Proposed Framework for Evaluating the Safety of Dietary Supplements -- For Comment

Committee on the Framework for Evaluating the Safety of Dietary Supplements, National Research Council

ISBN: 0-309-58358-6, 156 pages, web only, (2002)

FOR COMMENT

Proposed Framework for Evaluating the Safety of Dietary Supplements

Committee on the Framework for Evaluating the Safety of Dietary Supplements
Food and Nutrition Board
Board on Life Sciences
INSTITUTE OF MEDICINE
NATIONAL RESEARCH COUNCIL

NATIONAL ACADEMY PRESS
Washington, D.C.

NATIONAL ACADEMY PRESS 2101 Constitution Avenue, N.W. Washington, DC 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance. Support for this project was provided by Food and Drug Administration under contract number 223-00-2458. The views presented in this report are those of the Institute of Medicine Committee on the Framework for Evaluating the Safety of Dietary Supplements and are not necessarily those of the funding agencies.
This report is available for downloading as a pdf file at www.nap.edu and at www.iom.edu/fnb.
For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Knowing is not enough; we must apply.
Willing is not enough; we must do.
—Goethe

INSTITUTE OF MEDICINE

Shaping the Future for Health

THE NATIONAL ACADEMIES

National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Bruce M.Alberts is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm.A.Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V.Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Bruce M.Alberts and Dr. Wm. A.Wulf are chairman and vice chairman, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON THE FRAMEWORK FOR EVALUATING THE SAFETY OF DIETARY SUPPLEMENTS

BARBARA O. SCHNEEMAN *(Chair),* Departments of Nutrition and Food Science, Division of Clinical Nutrition and Metabolism, and Office of University Outreach, University of California, Davis
DANIEL L. AZARNOFF, D.L. Azarnoff Associates and Clinical/Regulatory Affairs, Cellegy Pharmaceuticals, South San Francisco, California
CINDY LYNN CHRISTIANSEN, Center for Health Quality, Outcomes, and Economic Research, Bedford V.A. Hospital, and Boston University School of Public Health, Massachusetts
ALICE M. CLARK, Office of Research and Sponsored Programs, University of Mississippi, Oxford
NORMAN R. FARNSWORTH, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago
ADRIANE FUGH-BERMAN, Department of Health Care Sciences, George Washington University School of Medicine, Washington, D.C. (until April 2002).
TED GANSLER, Medical Information Strategy, American Cancer Society, Atlanta, Georgia
PHILIP S. GUZELIAN, Department of Medicine, University of Colorado Health Sciences Center, Denver
ELIZABETH JEFFERY, Department of Food Science and Human Nutrition, University of Illinois at Urbana
JOSEPH LAU, Division of Clinical Care Research, New England Medical Center, Boston, Massachusetts
LARS NOAH, University of Florida College of Law, Gainesville (until January 2002)
SUSAN S. PERCIVAL, Department of Food Science and Human Nutrition, University of Florida, Gainesville
CHERYL L. ROCK, Department of Family and Preventive Medicine, University of California, San Diego, La Jolla

Consultants

EDWARD A. BORTNICHAK, Strategic Value Assessment, Sanofi-Synthelabo, New York, New York
KENNETH FISHER, Washington, D.C.
LEWIS A. GROSSMAN, Washington College of Law, American University, Washington, D.C.

Staff

ALLISON A. YATES, Study Director
MARILEE K. SHELTON, Program Officer
ALICE VOROSMARTI, Research Associate
VIVICA KRAAK, Research Associate
SYBIL BOGGIS, Senior Project Assistant

FOOD AND NUTRITION BOARD

Staff

BOARD ON LIFE SCIENCES

Staff

Foreword

The Committee on the Evaluation of the Safety of Dietary Supplement Ingredients was asked to develop a framework for use by the U.S. Food and Drug Administration (FDA) to evaluate the safety of dietary supplement ingredients. It should include, from a science-based perspective, a system for prioritizing review of dietary supplement ingredients that could be extended to new ingredients as notifications regarding intent to market were submitted by manufacturers. Although evaluation of data regarding the efficacy of such ingredients to maintain health is of interest to many, a review of these data was specifically not included in the charge to the committee. Thus, what follows in this report is a proposed framework for prioritizing and evaluating the safety of dietary supplements based on existing information available to FDA and others.

The committee is now in the process of evaluating six dietary supplement ingredients in a mock evaluation following the process outlined in this report. Our expectations is that by (1) the experience of applying the proposed framework to develop prototype monographs on these ingredients, albeit within the constraints of an outside organization, and (2) the review of comments solicited from various stakeholders regarding the proposed framework, the committee will be able to revise and further elaborate the proposed system, resulting in a final, fully developed framework to provide to FDA.

Although this study is under the primary management of the staff of the Food and Nutrition Board (FNB) of the Institute of Medicine (IOM), it is being conducted as a collaborative project within The National Academies by FNB and the Board on Life Sciences (BLS) of the Division of Earth and Life Studies.

The committee was assisted in this challenging first task by the invaluable contributions of a number of individuals. Christine Lewis Taylor, FDA's Project Officer, met with the committee early in its deliberations. We appreciated her clear presentation about the committee's task. The committee also recognizes the significant contributions made by two members of the committee who resigned during the development of the report, Lars Noah and Adrianne Fugh-Berman; their insights were very valuable to the development of the proposed process. We also acknowledge the real loss experienced by the committee and its progress in the untimely death of committee member Dr. Norman Gillis last year as the committee was just beginning this process. Finally, we gratefully appreciate the assistance of Stephen F. McNamara, of Hyman, Phelps, and

McNamara, for his technical review of Chapter 1, and of Janice Rice Okita, a new FNB program officer working on the monograph development phase of this project, for her assistance with the toxicology section in Chapter 4, Key Factors.

The committee was greatly assisted by the very able work of Marilee Shelton, program officer for BLS, who has provided significant assistance to the management and conceptual development of the framework; her efforts to the move the project forward have been key to the process. In addition, Allison Yates, Study Director, has provided valuable insight and input for accomplishing the task of the committee. We also greatly appreciate the able and dedicated assistance of Alice Vorosmarti, research associate; Vivica Kraak, research associate, who joined the project as Alice Vorosmarti went on leave; and Sybil Boggis, senior project assistant. We thank Gail Spears for her editorial advice, Gary Walker for financial management, and members of IOM's Office of Reports and Communication for assistance in the production and dissemination of the report. Finally, we would like to thank the FNB and BLS reviewers, Robert W. Russell, Tufts University; Robert J.Cousins, University of Florida; and Linda E. Greer, Natural Resources Defense Council for their comments on the clarity of the report.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's (NRC) Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Joseph Betz, National Institutes of Health
Joseph Borzelleca, Virginia Commonwealth University
D. Craig Brater, Indiana University School of Medicine
Steven Dentali, Dentali Associates
Sanford A. Miller, Virginia Polytechnic Institute and State University
R.William Soller, Consumer Healthcare Products Association
Meir Stampfer, Harvard University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Bernadette Marriott, Burroughs Wellcome Fund, appointed by the Institute of Medicine, and Catherine Woteki, Iowa State University, appointed by the National Research Council's Report Review Committee. The coordinator and monitor were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

As chair of the committee, I want to thank my fellow committee members for their commitment to the work of the committee under a rather demanding time schedule. Their quick and constructive responses to the many drafts of the report made meeting the deadline possible.

Barbara O. Schneeman, Committee Chair

Contents

APPENDIXES

Executive Summary

Consumer interest in health and self-care has expanded the market for a wide range of products including dietary supplements. Consumer use of dietary supplements has grown exponentially in the past decade, signifying increases for both traditional as well as new uses. As new formulations and products have come on the market, estimates of total sales have grown to $15.7 billion per year (Blendon et al., 2001; Nutrition Business Journal, 2000). As with conventional foods, many dietary supplements are probably safe when used as recommended. However, increased use of supplements, the broad spectrum of products that qualify as dietary supplements under the Dietary Supplement Health and Education Act of 1994 (DSHEA), and its requirement that the Food and Drug Administration (FDA) determine what is unsafe without requiring specific information on safety be presented by manufacturers prior to marketing, make regulation of dietary supplements a sizeable challenge.

THE COMMITTEE'S TASK

To monitor the continually evolving patterns of dietary supplement use and potential interactions with other consumed substances, FDA needs a cost-effective and scientifically based approach to considering the safety of dietary supplements. For these reasons, FDA turned to the Institute of Medicine (IOM) of The National Academies to provide a framework for evaluating the safety of dietary supplement ingredients. FDA requested that a committee of experts (1) develop a proposed framework for categorizing and prioritizing dietary supplement ingredients sold in the United States based on safety issues, (2) describe a process for developing a system of scientific reviews with specifications for evaluating the safety of dietary supplement ingredients, and (3) utilize the proposed framework to develop at least six scientific reviews or monographs as prototypes for the system after release of the proposed framework. The proposed framework is to include a methodology to review data with regard to the safety of dietary supplement ingredients, taking into consideration methods other expert bodies have used to categorize and review supplement safety and efficacy issues.

The proposed framework described in this report is now being released for comment and discussion to interested organizations and individuals; it is intended that at least one open forum will be held specifically to solicit input about the framework and its process for setting priorities and categorizing dietary supplement ingredients, as well as about the process for review and

evaluation of information in the development of the prototype monographs. Based on a review of comments received and experience gained from completion of the prototype monographs, the proposed framework will be modified as appropriate. The revised framework will be released in a final report of the committee. This final report will also include the six prototype monograph reviews as examples of how the framework as revised can be implemented.

TABLE ES-1 Current Status of Foods, Drugs, and Dietary Supplements under Food and Drug Administration (FDA) Regulation

Status	Dietary Supplements	Foods[a]	Food Additives	New Drugs[b]
Premarket approval required	No[c]	No[d]	Yes	Yes
Risk-benefit analysis conducted by FDA prior to marketing	No	No	No	Yes
Postmarket reporting or surveillance by industry required	No	No	Rarely	Yes
Burden of proof for demonstrating safety or lack thereof	FDA	FDA	Manufacturer	Manufacturer

[a] Foods (including conventional foods and dietary supplements), unlike drugs, are considered to be safe (reasonable certainty of no harm), and thus risk-benefit analysis is not applicable.

[b] This description applies to "new" drugs. Many over-the-counter drugs that are not "new drugs" are regulated under FDA's Over-The-Counter Drug Review procedures, which do not provide for postmarketing surveillance.

[c] A 75-day premarket notification, but not premarket approval, is required for dietary supplements containing ingredients not marketed before 1994.

[d] In 2001 FDA proposed a rule requiring marketers of food developed through biotechnology to notify the agency at least 120 days before commercial distribution and to provide information to demonstrate that the product is as safe as its conventional counterpart (FDA, 2001).

BACKGROUND

Current regulatory approaches to safety evaluation of dietary supplements in the United States are a product of several key pieces of legislation that span from the beginning to the end of the 20th century, culminating in the passage of DSHEA in 1994. The major controversy in considering the safety of dietary supplements has been whether supplements should be regulated as if they were conventional foods, food additives, or as drugs; foods are considered to be safe unless demonstrated otherwise, thus the government bears the burden to prove conventional foods are unsafe (see Table ES-1).

Since 1938 the drug industry has borne the burden of proof in establishing the safety of new drugs before they can be marketed, while the burden of establishing a food as unsafe has continued to remain with FDA. The 1938 Federal Food, Drug, and Cosmetic Act, which established the different burdens of proof, did not address when vitamins, minerals, and botanical products should be regulated as drugs as opposed to foods.

In 1958 the Food Additives Amendment defined food additives and provided that they must undergo a premarket approval process unless they were considered as generally recognized as safe (GRAS). FDA attempted to regulate the botanical industry by alleging that individual

botanical products were unapproved food additives, an effort eventually struck down by the courts.

