or product is not associated with mutagenicity, there should be no requirement for full-scale carcinogenicity studies, if there is prior marketing history.
- Animal safety studies, if relevant
  - Carcinogenicity studies:
    - NOTE: where there is not a history of use of the ingredient in humans, then consideration should be given to the need for carcinogenicity studies.
  - Organ-specific toxicity studies, if available  
Reproductive toxicity studies, if the new ingredient is intended for use by pregnant or nursing women;

Human Safety Information

- Clinical studies, if the product has not been marketed before in humans and if such studies are designed specifically for evaluating safety
- Supporting epidemiological studies pertaining to safety, if available
- Historical use information
- Information from post-marketing surveillance in foreign countries, if available

Other Safety Information

- Pertinent safety studies/information depending on the ingredient (e.g., allergenicity studies, in vitro studies, drug-DS interactions etc.)
- Other supporting information (e.g., information from national or international compendia)

Manufacturing Information

- Chemical composition of finished product (e.g., if a plant part, the Latin binomial and standardized common name; if an extract, the fixed ratio, type of extract, source of extract, etc.)
- Special manufacturing procedures
- Statement that GMPs are the basis for manufacturing and packaging

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Comments to the Institute of Medicine**c. Prioritization**

- Since there is a statutory timeframe for FDA comment to a 75-day notification procedure, each notification should be prioritized against this requirement.

**d. Categorization**

- Categorization of the safety review of the notification procedure should be as follows: sufficient information or insufficient information.
- However, care should be given not to create insurmountable hurdles to product development. As noted by Congress in its findings supporting DSHEA: “although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take any actions to impose regulatory barriers limiting or slowing the flow of safe products and needed information to consumers.”

**4. IOM’s Choice of Six Ingredient to “Beta-Test” the Framework**

CHPA recommends the following approach to identifying six ingredients to “beta-test” the framework proposed by the Association:

- **For the DSISR: Emergent Post-marketing Safety Reviews**
  - IOM should evaluate pyrrolizidine alkaloids (PAs), which are known hepatotoxic constituents of some botanicals. CHPA and AHPA have voluntary programs in which member companies have agreed not to market certain botanicals containing PAs.<sup>iii</sup>
  - IOM should review the current AER signal generators and choose two additional dietary supplements (excluding ephedra, which CFSAN informed IOM was being handled under a separate program activity for the Center).
- **For the DSISR: Prospective Post-marketing Safety Reviews**
  - IOM should choose three ingredients which are commonly used (i.e., have extensive exposure) and may have different potential toxicities (e.g., liver toxicity, drug-interactions, allergenicity).
- **For the DSISR: Prospective Pre-marketing Safety Reviews**
  - Given that the scientific framework for evaluating dietary supplement safety would be developed principally through the former two components of the DSISR, and that it is unclear which new dietary supplement may be submitted after IOM has developed its recommended framework, which may or may not be accepted by CFSAN, it is likely not fair, nor feasible, nor necessary to “beta-test” this component of the DSISR system.

## **Conclusion**

In conclusion, CHPA recommends that IOM consider a three component scientific framework for the evaluation of dietary supplement safety, which would be called a Dietary Supplement Ingredient Safety Review System. This framework would be composed of: (a) a system for post-marketing safety reviews of emergent safety issues; (b) a prospective post-marketing safety review seeking signals of potential toxicity for further evaluation and testing; and (c) a prospective pre-marketing safety review system for 75-day notifications. This recommended system is consistent with the framework set forth by the Dietary Supplement Health and Education Act.

WS/jq: DietSupp/NAS-IOM/IOM DS Safety Review/CHPA Comments to IOM 10-05-01

### ENDNOTES

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<sup>1</sup> Institute of Medicine: Revised Statement of Task. Framework for Evaluating the Safety of Dietary Supplements.

<sup>ii</sup> MedWatch: What is a Serious Adverse Event? An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is SERIOUS and should be reported when the patient outcome is:

Death: Report if the patient's death is suspected as being a direct outcome of the adverse event.

Life-Threatening: Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death. Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive drug dosing.

Hospitalization (initial or prolonged): Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event. Examples: Anaphylaxis; pseudomembranous colitis; or bleeding causing or prolonging hospitalization.

Disability: Report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life. Examples: Cerebrovascular accident due to drug-induced hypercoagulability; toxicity; peripheral neuropathy.

Congenital Anomaly: Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child. Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.

Requires Intervention to Prevent Permanent Impairment or Damage: Report if you suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient. Examples: Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone. <http://www.fda.gov/medwatch/report/DESK/ADVEVNT.HTM>

<sup>iii</sup> CHPA Voluntary Program: Pyrrolizidine Alkaloids:

- “Scope and Labeling: All products with botanical ingredients which contain toxic pyrrolizidine alkaloids \* should not be taken orally and should therefore bear the following cautionary statement on the label:
  - “For external use only. Do not apply to broken or abraded skin. Do not use while nursing.’
- Including but not limited to: *Alkanna tinctoria* (alkanet), *Anchusa officinalis* (bugloss), \* (borage), *Crotalaria* spp., *Cynoglossum* spp., *Erechtites hieraciifolia*, *Eupatorium cannabinum* (hemp agrimony), *Eupatorium purpureum* (Joe Pye), *Heliotropium* spp., *Lithospermum officinale* (European gromwell), *Packera candidissima*, *Petasites* spp. (e.g., Butterbur), *Pulmonaria* spp. (e.g., lungwort), *Senecio jacobaea* (European ragwort), *Senecio vulgaris* (groundsel herb), *Symphytum* spp. (comfrey), and *Tussilago farfara* (coltsfoot).
  - \* “Borage seed oil is specifically exempt from the above label recommendation.
- “In view of the fact that by statutory definition botanicals that are not orally ingested are not dietary supplements, pyrrolizidine alkaloids encompassed by this voluntary program are not dietary supplements.
- “Adopted: March 8, 2001. Implementation at next label printing, but not later than March 8, 2002.”