BOX ES-1 LEGAL DEFINITION OF A DIETARY SUPPLEMENT AS DEFINED BY THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994

The term dietary supplement:

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;
(B) a mineral;
(C) an herb or other botanical;
(D) an amino acid;
(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

Dietary supplements are further defined as products that are labeled as dietary supplements and are not represented for use as a conventional food or as a sole item of a meal or the diet. Supplements can be marketed for ingestion in a variety of dosage forms including capsule, powder, softgel, gelcap, tablet, liquid, or, indeed, any other form so long as they are not represented as conventional foods or as sole items of a meal or of the diet (FDCA, as amended, § 402).

In the 1970s FDA tried to implement tighter regulations on vitamin and mineral supplements, but its actions were restricted by Congress via the 1976 Vitamins and Minerals Amendments. After FDA made another attempt to enforce stricter adherence to regulations in 1993, Congress acted further to contain FDA's authority by passing DSHEA in 1994.

DSHEA established the first comprehensive definition of dietary supplements as foods (Box ES-1), along with legislative language defining procedures and regulations governing their marketing. Specifically, substances and products on the market in the United States prior to October 15, 1994 could continue to be marketed, but introduction of new products would require notification by the manufacturer to FDA 75 days prior to marketing. Most importantly, DSHEA established a regulatory framework for dietary supplements that defines FDA's authority over these products. It establishes that dietary supplements are to be considered equivalent to foods in that they are assumed safe unless FDA has evidence that proves otherwise.

It is this postmarket burden of proof that makes FDA's consideration of dietary supplement ingredients profoundly different from its consideration of substances such as food additives or drugs. Before marketing, food additives and drugs are required to undergo extensive safety evaluations by manufacturers that must prove them to be safe under conditions of use (see Table ES-1).

FINDINGS

In preparation for developing a framework and then prototype monographs of six selected dietary supplement ingredients, the committee was also charged with reviewing methods used by other expert bodies to categorize and review safety issues related to dietary supplements. The

committee reviewed published information about the approaches several organizations have taken to learn more about the limitations in the approaches, as well as their attributes. In reviewing these frameworks, the committee noted the following:

- The purpose of the efforts varied substantially from organization to organization, focusing on quality, efficacy, safety, or a combination of these.
- Most of the approaches were focused exclusively on botanical ingredients, others focused on medicinal substances. The reviewed approaches did not focus on the safety of dietary supplements of all types.
- The approaches did not develop a systematic method to provide a categorized list of ingredients based on their need for more immediate attention, although several placed ingredients after review in general categories such as unsafe, safe, or unsafe for particular populations.
- Often the approaches were not sufficiently detailed or transparent to give a complete picture of the data considered, the rationale behind the conclusions, and remaining unanswered questions regarding safety.

After reviewing approaches of other groups, the committee's first objective was to develop a clear understanding of the purpose of the study and the expectations of FDA and those of industry. The second primary objective was to develop a collective understanding of what was meant by a “framework” and to identify common characteristics of effective frameworks already in place. **To this end, the Committee defined a “framework” for safety evaluation of dietary supplement ingredients as “the processes by which FDA can screen, set priorities, and evaluate available information to make regulatory decisions regarding dietary supplement ingredients.”**

In reviewing the methods used by other expert bodies to consider the safety of substances, and in reviewing the discussions with the sponsors and other interested representatives, the following attributes of an ideal framework were identified:

- it must be workable and able to be integrated into FDA's program of work;
- it should provide guidance to organizing diverse information already available;
- it should categorize the diverse substances classified as dietary supplements based on a scientifically valid metric;
- it should establish a database for collection of information regarding potential safety concerns that can be updated as new information is available; and
- it should provide a method to integrate diverse information into a prioritization scheme so that efforts and resources can be maximally directed toward those dietary supplement ingredients with the greatest safety concerns.

Once the definition and attributes of a safety framework were understood, the committee then identified key factors that could be used in such a framework. Following this, the committee developed a methodology to screen, set priorities, and then conduct critical evaluations of safety, with the results being collated into a monograph format. As a result of the review of types of information thought to be available for some dietary supplement ingredients, “guiding principles” for consideration during all of the steps were established.

Finally, the initial steps of the framework were applied to a variety of dietary supplement ingredients. Six diverse dietary supplement ingredients that would be expected to be flagged in the screening step were identified to serve as prototypes to test the proposed framework during the second phase of the study. During this phase, monograph reviews will be developed and put through the final critical safety evaluation step of the proposed framework.

PROPOSED FRAMEWORK FOR EVALUATING THE SAFETY OF DIETARY SUPPLEMENT INGREDIENTS

The Proposed Framework for Evaluatiing the Safety Dietary Supplement Ingredients consists of three steps: Step One, screening/flagging; Step Two, priority setting; and Step Three, critical safety evaluation (See Table ES-2 and Figure ES-1). Ideally, a critical safety evaluation for each dietary supplement ingredient could eventually be completed, but to best leverage available resources, it is necessary to determine which supplement ingredients warrant attention first. The first two steps in the process, screening/flagging and priority setting, are designed to set priorities for reviewing dietary supplement ingredients based on concern.

Key Factors Used in the Framework

In any scientific evaluation there are different types of data that are useful, or "factors" to consider, when collecting and sorting information (see Chapter 4). Different factors contribute to each step of the framework to a different degree, with different sources of information necessary to examine and evaluate the factors in the various steps of the processes proposed.

One key factor that should contribute to decision making at all three steps of the process is *human data.* Additional factors that should be considered are *animal data,* followed by information about the *biological activity of structurally related and taxonomically related substances,* and *in vitro evidence* of adverse effects. The potential for interactions among dietary supplement ingredients and other ingested substances or medical treatments are considered within each of these categories. An additional question considered only in the initial screening/flag step is whether the *ingredient is new to the United States,* as defined by DSHEA.

Other important factors integral to the framework are referred to as modifying factors. Whether *particular subpopulations are especially vulnerable t*o the adverse effects of particular dietary supplement ingredients is considered with the data for each of the above factors. Second, the overall *prevalence of use* of the dietary ingredient in the United States is considered during the sorting process to increase the priority for review within a priority group.

Step One: Screening/Flagging

The screening process was developed on the premise that it is not feasible for FDA to extensively search for information about each and every dietary supplement ingredient immediately. Readily available information can be used to flag substances that warrant further attention, while maintaining enough sensitivity to minimize false negatives and not omit any items with potential safety concerns.

To flag substances warranting some level of attention, "yes or no" questions were developed to identify ingredients to undergo Step Two, priority setting:

TABLE ES-2 Overall Framework

Step in the Process	Step One: Screening/Flagging	Step Two: Priority Setting	Step Three, Part A: Draft Monograph Preparation and Monograph Review by the Food and Drug Administration (FDA)	Step Three, Part B: Critical Safety Evaluation
Which ingredients	All ingredients are considered "New" ingredients are automatically flagged	Ingredients flagged in screening step	Ingredients with highest priority based on Step Two ranking	Monographed ingredients for which a decision is not clear cut or for which further input is desired
Completed by	FDA	FDA	FDA or contractor	External advisory committee
Factors and modifiers used	Human data: serious adverse events only Other concerns,[a] as they come to FDA's attention	Human data Animal data Biological activity of structurally related and taxonomically related substances In vitro data Vulnerable group use (modifies other factors) Prevalence of use (modifies priority ranking)	Human data Animal data Biological activity of structurally related and taxonomically related substances In vitro data Vulnerable group use considered with other factors	Human data Animal data Biological activity of structurally related and taxonomically related substances In vitro data Vulnerable group use (considered with other factors)
Level of information search	Easily obtainable information (see Table 4–1)	Literature search is more comprehensive	Comprehensive Request industry data and data from other stakeholders	Comprehensive Public input
Depth of evaluation	Low level evaluation: is there evidence suggesting a concern *may* exist?	Weighting based on evidence of possible risk, potential seriousness of harm, and relative importance of factor	Comprehensive: totality of evidence is considered, including data requested from industry and other stakeholders	Totality of evidence; monograph reviewed and revised
Goal	Ingredients warranting further investigation are flagged	Table of ingredients sorted into priority groups for further evaluation	Monograph *AND* FDA decision for action/inaction *OR* Referral to external advisory committee	Monograph with conclusions of external advisory committee

[a] The term "other concerns," as described in Chapter 3, encompasses concerns FDA becomes aware of without extensive information searching. These may include concerns expressed by other regulatory agencies, concerns expressed in secondary literature, or concerns expressed by other organizations.

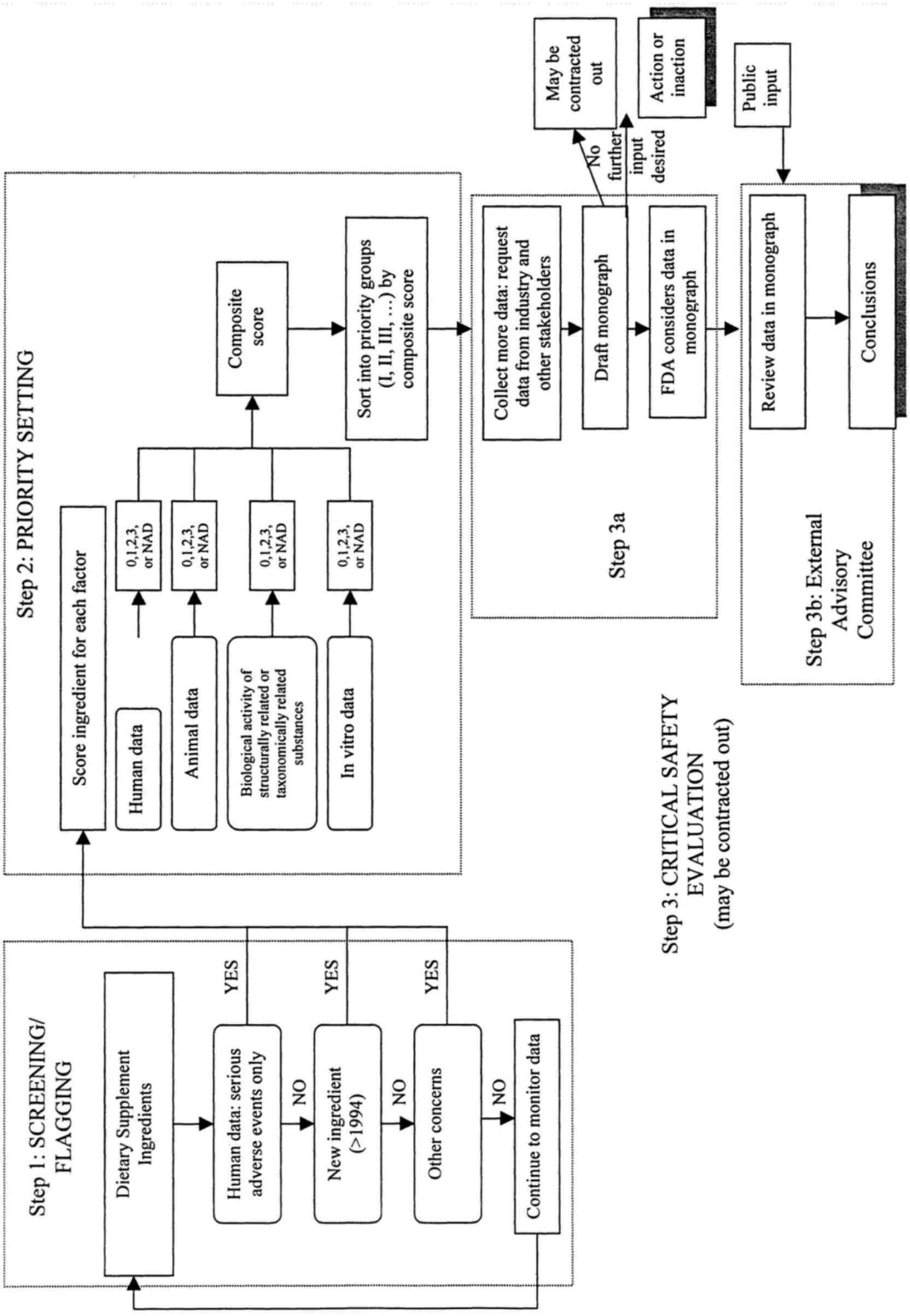

FIGURE ES-1 Flowchart of Overall Framework

1. Has a 75-day new ingredient notification been filed with FDA for the ingredient in question?
2. For the ingredient in question, are there potentially serious[1] adverse events in humans reported through MedWatch, poison control centers, or clinical studies that illustrate a pattern (in terms of the type of incident reported) that are well-documented in the medical literature, or that may be plausibly linked to the dietary supplement ingredient? Does the number of serious adverse events reported in humans appear high compared to the ingredient's prevalence of use? Does it seem plausible that particular subpopulations are particularly susceptible to serious adverse events?
3. Has the ingredient been brought to FDA's attention because of concerns other than new ingredient status or human adverse event data described above? A preliminary evaluation of concerns that have come to FDA's attention will allow FDA to determine which of these ingredients should move into priority setting.

In keeping with the philosophy that the screening step should be relatively simple and straightforward, answering these questions does not involve evaluation or weighting of the evidence. A single “yes” to any one question is sufficient to move the ingredient to the next step.

Step Two: Priority Setting

The goal of the priority-setting process (Step Two) is to identify those dietary supplement ingredients that require the most immediate attention of FDA for in-depth safety evaluation. The priority-setting process differs from the initial screening process in four fundamental ways:

- additional factors are considered;
- additional information is obtained;
- the evidence of possible risk, as well as the seriousness of potential harm is judged to some degree; and
- the different factors are weighted differently, based on importance.

Scoring and Sorting the Data

A sorting matrix is proposed to consider the importance of the information available for each key factor and to sort the ingredients accordingly. The available data for each of the four key factors (human data, animal data, biological activity of structurally related and taxonomically related substances, and in vitro data) are examined for all dietary supplement ingredients that were flagged in the screening process. A judgment is made of both the potential seriousness of the physiological effect suggested by the data and the strength of the evidence that the effect may occur. Based on this judgment, the data for each factor are judged and then assigned either a numerical value of 0 to 3, or NAD (no appropriate data), to indicate the evidence of possible risk and the potential seriousness of harm suggested by the data. A score of 3 is assigned for each factor where the data suggest both a potentially serious and very relevant harm and strong

[1] The term “serious” is used throughout the report. *Serious* adverse events are defined in the 1996 *Guideline for Good Clinical Practice* issued by the International Committee on Harmonization and endorsed by FDA. A serious adverse event is an untoward effect that is a death, life-threatening event, initial or prolonged hospitalization, disability, congenital anomaly, birth defect, or other important medical event.

evidence of possible risk, or there is strong evidence suggesting a possible risk of serious drug interaction. A 0 is assigned when there is strong evidence that there is no potential *serious* harm. Scores of 1 and 2 are not explicitly defined but result from a judgment of relative concern, as described in Chapter 5. For each ingredient, the numerical values for each factor are recorded (see Table ES-3 for a matrix listing fictitious ingredients). The ingredients in the matrix are then sorted into a list in descending priority, based on the scores, as described in the next section.

TABLE ES-3 Matrix of Scores Used in Establishing Relative Priority Among Dietary Supplements

Ingredient Name	Human Data	Animal Data	Biological Activity of Structurally Related or Taxonomically Related Substances	In Vitro Data
Yellow plant extract	3	1	2	2
Vitamin X	2	NAD	2	NAD[a]
Animal tissue	2	1	1	1

[a] NAD=no appropriate data.

Sorting the Ingredients by Scores

After data for an increasing number of dietary supplement ingredients are reviewed and a numerical score is assigned for each of the key factors, the list of ingredients can be sorted into categories of relative priority (called Priority Groups) based on the assigned scores.

In the proposed scheme, priority setting is accomplished through a multi-step sorting mechanism that reflects the importance of the different numerical scores and the hierarchical importance of the different factors when considering the safety of dietary supplement ingredients. Two of the key factors—human data and animal data—are placed at the top of hierarchy of data types. Ingredients with scores of 3 in both of these factors are therefore placed in the highest priority category, Priority Group I, as illustrated in Table ES-4.

Ingredients that were assigned a score of 3 for the human data, but not for the animal data, are categorized as Priority Group II. Ingredients that were assigned a score of 3 in animal data, but not in human data, are categorized as Priority Group III. Priority Group IV includes ingredients that were assigned a score of 3 for either the structure/taxonomy or the in vitro data, but not in the human or animal data. Finally, Priority Group V includes ingredients that did not receive a score of 3 in any of the key factors.

This priority-setting approach of scoring and then sorting into priority groups allows FDA to consider the different factors independently and individually for each ingredient, rather than having to compare them to all the ingredients that are being considered.

Step Three: Critical Safety Evaluation

The screening/flagging and priority-setting steps outlined in the previous sections result in the identification of priority groups of supplement ingredients based on level of priority for in-depth review. The evaluation process begins with completing the data collection, as shown in the flowchart (Figure ES-1). Much data will already have been obtained during the priority-setting step, but efforts should now be expanded to systematically search for relevant information from

additional sources as well. At this stage in the review, there is sufficient concern about the safety of the ingredient to justify FDA's request for more information to be volunteered by the industry, including data on safety. All the available information collected should be collated into a "Dietary Supplement Ingredient Safety Review Monograph," a task that might be appropriate for FDA to contract out if adequate resources are not available to prepare it internally.

TABLE ES-4 Matrix for Priority Establishment Based on Factor Analysis

Priority Group	Human Data	Animal Data	Bioactivity of Structurally Related or Taxonomically Related Substances	In Vitro Data	Number of Combinations (Total=625)	Characteristics of Priority Group
I	3	3			25	Two 3s in first two factors
II	3				100	3 in human data
III		3			100	3 in animal data
IV			3		144	One or two 3s in structure/ taxonomy or in vitro factors
				3		
V					256	No 3s in any key factor

After preparing the monograph that describes the available information and where information is missing, FDA should consider the totality of the scientific information collected. FDA should decide, based on the weight of the evidence, whether information in the monograph is conclusive enough to clearly indicate that action or inaction is appropriate. If the data are not sufficiently clear to make action or inaction obvious, or for any other reason FDA deems that external opinions may be valuable, an external advisory committee can be brought in to work on the issue.

After reviewing the information collected in the monograph and obtained from public comment sessions, the external advisory committee should revise the monograph to create a picture of the scientific information available. The advisory committee should evaluate the available scientific information and reach conclusions where possible, describing what is known about the safety of the ingredient based on the weight of the scientific evidence. The advisory committee's conclusions should include comments about the risk and hazards that may be associated with the general population ingesting the ingredient, as well as risks that may be of particular concern to certain segments of the population. After the advisory committee's conclusions are shared with FDA, the monograph and the advisory committee's conclusions should be posted on FDA's website.

Guiding Principles to Follow in Evaluating Data in the Framework

"Guiding principles" were developed to address the qualitative aspects of data review in the critical safety evaluation and for consideration when scoring during the priority-setting step. These guiding principles are:

- **A credible report of a serious adverse event in humans that is associated with use of a dietary supplement ingredient raises concern about the ingredient's safety and requires further information gathering and evaluation. A final judgment on the safety of the supplement ingredient, however, will require a consideration of the totality of the evidence. Historical use should not be used as prima facie evidence that the ingredient does not cause harm. It is appropriate, however, to give considerable weight to a lack of adverse events in large, high-quality, randomized clinical trials or cohort studies (prospective or retrospective) that are adequately powered and designed to detect adverse effects.**
- **Even in the absence of adverse events in humans, evidence of harm from laboratory animal studies can be indicative of potential harm to humans. This indication may assume greater importance if the route of exposure is similar (e.g., oral), the formulation is similar, more than one species shows the same toxicity, and the general characteristics of good animal studies as described in Chapter 4 are met. Particular weight is placed on evidence of certain types of delayed effects that are less likely to be detected in humans, such as cancer, developmental toxicity (including teratogenicity), and reproductive toxicity.**
- **The presence of constituents structurally similar to known toxic or potentially harmful compounds and plants taxonomically related to known toxic plants suggests increased risk, and therefore higher priority, unless there is evidence that the compound is not toxic or harmful, the compound is present in concentrations that will not lead to harm, or there is other evidence supporting the safety of the ingredient.**
- **In vitro studies can serve as signals of potential harmful effects in humans, but not as independent indicators of risk of harm unless an ingredient causes an effect that has been associated with harmful effects in animals or humans, and there is evidence that ingredient or its metabolites reach physiological sites where harm may occur. Alone, they should serve only as hypotheses generators and as indicators of possible mechanisms of harm when the totality of the data from the different factors is considered.**

Attributes of the Proposed Framework

There are a number of attributes of the framework proposed, and there are also a few limitations. This framework integrates a variety of available evidence about safety, balancing the value of different types of evidence and also integrating usage information to enhance the public-health impact of the work. Using the framework, FDA can be both proactive and reactive, as well as provide an open and transparent process helpful to the general public and the industry.

The proposed framework focuses on how to consider the *safety* of dietary supplement ingredients rather than offering guidance on how to consider their benefits and role in health. This was a key point of FDA's request to IOM, and is appropriate since dietary supplements are regulated as foods that must be safe, rather than as drugs requiring a risk-benefit analysis. A strength of the proposed framework is that it allows the incorporation of several different types

of data that may be available, providing a mechanism to evaluate the totality of the available data. The priority-setting step weights the different kinds of data available.

When considering the various types of data, the framework outlines how to consider both the strength of the evidence and the seriousness of harm suggested by the evidence. The evidence of possible risk incorporates both the methodological quality and the quantity of the available evidence, components that are important when considering any scientific data. Considering the potential seriousness of harm enables higher priority to be given to items that are of most concern because of their potential to adversely affect human health.

In addition to the methodology outlined for integrating various types of information, the proposed framework is also practical because it allows FDA to respond to new information in that the categorization of priorities easily changes to reflect new data.

Limitations are also inherent in the proposed framework. By definition, this framework cannot be used to consider the possible benefits of consuming dietary supplements. Another limitation is that, as with any evaluation of dietary supplement ingredients under the current regulatory scheme, this framework's evaluation of safety depends on publicly available data or data made available voluntarily by industry. A major component of this framework in particular is human data, which unfortunately can be highly variable in quality and quantity.

INGREDIENTS FOR PROTOTYPE MONOGRAPH REVIEWS

The second phase of FDA's charge to the Committee on a Framework for Evaluating the Safety of Dietary Supplements is, after release of the proposed framework for comment, to develop at least six scientific reviews as prototypes for the system outlined in the framework. The six supplement ingredients selected for the prototype reviews include the following (in no particular order other than alphabetical): chaparral, chromium picolinate, glucosamine, melatonin, saw palmetto, and shark cartilage. These six ingredients were selected to fulfill specific criteria. They include at least one botanical, one vitamin or mineral, one animal product, and one hormonal product. The selected ingredients also include substances for which a range of different types of available information and a range in quality of information available is anticipated. Ingredients included are those that would be expected to be flagged in the screening process and therefore enter the priority-setting step. Based on very preliminary data, it is also expected that this list includes substances that when initially reviewed in the priority-setting step, would not all be placed in the top priority category.

SECOND PHASE OF THIS STUDY

The second phase of this study will be to oversee the preparation of prototype monographs on the six ingredients, following the framework outlined in this report. As outlined in Chapter 6, industry will be requested to provide safety information about the ingredients undergoing in-depth safety evaluation. Panels will be organized to review information included in draft monographs and to arrange for public input on the evidence about safety.

During this phase, comments regarding the proposed framework detailed in this report will be solicited, reviewed, and revisions made as appropriate, followed by release of a revised framework and the six prototype monographs as examples of the safety evaluation envisioned.

1

Introduction and Background

A significant number of new dietary supplement products have appeared in the marketplace since the U.S. Congress passed the Dietary Supplement and Health Education Act (DSHEA) of 1994 (P.L. 103–417). At the time DSHEA was enacted, an estimated 600 U.S. dietary supplement manufacturers produced about 4,000 products (Commission on Dietary Supplement Labels, 1997). The Food and Drug Administration (FDA) estimates that more than 29,000 different dietary supplements are now available to consumers and an average of 1,000 new products are developed annually (Sarubin, 2000).

Consumer interest in health and self-care has been identified as providing the impetus for the expanded market of a wide range of products that includes dietary supplements (Prevention Magazine, 2001). Since 1994, sales of dietary supplements have increased to an estimated $15.7 billion per year (Blendon et al., 2001; Nutrition Business Journal, 2000). Of this total, it is estimated that Americans spend about $700 million per year on herbal supplements (Stein, 2000).

Vitamin and mineral supplement use by the U.S. population has been a growing trend since the 1970s (Bender et al., 1992; Subar and Block, 1990), suggesting that Americans are becoming more receptive to alternatives to conventional food sources for nutritional health benefits (ADA, 2000). This is despite research-based dietary recommendations supporting the position that the best nutrition strategy for optimal health and reducing the risk of chronic disease is to obtain adequate nutrients from a wide variety of foods (Hunt, 1996; Hunt and Dwyer, 2001).

Within its definition of supplements, DSHEA included ingredients that have not traditionally been recognized as nutrients or as having nutritional functions, such as botanicals and hormones (Nesheim, 1999). As with conventional foods, many dietary supplements are considered to be “safe”—that is, there exists a reasonable certainty of no harm when used as recommended. However, questions have been raised about the safety of some dietary supplements. When these questions are raised, FDA must rapidly review and further evaluate the safety of the ingredients. This has created a sizeable regulatory challenge for FDA because of the increased availability and use of supplements, as well as the broad spectrum of ingredients that qualify as dietary supplements under the DHSEA legislation.

COMMITTEE CHARGE

To expeditiously and efficiently monitor the continually evolving and growing patterns of dietary supplement use, as well as their potential interactions with other consumed substances, FDA needs a cost-effective and scientifically sound approach to consider the safety of dietary supplement ingredients. For these reasons, FDA turned to the Institute of Medicine (IOM) of The National Academies to propose a framework for evaluating the safety of dietary supplement ingredients marketed in the United States. Specifically, FDA requested that an IOM committee (1) develop a proposed framework for categorizing and prioritizing dietary supplement ingredients based on safety issues, (2) describe a process for developing a system of scientific reviews with specifications for evaluating the safety of dietary supplement ingredients, and (3) develop at least six scientific reviews as prototypes for the system. The proposed framework is to include a methodology to review data with regard to the safety of dietary supplement ingredients, taking into consideration methods other expert bodies have used to categorize and review supplement safety and efficacy issues. FDA, in its request to IOM, asked that a framework for setting priorities and evaluating the safety of dietary supplement ingredients be proposed and released for comment, followed by the development of six prototype monograph reviews using the procedures outlined in the proposed framework. After development of the prototype monograph reviews, and based on comments received, the framework is to be revised based on the experience and concerns identified following its release.

The committee held four meetings while preparing the proposed framework. Three of these meetings included open sessions so the committee could hear from the sponsor and a number of individuals and organizations regarding aspects of evaluating the safety of dietary supplements. In addition, representatives of a number of agencies and organizations that currently evaluate chemical substances for various attributes were invited to discuss their methodologies and frameworks for approaching reviews of such substances. (See Appendix F for a list of those presenting at the open sessions of the committee.)

GENERAL BACKGROUND INFORMATION ABOUT DIETARY SUPPLEMENTS

Many of the substances currently marketed as dietary supplements fall into the following categories: vitamins, minerals, herbs or other botanicals, amino acids, animal-derived products, hormones and hormone analogs, enzymes, and concentrates, metabolites, constituents, or extracts of these.[2] Within each of these categories, products may be pure single entities of known or unknown chemical components, mixtures in which all or some components are known, or mixtures of unknown chemical components.

National surveys such as the Third National Health and Nutrition Examination Survey and the 1987 and 1992 National Health Interview Surveys indicate that 40 to 46 percent of Americans reported taking at least one vitamin or mineral supplement at some time within the month surveyed (Balluz et al., 2000; Slesinski et al., 1995). Several investigations have explored *nutrient supplement* (thought to be primarily vitamin and mineral formulations) use prevalence and trends in the United States (Balluz et al., 2000; Bender et al., 1992; Kim et al., 1993; Koplan et al., 1986; Slesinski et al., 1995; Subar and Block, 1990), as well as motivations for taking

[2] While these are not dietary supplement categories specified by DSHEA, they illustrate the diversity of products currently marketed as dietary supplements. The 1994 DSHEA description of what constitutes dietary supplements can be found in Box 1–1.

vitamin and mineral supplements (Neuhouser et al., 1999) and characteristics of users versus nonusers (Dwyer et al., 2001; Ford, 2001; Hartz et al., 1988; Lyle et al., 1998; Nayga and Reed, 1999; Pelletier and Kendall, 1997; Subar and Block, 1990). However, knowledge about the use prevalence and trends of *dietary supplements* (which include nonvitamin, nonmineral supplements) is limited (Radimer et al., 2000). Data from national surveys collected before the enactment of DSHEA in 1994 may not reflect current supplement consumption patterns (Costello and Grumpstrup-Scott, 2000), and there are limitations to interpreting user characteristics from sales data (Radimer et al., 2000).

Existing studies of reported dietary supplement use suggest an association between increased use of dietary supplements by older individuals and those who report having more healthful lifestyles (Radimer et al., 2000). The most frequent reason given for dietary supplement use in one national survey was desire for self-care (Prevention Magazine, 2001). Some consumers report using supplements because of a belief that these products will ensure good health.

Generally, labeling for a dietary supplement may not claim to "diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases" (DSHEA, P.L. 103–417, § 6, 1994; FDCA, 21 U.S.C. § 343(r)(6)(C), 2001). Despite the legal classification, consumers have reported using supplements for very specific purposes such as treating and preventing illnesses, colds, and flu; increasing "mental sharpness"; and alleviating depression (Prevention Magazine, 2001). Studies conducted among teenagers suggest that dietary supplements are used to enhance athletic performance, build muscle, or lose weight (FDA, 1994; Jonnalagadda et al., 2001; McGuine et al., 2001; Metzl et al., 2001; Smith and Dahm, 2000; Wallace, 2001).

There is also a reported link of more frequent dietary supplement use among Americans with one or more health problems (Bender et al., 1992), with specific diseases such as breast cancer (Newman et al., 1998), with higher alcohol consumption, and with obesity (Radimer et al., 2000). Evidence suggests that supplement use may not be associated with better food intake in all populations, and may differ by ethnicity and across income strata (Pelletier and Kendall, 1997; Pelletier et al., in press).

Results from a recent national survey of 2,000 adults indicated that 85 percent of respondents had used one or more dietary supplements in the previous 12 months (Prevention Magazine, 2001). If this sample of U.S. consumers was representative of the total population, it would translate into more than 44 million consumers using botanical remedies and an estimated 24 million using specialty supplements (e.g., bee pollen, dehydroepiandrosterone [DHEA], chondroitin sulfate, kava kava, shark cartilage, and S-adenosylmethionine [SAMe]) (Prevention Magazine, 2001; Radimer et al., 2000; Ramos, 2000).

Consumer Expectations About Dietary Supplement Safety

The American public may assume that dietary supplements are subject to existing government regulations similar to those required for over-the-counter (OTC) medications sold without a prescription. In actuality, dietary supplements are subject to different regulatory requirements in comparison with OTC medications. With the passage of DSHEA, the burden of proof concerning the safety of dietary supplements was placed on FDA by requiring FDA to determine that a substance was unsafe rather than requiring a manufacturer to provide data supporting its safety (Blendon et al., 2001). New dietary supplement ingredients (those not marketed prior to passage of DSHEA), however, must provide advanced notification to FDA prior to marketing.

Only a few national surveys exploring the views and perceptions of Americans regarding dietary supplements have been conducted. One compilation was based on four national opinion surveys conducted from 1996 to 1999 by the Roper Center for Public Opinion; however, supplement users were not differentiated from nonusers, thereby limiting the usefulness of the findings (Blendon et al., 2001). Another survey that explored general patterns of medication use in the ambulatory adult population from 1998 to 1999 also examined use of vitamins and minerals, as well as herbals and dietary supplements. The Sloan Survey, conducted among 2,590 U.S. consumers, found that 16 percent of prescription drug users also took an herbal or other dietary supplement (Kaufman et al., 2002). A third telephone survey, conducted by the Princeton Survey Research Associates for Prevention Magazine, used a nationally representative sample of 2,000 U.S. adults. The results suggested a high degree of consumer confidence in supplements based on the finding that nearly two-thirds of respondents believed that herbal supplements were either safe or completely safe (Prevention Magazine, 2001).

Another analysis used two separate data sources that compared the views of dietary supplement users to nonusers. The first survey, designed collaboratively between researchers at National Public Radio, the Kaiser Family Foundation, and the John F.Kennedy School of Government, used telephone interviews conducted by the Princeton Survey Research Associates with 1,200 randomly selected adults in 1999. A second survey was conducted with 1,013 randomly selected adults (Blendon et al., 2001). Results from the analysis of the two surveys revealed that regular dietary supplement users reported not discussing dietary supplements use with their physicians because they believed that the physicians knew little or nothing about these products and may be biased against them. In addition, many users felt so adamant about the potential health benefits of some of the products used that they would continue to take them even if the products were shown to be ineffective in scientifically conducted clinical studies. Despite these beliefs, the analysis also revealed that there was broad public support for increased government regulation of these products. The majority of those surveyed supported the following positions:

- FDA should be required to review the safety of new dietary supplements prior to their sale.
- FDA should be granted increased authority to remove from the market products that are shown to be unsafe.
- Government regulation should have the capacity to ensure that advertising claims about the health benefits of dietary supplements are truthful (Blendon et al., 2001).

History of the Federal Regulation of Dietary Supplements

A framework for the evaluation of safety of dietary supplement ingredients must be carried out within the regulatory environment under which the ingredients are to be evaluated. Many herbals and other botanicals have been used much longer than many other types of dietary supplements currently in use, with ancient cultures employing them medicinally. People have long used plants and other substances to supplement their diets in an attempt to prevent or ameliorate specific symptoms. Patent medicines became popular in the 1800s as advertising increased and the lack of available trained medical personnel and the inability of conventional medicines to adequately treat many diseases drove consumers to look elsewhere for help. Such products were often secret formulations and directly marketed to consumers (CDER, 2002).

The growing pharmaceutical industry marketed its medicines directly to health professionals. In both cases, there were few regulations to control unsubstantiated claims to assist the consumer or health professional in distinguishing between valid and false assertions made by purveyors of the different products. While some efforts were made by states, federal regulation of these substances and products in the 1800s was essentially nonexistent (Millikan, 1999).

Food and Drugs Act of 1906

The Food and Drugs Act of 1906, and its companion bill, the Meat Inspection Act of 1906, were the earliest comprehensive efforts by the U.S. government to bring greater emphasis both to the safety of marketed products and to the accurate characterization of the benefits derived from their use. The 1906 acts resulted from a convergence of public, industry, and scientific support that was partially motivated by concern about the safety of food and patent medicines and widespread fraud in the growing food and drug industry. The triggering event was the exposure of unsafe conditions in the meat packing industry (Sinclair, 1906). The passing of the 1906 acts has also been attributed to industry's desire to restore competitiveness to their products in weak foreign and domestic markets (Barkan, 1985).

The 1906 acts established the broad authority of the federal government to protect the public from adulterated or misbranded food and drugs, and thus imposed new regulations on the food and drug industries. Specifically, the laws introduced accountability by requiring that regulated products be labeled accurately and that they be safe. However, under the Food and Drugs Act, FDA bore the burden of establishing that a food or drug was unsafe before it could take action against the product.

Federal Food, Drug, and Cosmetic Act of 1938

A movement for increased regulation of ingested substances came about in the 1930s, eventually culminating in the U.S. Congress passing the 1938 Federal Food, Drug, and Cosmetic Act (FDCA, P.L. 75–717, 52 Stat. 1040 [1938], as amended 21 U.S.C. § 301 et seq., 2001). The FDCA replaced the 1906 law that had become obsolete due to the technological changes in the production and marketing of food and drugs (FDA, 1981). This new Act created a complex system of federal regulations for foods, drugs, cosmetics, and medical devices. Some of the more important changes implemented by the FDCA were further introduction of food standards[3] and changing the focus of FDA from that of a policing agency that had been concerned primarily with confiscating adulterated drugs to that of a regulatory agency involved with the oversight of evaluating new drugs (Wax, 1995).

The FDCA transferred the responsibility of proving the safety of new drugs to the drug manufacturer and required manufacturers to submit new drug applications (NDAs) establishing safety to FDA before marketing.[4] While FDA no longer had the responsibility of establishing that an unapproved new drug was unsafe before taking action against it, FDA continued to be

[3] Food standards were required to promote honesty and fair dealing in the interest of consumers (FDA, 1981). The standards consisted of definitions of what constituted a food (e.g., mayonnaise must contain a certain percentage of egg and oil).

[4] In 1962, the FDCA was amended to require NDAs to establish the efficacy, as well as the safety, of new drugs.

responsible for establishing that a conventional food product was unsafe, as it does to this day[5] (Commission on Dietary Supplement Labels, 1997).

The FDCA contained provisions that applied to foods, drugs, and cosmetics. The application of these provisions to products containing a vitamin, mineral, or botanical ingredient (whether it was considered a drug or a food, for example) depended on the product's *intended* use, as determined usually by the labeling and advertising claims for the product.

The 1938 Act contains a number of definitions that guide FDA actions according to the regulations derived from it. One definition of a drug is an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals…"; a second definition is "articles (other than food) intended to affect the structure or any function of the body of man or other animals…"; and a third definition states that a product is a drug if it is "recognized in the official U.S. Pharmacopeia (USP), official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them." (FDCA, P.L. 75–717, 52 Stat. 1040 [1938], as amended 21 U.S.C. § 321(g), 2001).

The 1938 Act contains no specific provisions for vitamin, mineral, or botanical products, except in Section 403(j), which indicates that a food is misbranded if it is claimed to be "for special dietary uses" but its label does not bear FDA-prescribed statements about its "vitamin, mineral, and other dietary properties" sufficient to inform the consumer about its value for such uses (FDCA, P.L. 75–717 § 403(j), as amended 21 U.S.C. § 343(j), 2001).

Congress intended that this Section [403(j)] would allow FDA to regulate claims for vitamins, minerals, and botanical foods more closely than for conventional foods (Pendergast, 1997). However, in enacting Section 403 (j), it has been asserted that FDA was most concerned with the problems of nutritional deficiency and inadequacy of the diet, and thus did not address either acceptable claims for vitamins, minerals, and botanical products or when these products should be regulated as drugs as opposed to foods (Pendergast, 1997).

Early Attempts to Regulate the Industry

Eventually FDA did focus attention on claims for vitamins, minerals, and especially botanical products. FDA began to use extensive litigation directed at claims to regulate the botanical industry in the 1940s. Botanical products were treated as unapproved drugs not only if they made claims concerning the treatment or prevention of disease, but also if they made claims concerning the products' effects on the structure and function of the body —a type of claim foods were allowed to make without being considered drugs. FDA also took action against manufacturers making therapeutic claims for vitamins and minerals (FDA, 1941).

At that time, FDA did not rigorously apply the FDCA's definition of drugs (those listed in the USP, National Formulary, or the Homeopathic Pharmacopoeia of the United States), a definition that would have included most vitamins and minerals and many botanical preparations. In 1944, when FDA charged that certain vitamin B capsules were misbranded as food and drugs, the courts dismissed the food counts, holding that the capsules were drugs by definition because vitamin B was listed in the USP (Pendergast, 1997). FDA did not fully exploit this reasoning in future cases, however, and appeared to abandon this legal theory after several

[5]However, food colors, binders, and other food additives must be approved for safety or determined to be generally recognized as safe (GRAS) prior to use (only the dietary supplement ingredient in a marketed supplement is exempted from food additive regulations), thus technical ingredients are subject to FDA requirements for preapproval.

court cases in the 1960s, declaring that a USP listing was insufficient to confer drug status on a product (FDA, 1966).

FDA's focus on regulation of labeling claims it deemed unapproved and indicative of drug status was closely followed by increased use of publications such as self-help books and magazine articles that explained claims and intended uses. This approach was a "possible way [for supplement manufacturers] to avoid the FDA [enforcement]" (Pendergast, 1997). Debate about what constituted "labeling" ensued as FDA attempted to broaden labeling to include books and other materials. Characterization that this approach restricted the First Amendment right to free speech resulted in a number of court battles between the 1940s and 1960s.[6] The resulting debate about First Amendment rights and labeling restrictions has been considered by some to be a significant factor that eventually led to DSHEA as an attempt to resolve the situation (McNamara, 1995). (The importance of DSHEA is described in greater detail later in the text.)

Food Additives Amendment of 1958

Another major approach instituted by FDA that has been identified as a factor leading to the passage of DSHEA was its application of the Food Additives Amendment (FAA) of 1958 (P.L. 85–929, 1958) to botanical products (Kirschman, 1988). The result of FAA was to shift the burden of proof of safety away from FDA for a substance added to food. Manufacturers were required to obtain premarket approval from FDA unless the substance at issue could be considered as "generally recognized as safe" (GRAS) or had been sanctioned by FDA or the U.S. Department of Agriculture prior to 1958. A food additive is defined as "any substance the intended use of which results, or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food…that are not GRAS for intended use" (FDCA, P.L. 75–717, as amended 21 USC § 321(s), 2001).

FDA instituted action against many popular dietary supplement ingredients based on contentions of unapproved food additive status. FDA contended that even single ingredient supplements in capsule form contained unapproved food additives. For example, FDA argued unsuccessfully that black currant seed oil in a capsule was a food additive (United States v. Two Plastic Drums…Black Current Oil, 984 F.2d 814 [7th Cir. 1993]). Although the courts struck down FDA's effort with black currant seed oil, FDA's application of the food additive provisions to botanical products and other dietary supplement ingredients has also been considered a major precipitating factor in the eventual passage of DSHEA (Kirschman, 1998).

1976 Proxmire Amendments

By the 1960s regulation of botanical, vitamin, and mineral supplements was not consistent and was based on a combination of enforcement and judicial decisions. Court actions required long periods of time and considerable resources; thus FDA attempted to have broader impact on dietary supplement use by implementing tighter regulations on vitamin and mineral supplements. In 1973 FDA issued regulations prohibiting certain representations on vitamin and mineral supplement labels, establishing standards of identity for vitamin and mineral supplements, and establishing that preparations containing more than 150 percent of the U.S. Recommended Dietary Allowance (U.S. RDA) per serving were drugs. Both industry and consumers protested

[6] *See* United States v. Detroit Vital Foods, 218 F. Supp. 208 [E.D. Mich. 1963]; United States v. Articles of Drug…Honey, 344 F.2d 288 [6th Cir. 1965]; United States v. Kordel, 164 F2d 913 [7th Cir. 1947], aff'd, 335 U.S. 345 [1948]; United States v. "Sterling Vinegar and Honey"…Balanced Foods, 338F.2d 157 [2d Cir. 1964].

these actions, eventually leading Congress to enact the 1976 Vitamins and Minerals Amendments, also known as the "Proxmire Amendments," that prevented FDA from establishing standards limiting the potency of vitamins and minerals in food supplements or from regulating them as drugs based solely on potency (Pendergast, 1997). FDA revised its vitamin-mineral regulations in response to this legislation and, after a subsequent court challenge, ultimately revoked the regulations in 1979 (FDA, 1979).

The Nutrition Labeling and Education Act and Health Claims

With the suppression of FPDA's attempts at more restrictive rulemaking, the realm of products sold as dietary supplements continued to expand and included botanicals and amino acids, as well as vitamin and mineral products. This expansion during the late 1970s and the 1980s was accompanied by reports of serious illnesses attributed to a few of the dietary supplements available at that time. In 1978, for example, an infant with colic was reportedly given a fatal dose of a potassium chloride supplement based on erroneous advice in a parenting book, despite medical knowledge that use of such doses of the supplement would induce cardiac arrest (Wetli and Davis, 1978). In 1989 there were widespread reports that certain tryptophan supplements were associated with eosinophilia-myalgia syndrome. After considerable in-house research by FDA, evidence surfaced that the problem might have been associated with the manufacturing process and FDA took actions that led to the removal of tryptophan from the market.

By this time mounting scientific evidence had led several food companies to start promoting their conventional foods based on the potential of some of the ingredients or substances found in the food to reduce the risk of specific diseases. Some have purported that when dietary supplements made similar claims, FDA treated them more harshly, considering them to be unapproved drugs (Pendergast, 1997). This purportedly unequal approach toward regulating supplements versus foods supposedly became more evident when in 1987 FDA described criteria for what it would consider as an acceptable health claim (FDA, 1987). These proposed rules indicated that it might be more difficult for dietary supplement claims to meet FDA's criteria, which could be interpreted as acknowledging that foods and dietary supplements were not the same (Pendergast, 1997). The Nutrition Labeling and Education Act (NLEA), which was passed in 1990 (P.L. 01–635), explicitly authorized "health claims,"[7] but did not silence the controversies surrounding the different treatment of supplements and foods (Pendergast, 1997). Among other things, the NLEA provided that health claims describing the relationship of a nutrient to a disease or health-related condition were allowed for both traditional foods and dietary supplements if the claims complied with FDA regulations. FDA was charged with proposing the criteria needed for foods or supplements to make health claims. Some contend that concerns that FDA would treat supplements too harshly also contributed to the passage of DSHEA (Pendergast, 1997).

The Dietary Supplement and Health Education Act

In order to provide additional guidance, in 1993 FDA issued an advanced notice of proposed rulemaking regarding dietary supplements, which was accompanied by the suggestion that some

[7] A health claim is a claim that "characterizes the relationship" between a substance in a food and damage, disease, or dysfunction of the human body. In effect, this allows a claim that otherwise would be regarded as an illegal drug claim when made for a food.

products marketed as dietary supplements might be more appropriately considered under other regulatory categories. Amino acids, for example, might be considered unapproved food additives, and some botanicals might be more appropriately considered as drugs (FDA, 1993). Vitamins and minerals were also considered a potential target of regulation, as FDA suggested that their strength should be limited to levels that approximated the U.S. RDAs (FDA, 1993).

Industry and consumers reacted quickly and strongly to these potential regulatory restrictions. Extensive public debate ensued over the importance of dietary supplements in health, consumers' freedom to access information about supplements, and the controversy over FDA's regulatory approach. As a result, Congress passed legislation limiting FDA regulation of dietary supplements. This legislation, the Dietary Supplement Health and Education Act (DSHEA), was signed into law in 1994.

The Regulatory Implications of DSHEA. DSHEA is the most important dietary supplement legislation enacted to date. In its findings, Congress recognized the wide use of dietary supplements and stated in the legislation that currently available dietary supplements are generally safe. Passage of DSHEA was based on the concept that "legislative action that protects the right of access of consumers to safe dietary supplements is necessary to promote wellness" (DSHEA, P.L. 103–417, § 2, 1994; OIG, 2001). DSHEA established the first comprehensive definition of dietary supplements (Hoffman, 2001) (see Box 1–1). More importantly, DSHEA established a new regulatory framework for dietary supplements that limits FDA's authority over these products, as compared to its authority over food additives and drugs (see Table 1–1 for comparison).

BOX 1–1 LEGAL DEFINITION OF A DIETARY SUPPLEMENT AS DEFINED BY THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994

The term dietary supplement:

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;
(B) a mineral;
(C) an herb or other botanical;
(D) an amino acid;
(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

Dietary supplements are further defined as products that are labeled as dietary supplements and are not represented for use as a conventional food or as a sole item of a meal or the diet. Supplements can be marketed for ingestion in a variety of dosage forms including capsule, powder, softgel, gelcap, tablet, liquid, or, indeed, any other form so long as they are not represented as conventional foods or as sole items of a meal or of the diet (FDCA, as amended, § 402).

TABLE 1–1 Current Status of Foods, Drugs, and Dietary Supplements under Food and Drug Administration (FDA) Regulation

Status	Dietary Supplements	Foods[a]	Food Additives	New Drugs[b]
Premarket approval required	No[c]	No[d]	Yes	Yes
Risk-benefit analysis conducted by FDA prior to marketing	No	No	No	Yes
Postmarket reporting or surveillance by industry required	No	No	Rarely	Yes
Burden of proof for demonstrating safety or lack thereof	FDA	FDA	Manufacturer	Manufacturer

[a] Foods (including conventional foods and dietary supplements), unlike drugs, are considered to be safe (reasonable certainty of no harm), and thus risk-benefit analysis is not applicable.

[b] This description applies to "new" drugs. Many over-the-counter drugs are regulated under FDA's Over-The-Counter Drug Review procedures, which do not provide for postmarketing surveillance.

[c] A 75-day premarket notification, but not premarket approval, is required for dietary supplements containing ingredients not marketed before 1994.

[d] In 2001 FDA proposed a rule requiring marketers of food developed through biotechnology to notify the agency at least 120 days before commercial distribution and to provide information to demonstrate that the product is as safe as its conventional counterpart (FDA, 2001).

DSHEA specifically exempts dietary ingredients in dietary supplement products from being regulated under the category of food additives. Because FDA does not have the authority to consider the dietary ingredients as food additives, there is no procedure for a manufacturer to obtain premarket approval or establish GRAS status. Thus, DSHEA eliminates one of the key approaches FDA had taken to restrict the availability of some dietary supplements, especially multi-ingredient products.

DSHEA also establishes safety standards for dietary supplements. It states that a dietary supplement will be considered adulterated (i.e., illegal) if it "presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling" (DSHEA, P.L. 103–417, § 4, 1994, as codified in FDCA 21 U.S.C. § 342, 2001). Most importantly, it is clear from the law that FDA bears the burden of proof if it decides to assert that a supplement is adulterated. In summary, while a manufacturer is charged with ensuring the safety of its products, the manufacturer is not required to reveal the basis of its safety determination unless the Secretary of the Department of Health and Human Services declares that the product poses an imminent hazard or FDA brings an action in court alleging the product is adulterated (Box 1–2).

DSHEA and New Dietary Ingredients Marketed After 1994. DSHEA provided additional requirements for supplements containing "new dietary ingredients" that were not marketed in the United States before October 15, 1994. Such products are deemed adulterated under DSHEA unless the new ingredient has been present in the conventional food supply in a form in which the food has not been chemically altered, or there is a "history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling…will reasonably be expected to be safe" (DSHEA, P.L. 103–417, § 8,

1994). In addition, the law requires that to avoid adulteration in the latter instance, the manufacturer or distributor must provide FDA with the information that is the "…basis on which [it] has concluded that the dietary supplement containing [the new] ingredient will reasonably be expected to be safe" (DSHEA, P.L. 103–417, § 8, 1994) at least 75 days prior to marketing the ingredient. If FDA does not reply to the notification within 75 days, the company is free to market the ingredient. FDA may examine the submission and conclude that it does not provide sufficient evidence to demonstrate that the ingredient is safe. If a manufacturer or distributor that receives such a response nonetheless chooses to market the product, FDA will consider the product adulterated and the government may take legal action against it. In any such proceeding, the government bears the burden of proof.

BOX 1–2 SAFETY STANDARDS FOR DIETARY SUPPLEMENTS AS ESTABLISHED BY DSHEA

Section 4. Safety of Dietary Supplements and Burden of Proof on FDA.
DSHEA amends § 402 (21 U.S.C. 342) by adding the following:
(f) (1) If it is a dietary supplement or contains a dietary ingredient that—

(A) presents a significant or unreasonable risk of illness or injury under—

(i) conditions of use recommended or suggested in labeling, or
(ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;

(B) is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury;

(C) the Secretary declares to pose an imminent hazard to public health or safety, except that the authority to make such declaration shall not be delegated and the Secretary shall promptly after such a declaration initiate a proceeding in accordance with sections 554 and 556 of title 5, United States Code to affirm or withdraw the declaration; or

(D) is or contains a dietary ingredient that renders it adulterated under paragraph [402](a)(1) under the conditions of use recommended or suggested in the labeling of such dietary supplement.

In any proceeding under this paragraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated. The court shall decide any issue under this paragraph on a de novo basis.

(2) Before the Secretary may report to a United States attorney a violation of the paragraph (1)A for a civil proceeding, the person against whom such proceeding would be initiated shall be given appropriate notice and the opportunity to present views, orally and in writing, at least 10 days before such notice, with regard to such proceeding.

SOURCE: FDCA, P.L. 75–717 § 402, as amended 21 U.S.C. § 342(f), 2001.

The manufacturer or distributor is responsible initially for determining whether or not an ingredient is new and thus whether to submit information to FDA before marketing a product containing that ingredient (FDCA, P.L. 75–717 (1938), as amended 21 U.S.C. § 413 [350b]a, 2001). If FDA disagrees with a company's decision to market a product without submitting a 75-day notification, the government bears the burden of proof to show that the substance is a new dietary ingredient requiring such a submission and that the product is therefore adulterated.

It is important to note that the 75-day notification period is required for new dietary *ingredients,* but not new products. A product that is a new combination of ingredients marketed prior to October 1994 does not require submission of a 75-day notification (FDCA, P.L. 75–717 (1938), as amended 21 U.S.C. § 413 [350b]a, 2001).

Although less relevant to this report, DSHEA also provided for a government commission to consider the marketing and labeling of dietary supplements. The findings of this commission are described in the *Report of the Commission on Dietary Supplement Labels* (Commission on Dietary Supplement Labels, 1997), which addressed health claims, nutritional support statements, substantiation files for claims and safety, and publications used in conjunction with sales.

Food and Drug Administration Actions

Dietary supplement manufacturers are generally not required to share their basis for safety determinations with FDA before marketing. Therefore, FDA determines safety from publicly available information it collects and from data that it generates in its own laboratories. FDA may not be able to gather enough data to be confident about the safety of a particular product, but unless it can be proven in court that a substance does not meet the standard of safety—representing a reasonable certainty of no harm—FDA cannot remove it from the marketplace. FDA has responded to concerns by warning consumers, health providers, or industry of the specific concerns. On occasion, FDA actions have led to voluntary product recall by manufacturers (East Earth Herb, 2000; FDA, 2000; Vital Nutrients, 2001). Examples of warnings about specific dietary supplement ingredients issued in response to a variety of potential health problems identified by FDA as possible concerns are listed in Appendix D.

Good Manufacturing Practices

As is apparent from the example of contaminated plantain noted in Appendix D, FDA must consider more than the “inherent” safety of specific dietary supplement ingredients to adequately evaluate the potential for public health concerns. Because supplement *products* vary in their quality and composition, the inherent safety of the ingredients on the label is not the only important variable that is likely to impact the safety of specific products. Dietary supplement products tainted by improper raw materials, heavy metals, pesticides, and microorganisms, for example, can be unsafe due to these contaminants. DSHEA provides that FDA may define current Good Manufacturing Practices (GMPs) for dietary supplement production. GMPs are to address the aspects of product manufacturing that impact safety of the final product. They would not, however, take into consideration whether the dietary supplement ingredients themselves are safe—that is the goal of the framework proposed in this report.

FDA has not yet published proposed or final GMPs for the dietary supplement industry, although such rules are in development. In this report, the committee is charged to consider aspects of the inherent safety of dietary supplement ingredients in developing a proposed

framework for safety evaluation; FDA is in the process of completing and issuing GMPs to cover safety issues resulting from other aspects of safety of dietary supplements.

REFERENCES

ADA (American Dietetic Association). 2000. Nutrition and You: Trends 2000. What do Americans think, need, expect? *J Am Diet Assoc* 100:626–627.

Balluz LS, Kieszak SM, Philen RM, Mulinare J. 2000. Vitamin and mineral supplement use in the United States: Results from the Third National Health and Nutrition Examination Survey. *Arch Fam Med* 9:258–262.

Barkan ID. 1985. Industry invites regulation: The passage of the Pure Food and Drug Act of 1906. *Am J Public Health* 75:18–26.

Bender MM, Levy AS, Schucker RE, Yetley EA. 1992. Trends in prevalence and magnitude of vitamin and mineral supplement usage and correlation with health status. *J Am Diet Assoc* 92:1096–1101.

Blendon RJ, DesRoches CM, Benson JM, Brodie M, Altaian DE. 2001. Americans' views on the use and regulation of dietary supplements. *Arch Intern Med* 161:805–810.

CDER (Center for Drug Evaluation and Research). *The Patent Medicine Menace.* Online. Food and Drug Administration. Available at http://www.fda.gov/cder/about/history/gallery/galleryintro.htm. Accessed March 4, 2002.

Commission on Dietary Supplement Labels. 1997. *Report of the Commission on Dietary Supplement Labels.* Washington, DC: U.S. Government Printing Office.

Costello RB, Grumpstrup-Scott J. 2000. Zinc: What role might supplements play? *J Am Diet Assoc* 100:371–376.

Dwyer JT, Garceau AO, Evans M, Li D, Lytle L, Hoelscher D, Nickas TA, Zive M. 2001. Do adolescent vitamin-mineral supplement users have better nutrient intakes than nonusers? Observations from the CATCH tracking study. *J Am Diet Assoc* 101:1340–1346.

East Earth Herb. 2000. *East Earth Herb Recalls Jade Pharmacy Brand Meridian Circulation and Quell Fire Because of Possible Health Risk.* Online. November 21. News release. Available at http://www.fda.gov/oc/po/firmrecalls/eastearth11_00.html. Accessed March 3, 2002.

FDA (Food and Drug Administration). 1941. Regulations for the enforcement of the Federal Food, Drug, and Cosmetic Act. *Fed Regis* 6:5921–5926.

FDA. 1966. Dietary supplements and vitamin and mineral-fortified foods. *Fed Regis* 31:15730–15736.

FDA. 1979. Vitamin and mineral drug products for over-the-counter human use. *Fed Regis* 44:16125–16200.

FDA. 1981. The story of the laws behind the labels part II: 1938—The Federal Food, Drug, and Cosmetic Act. *FDA Consumer.* Online. Available at http://vm.cfsan.fda.gov/~1rd/historla.html. Accessed June 6, 2002.

FDA. 1987. Food labeling; public health messages and label statements. Proposed rules. *Fed Regis* 52:28843–28849.

FDA. 1993. Regulation of dietary supplements. Advanced Notice of Proposed Rulemaking 21, CFR Chapter 1. *Fed Regis* 58:33690.

FDA. 1994. *Adverse Events with Ephedra and Other Botanical Dietary Supplements.* Online. FDA Medical Bulletin. Available at http://vm.cfsan.fda.gov/~dms/ds-ephe2.html. Accessed March 7, 2002.

FDA. 2000. *FDA Warns Against Consuming Dietary Supplements Containing Tiratricol.* Online. FDA Talk Paper. November 21. Available at http://www.fda.gov/bbs/topics/ANSWERS/ ANS01057.html. Accessed March 8, 2002.

FDA. 2001. Premarket notice concerning bioengineered foods. *Fed Regis* 66:4706–4738.

Ford ES. 2001. Vitamin supplement use and diabetes mellitus incidence among adults in the United States. *Am J Epidemiol* 153:892–897.

Hartz SC, Otradovec CL, McGandy RB, Russell RM, Jacob RA, Sahyoun N, Peters H, Abrams D, Scura LA, Whinston-Perry RA. 1988. Nutrient supplement use by healthy elderly. *J Am Coll Nutr* 7:119–128.

Hoffman FA. 2001. Regulation of dietary supplements in the United States: Understanding the Dietary Supplement Health and Education Act. *Clin Obstet Gynecol* 44:780–788.

Hunt JR. 1996. Position of the American Dietetic Association: Vitamin and mineral supplementation. *J Am Diet Assoc* 96:73–77.

Hunt JR, Dwyer J. 2001. Position of the American Dietetic Association: Food fortification and dietary supplements. *J Am Diet Assoc* 101:115–132.

Jonnalagadda SS, Rosenbloom CA, Skinner R. 2001. Dietary practices, attitudes, and physiological status of collegiate freshman football players. *J Strength Cond Res* 15:507–513.

Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. 2002. Recent patterns of medication use in the ambulatory adult population of the United States. The Sloan Survey. *J Am Med Assoc* 287:337–344.

Kim I, Williamson DF, Byers T, Koplan JP. 1993. Vitamin and mineral supplement use and mortality in a U.S. cohort. *Am J Public Health* 83:546–550.

Kirschman JC. 1998. Effective regulatory approval process for food ingredient technologies. *Crit Rev Food Sci Nutr* 38:465–510.

Koplan JP, Annest JL, Layde PM, Rubin GL. 1986. Nutrient intake and supplementation in the United States (NHANES II). *Am J Public Health* 76:287–289.

Lyle BJ, Mares-Perlman JA, Klein BEK, Klein R, Greger JL. 1998. Supplement users differ from nonusers in demographic, lifestyle, dietary and health characteristics. *J Nutr* 128:2355–2362.

McGuine TA, Sullivan JC, Bernhardt DT. 2001. Creatine supplementation in high school football players. *Clin J Sport Med* 11:247–253.

McNamara SH. 1995. Dietary supplements of botanicals and other substances: A new era of regulation. *Food Drug Law J* 50:341–348.

Metzl JD, Small E, Levine SR, Gershel JC. 2001. Creatine use among young athletes. *Pediatrics* 108:421–125.

Millikan LE. 1999. Anecdotal therapies. *Adv Exp Med Biol* 455:407–411.

Nayga RM, Reed DB. 1999. Factors associated with the intake of dietary supplements. *Fam Econ Nut Rev* 12:43–48.

Nesheim MC. 1999. What is the research base for the use of dietary supplements? *Public Health Nutr* 2:35–38.

Neuhouser ML, Patterson RE, Levy L. 1999. Motivations for using vitamin and mineral supplements. *J Am Diet Assoc* 101:1340–1346.

Newman V, Rock CL, Faerber S, Flatt SW, Wright FA, Pierce JP. 1998. Dietary supplement use by women at risk for breast cancer recurrence. *J Am Diet Assoc* 98:285–292.

Nutrition Business Journal. 2000. *U.S. Consumer Supplement Use Summary 1999.* Online. Available at http://www.nutritionbusiness.com/sub/consume.xls. Accessed March 1, 2002.

OIG (Office of Inspector General). 2001. *Adverse Event Reporting for Dietary Supplements. An Inadequate Safety Valve.* OEI-01–00–00180. Boston, MA: OIG, Food and Drug Administration.

Pelletier DL, Kendall A. 1997. Supplement use may not be associated with better food intake in all population groups. *Fam Econ Nutr Rev* 10:32–44.

Pelletier DL, Kraak V, Dollahite JS. In press. Food, health, and supplements: Beliefs among food stamp eligible women and implications for food stamp policy. *Fam Econ Nutr Rev.*

Pendergast WR. 1997. Dietary supplements. In: Brady RP, Cooper RM, Silverman RS, eds. *Fundamentals of Law and Regulation. An In-depth Look at Foods, Veterinary Medicines, and Cosmetics.* Washington, DC: Food and Drug Law Institute. Pp. 257–283.

Prevention Magazine. 2001. *Consumer Use of Dietary Supplements.* Emmaus, PA: Rodale. Pp. 1–79.

Radimer KL, Subar AF, Thompson FE. 2000. Nonvitamin, nonmineral dietary supplements: Issues and findings from NHANES III. *J Am Diet Assoc* 100:447–454.

Ramos L. 2000. SAMe as a supplement: Can it really help treat depression and arthritis? *J Am Diet Assoc 100:414.*

Sarubin A. 2000. *The Health Professional's Guide to Popular Dietary Supplements.* Chicago, IL: American Dietetic Association.

Sinclair U. 1906. *The Jungle.* New York: Doubleday, Page & Company.

Slesinski MJ, Subar AF, Kahle LL. 1995. Trends in use of vitamin and mineral supplements in the United States: The 1987 and 1992 National Health Interview Surveys. *J Am Diet Assoc* 95:921–923.

Smith J, Dahm DL. 2000. Creatine use among a select population of high school athletes. *Mayo Clin Proc* 75:1257–1263.

Stein K. 2000. Herbal supplements and prescription drugs. A risky combination? *J Am Diet Assoc* 100:412.

Subar AF, Block G. 1990. Use of vitamin and mineral supplements: Demographics and amounts of nutrients consumed. The 1987 Health Interview Survey. *Am J Epidemiol* 132:1091–1101.

Vital Nutrients. 2001. *Vital Nutrients Recalls Joint Ease and Verified Quality Brand Joint Comfort Complex Because of Adverse Health Risk Associated with Aristolochic Acid.* Online. May 21. News release. Available at http://www.fda.gov/oc/po/firmrecalls/vital5_01.html. Accessed March 8, 2002.

Wallace P. 2001. Insurer to warn schools of “dangerous” sports supplements. *Food Chem News* VOL:21–22.

Wax PM. 1995. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. *Ann Intern Med* 122:456–461.

Wetli CV, Davis JH. 1978. Fatal hyperkalemia from accidental overdose of potassium chloride. *J Am Med Assoc* 240:1339.

2

Approaches Used by Others to Consider Dietary Supplement Safety and Other Existing Safety Frameworks

The safety and efficacy of dietary supplement ingredients have been considered by a number of organizations, each of which has a framework or methodology for reviewing dietary supplements. A review of these methods was the first step in developing a framework useful to the Food and Drug Administration (FDA) for prioritizing and evaluating the safety of dietary supplement ingredients. Given that these organizations have considered different aspects of dietary supplement ingredients, it was important to consider the relevance of the methods or frameworks they have used to organize and review dietary supplement safety issues. Similarly, frameworks and methodologies have been developed for reviewing the safety of other types of substances: in foods, in pharmaceuticals, and in the environment. These are also reviewed to identify aspects that might be applicable to developing a framework for the safety evaluation of dietary supplement ingredients. Based on the above reviews, discussion in open sessions with many individuals, and the consensus of the committee, attributes of an ideal framework for setting priorities and evaluating dietary supplement ingredients were developed.

OTHER APPROACHES FOR CONSIDERING DIETARY SUPPLEMENT SAFETY

Several organizations have compiled information on the safety, efficacy, or quality of dietary supplements. To aid in the development of the framework in this report, samples of these materials were used to construct an overview of the approaches taken by these organizations. The approaches are described briefly below and in Table 2–1; more detailed descriptions are provided in Appendix A. The Appendix is based on the information provided by the organizations or in published descriptions of their approaches. Inclusion on this list does not constitute endorsement of these sources of information, nor should the list be considered exhaustive of all efforts to consider safety, efficacy, and/or quality of dietary supplements. The committee chose to focus its review on approaches that seemed to be the products of organization-sponsored or government-sponsored committee efforts or a peer-reviewed process. Additional publications, although not reviewed by the committee, might also be informative (Foster and Tyler, 1999; Grieve, 1996).

TABLE 2–1 Key Components of Approaches Used by Other Organizations to Evaluate Dietary Supplements

Organization	Purpose of Evaluation	Selection and Types of Substances for Review	Product Endpoints
Agency for Healthcare Research and Quality	Effectiveness Safety	Variety of types Reports done at request of other agencies and organizations	Summary report
U.S. Pharmacopeia-National Formulary (USP-NF)	Quality	Variety of types Selection based on: Safety Extent of use Assessment by pharmacognosists Ability to meet USP-NF monograph requirements Evidence of historical use in traditional medicine	Monographs in USP or NF
USP Dietary Supplement Verification Program	Quality	Variety of types Selection is via manufacturer sponsorship	USP certification mark or no mark
American Herbal Pharmacopoeia	Effectiveness Quality and analytical methods Safety	Botanicals commonly used in the United States Selection based on: Recommendations of a prioritization committee (professional herbalists, herbal industry, and herbal educators) Monograph sponsorship (interested organizations or companies) Selection by other groups	Summary monographs
American Herbal Products Association	Safety	Botanical ingredients sold in North America	Classification as Class 1, 2, 3, or 4
Natural Medicines Comprehensive Database	Effectiveness Safety	Variety of natural medicines sold in the United States and Canada	Summary monographs Safety assessment classification: Likely safe Possibly safe Possibly unsafe Likely unsafe Unsafe
World Health Organization	Effectiveness Safety Quality	Botanicals Selection based on extent of use, worldwide importance, and availability of data	Summary monograph

Organization	Purpose of Evaluation	Selection and Types of Substances for Review	Product Endpoints
Commission E	Effectiveness Safety	All medicinal plants and phytomedicines in the German marketplace	Summary monographs classified as: Positive (approved) Negative (unapproved) Negative-null (unapproved)
Health Canada Natural Health Products Directorate[a]	Safety Quality Effectiveness	Vitamin and mineral supplements, botanical products, homeopathic preparations, and traditional Chinese, Ayurvedic, and native North American medicines	Authorization for sale/product license
European Scientific Cooperative on Phytotherapy	Effectiveness Safety	Phytomedicines used within the European Community	Summary monographs

[a] The Health Canada regulatory framework for natural health products is proposed—not finalized.

Agency for Healthcare Research and Quality

The Agency for Healthcare Research and Quality (AHRQ), a branch of the U.S. Department of Health and Human Services, is in the process of producing "evidence-based reports" for a limited number of dietary supplements. The evidence reports include information on safety and efficacy and are developed using a systematic analysis of the relevant scientific data that employs a weighting/ranking methodology to consider the data and well-defined criteria for making judgments. AHRQ has contracted this work to several institutions referred to as Evidence-based Practice Centers. Reports on garlic and milk thistle have been released and a report on ephedra is in development (AHRQ, 2002). These reports are designed to differentiate the types of evidence and the strength of the evidence. Due to the exhaustive nature of the reports, they are resource intensive.

U.S. Pharmacopeia-National Formulary

The U.S. Pharmacopeia-National Formulary (USP-NF), a nongovernment, nonprofit organization, develops monographs on standards of identity, strength, quality, purity, packaging, and labeling of drugs sold in the United States. These monographs are not focused on the inherent safety of the substance.[8] The USP standards are recognized by Congress in the Federal Food, Drug, and Cosmetic Act of 1938 (21 U.S.C. § 321 *et seq.*) as the official compendium of the United States, making its established standards for drugs essentially similar to federal regulations (USP, 2002a).

[8] From 1995 to 1998, USP developed prototype *information* monographs on several botanicals, in addition to standards monographs. Subsequently, an information monograph addressing the safety and efficacy of saw palmetto was published on the Internet in 2000. Dietary supplement information monographs are no longer produced due to lack of funding (Personal communication, S.Srinivasan, USP, June 19, 2002).

In 1990 USP-NF decided to include monographs for vitamins and minerals and in 1995, after passage of the Dietary Supplement Health and Education Act, USP-NF decided to include monographs for botanical dietary supplements (CRN, 1998). The criteria for identification and prioritization of botanicals for monograph development include absence of safety concerns, extent of use by consumers, interest from regulatory agencies, positive assessment by recognized pharmacognosists, and suitability of the botanical preparation for meeting typical requirements of USP-NF monographs (USP, 2000a, 2002b). Depending on its approval status, botanical monographs are admitted either to the USP or to the NF. A botanical monograph is placed in the USP if the botanical has an FDA- or USP-approved use. Otherwise, it is placed in the NF. Monographs are not developed for botanical dietary supplements that the USP believes may be associated with a significant safety risk (USP, 2000a, 2002b).

U.S. Pharmacopeia Dietary Supplement Verification Program

Distinct from its development of the USP-NF monographs, USP launched the Dietary Supplement Verification Program (DSVP) in November 2001. The program identifies dietary supplement products that contain all the ingredients listed on their product labels. Manufacturers sponsor products that are tested and reviewed by USP; if the product meets the DSVP requirements, the product will be granted a USP certification mark. This mark is intended to signify that the product (1) contains the ingredients stated on the label in the declared amount and strength, (2) meets stringent standards for product purity, (3) meets specified limits on known contaminants, and (4) has been manufactured under good manufacturing practices according to the USP-NF General Chapter on Manufacturing Practices for Nutritional Supplements and the FDA's Advance Notice of Proposed Rulemaking for good manufacturing practices (Personal communication, S.Srinivasan, USP, February 14, 2002; USP, 2001). The DSVM certification mark is not intended to imply safety or efficacy of dietary supplement ingredients.

Other organizations are also undertaking similar efforts to verify label contents, such as ConsumerLab (http://www.consumerlab.com/) and the National Science Foundation International (http://www.nsf.org/consumer/consumer_dietary.html).

American Herbal Pharmacopoeia

The American Herbal Pharmacopoeia (AHP), a nonprofit organization, develops monographs on the quality, effectiveness, and safety of botanical medicines commonly used in the United States. The monographs, developed for Ayurvedic,[9] Chinese, and Western botanicals, include information on traditional use and information from scientific sources (CRN, 1998). Botanicals are selected for monograph development based on judgment about the extent of use, the unique value of the botanical, and sponsorship by other interested organizations or companies (AHP, 2002).

In preparing the monographs, literature searches are conducted in order to review reported side effects, contraindications, and negative interactions of a botanical. AHP monographs are relatively detailed compared to monographs produced by other organizations. They are released individually as they are completed; 12 have been released since 1994 (AHP, 2002).

[9] Ayurvedic is a complex system of health care that includes diet and lifestyle practices (i.e., meditation, yoga, and herbs) in order to maintain the body's equilibrium. Ayurvedic medicines are derived from plants and are used in conjunction with modern medicine for health maintenance and restoration (Chopra and Doiphode, 2002).

American Herbal Products Association

The American Herbal Products Association (AHPA), a national trade association for the herbal products industry, published *The Botanical Safety Handbook* in 1997. This book reviewed approximately 500 herbs that were on the market in the United States (McGuffin et al., 1997). The focus of the reviews in this book is on safety, and entries include data on human and animal toxicity, traditional use, regulatory status in various countries, and current use of herbs in the United States, China, India, Europe, and Australia. The AHPA safety classification system consists of four safety classes: Class 1 botanicals that can be safely consumed when used appropriately, Class 2 botanicals for which certain restrictions apply, Class 3 botanicals for which significant data exist to recommend special labeling, and Class 4 botanicals for which there is insufficient data for classification.

Natural Medicines Comprehensive Database

The Natural Medicines Comprehensive Database (NMCD) is published by *Pharmacist's Letter* and *Preserver's Letter.* This database reviews many “natural medicines” on the market in North America, reviewing safety and efficacy for a large number of dietary supplement ingredients. Information on the different substances reviewed is available by subscription online and in printed version (NMCD, 2002). According to the organization, the safety evaluation relies primarily on human data, and animal data are rarely used (Personal communication, P.Gregory, NMCD, November 21, 2001). Each product is rated as: (1) likely safe (general agreement among reliable references that the product is safe when used appropriately, or a governmental body has approved its use), (2) possibly safe (product might be safe when used appropriately or there are human studies that report no serious adverse effects), (3) possibly unsafe (some data suggest that product use might be unsafe), (4) likely unsafe (agreement among reputable references that the product can be harmful or reliable reports of harm), or (5) unsafe (general agreement among reliable references that the product should not be used, reliable reports of clinically significant harm, or safety warnings issued by a reliable agency).

World Health Organization

The World Health Organization (WHO) has developed international specifications for the most widely used medicinal plants, a number of which are also used as dietary supplements in the United States. WHO published its first volume of 28 monographs on selected medicinal plants and is in the process of publishing two additional volumes. The monographs contain information on the safety, effectiveness, and quality control of botanical medicines (WHO, 1999). Specifically, they present descriptive information, purity tests, chemical constituents, medicinal uses, clinical studies, pharmacology, contraindications, warnings, precautions, adverse reactions, and posology. The medicinal plants in the compilation are not categorized on the basis of safety.

Commission E

The Commission E was a 24-member committee established in 1979 by the German Minister of Health to review botanical drugs and preparations from medicinal plants. Over a period of about 15 years Commission E reviewed more than 300 botanicals used in German folk medicine for both safety and effectiveness using scientific literature, unpublished proprietary data

submitted by manufacturers (chemical, toxicological, pharmacological, and clinical testing data), summaries produced by an umbrella organization of approximately 120 pharmaceutical manufacturers, and public input (Blumenthal, 1998; Personal communication, H.Schilcher, Commission E, March 19, 2002). The published monographs do not include references and are relatively short. Each monograph provided one of three approval ratings for the substance reviewed: (1) positive (approved—substance is considered reasonably safe when used according to the dosage, contraindications, and other warnings specified in the monograph), (2) negative (unapproved—safety concerns outweigh the potential benefits of a substance), or (3) negative-null (unapproved—no risk was found, but also no substantiation of efficacy). The Commission E monographs are published in German, and the American Botanical Council has published them in English (Blumenthal, 1998). Additional information about Commission E is included in Appendix A.

Health Canada Natural Health Products Directorate

In Canada vitamin and mineral supplements, botanical products, homeopathic preparations, and traditional Chinese, Ayurvedic, and native North American medicines are considered to be natural health products (NHPs). At present, these products are regulated as either foods or drugs.

In response to consumer demand both for enhanced access to natural health products and for assurances of safety and quality, the Natural Health Products Directorate was established within Health Canada. The Directorate has developed a proposed regulatory framework for NHPs, which would be considered a subset of drugs under the Food and Drugs Act. The NHP Regulations were published for comment in December 2001 (Department of Health, 2001).

The main components of the NHP Regulations are definitions and requirements for product licensing, site licensing, good manufacturing practices, clinical trials, packaging, labeling, and reporting of adverse reactions. Under product licensing, each NHP sold in Canada will undergo an assessment before it is authorized for sale. The application for a product license would be required to provide specific information about the NHP, including the quantity of medicinal ingredients it contains, the specifications, the intended use or purpose, and supporting safety and efficacy data. Most relevant to the consideration of dietary supplement ingredient safety, the directorate has not released standards of evidence for safety for public comment.

European Scientific Cooperative on Phytotherapy

The European Scientific Cooperative on Phytotherapy (ESCOP) is an umbrella organization of national associations for phytotherapy from countries both within and beyond the European Union. The Scientific Committee of ESCOP, a subgroup of delegates from participating member countries, has created monographs on the medicinal uses and safety of medicinal plants widely used in Europe (information on quality is not included). The monographs are published as fascicules, each containing 10 monographs; 6 fascicules on 60 botanicals have been completed (ESCOP, 2001).

The Physician's Desk Reference for Herbal Medicines and the Physician's Desk Reference for Nutritional Supplements

In 1998 the Physicians' Desk Reference (PDR) organization broadened its scope from producing a widely used collection of information on prescription drugs by also producing a

collection of information on botanical medicines. This publication was the first edition of the *PDR for Herbal Medicines,* which provides monographs for approximately 700 medicinal herbs. The monographs contain information on efficacy, safety, potential interactions, precautions, adverse reactions, and dosage. For 300 of these monographs, the findings and assessments were taken from the German Commission E report. Other monographs, as well as the reports of another PDR publication, the *PDR for Nutritional Supplements,* do not appear to be the products of the type of committee effort or to involve the type of peer-review process envisioned as ideal by the committee.

ANALYSIS OF DIFFERENT APPROACHES TO DIETARY SUPPLEMENT EVALUATION

By reviewing the approaches other groups have taken to consider dietary supplements, the observations that follow about positive and negative attributes of each approach have influenced the development of the proposed framework and system for preparing safety monographs. The type of information evaluated and the purpose of the review varied substantially from organization to organization. Most notably, the USP verification program focused on quality, specifically determining if the ingredients in a product were prepared according to good manufacturing practices, and verifying that the label matched the contents. Although USP indicated that it would consider whether a substance was safe in deciding whether or not to accept it into the program, there seemed to be less methodical emphasis on the inherent safety of the ingredients. Several other organizations placed emphasis on whether the ingredient was efficacious—a worthy objective, but one that fell outside of this committee's charge. Most of the approaches reviewed were focused exclusively on botanical ingredients or products, rather than on dietary supplements of all types. The charge to this committee was to include all types of dietary supplements in its efforts.

Perhaps most notably, the approaches considered did not describe a systematic method of determining which ingredients needed immediate attention first, a key component of the PDA's charge to the committee. AHPA's *Botanical Safety Handbook,* the Natural Medicines Comprehensive Database, and the Commission E monographs are three examples of monograph collections that did sort ingredients into several categories (e.g., approved, unapproved, possibly safe). These approaches, however, sorted ingredients into several categories after reviewing collected data, rather than sorting all ingredients by relative priority *before* undertaking an exhaustive evaluation of the data—as the proposed framework is charged with accomplishing.

A number of the sample monographs considered were not sufficiently detailed or adequately transparent to give a complete picture of the data types and sources considered, the rationale behind the conclusions, and/or the remaining unanswered questions about safety. Monographs from several organizations were brief, without an adequate description of the different types of available data. Without substantial detail in the monograph, it was not always clear as to how or why a conclusion about the safety of the ingredient was reached.

Understandably, considering the “weight of the evidence” requires expert judgment to a certain degree, but it was not always apparent what role expert opinion and experience played. The information that forms the basis for the Commission E monographs, for example, is kept confidential and includes proprietary data. In the committee's judgment, it is important that the process be transparent and the bases of judgments be clearly described and consistently applied to the fullest extent possible, including providing opportunities for public input from industry,

scientists, and other interested parties. Also important is a description of where the scientific data may be difficult to interpret and where questions about safety remain unanswered.

Another observation is that most of the reviews focused on ingredients, rather than on specific products or combinations of ingredients. An exception is that the USP verification program, which focuses on specific products because USP is paid to look at specific products by manufacturers. Commission E is another exception—it considered the safety of fixed combinations of botanical products, an important approach given the widespread marketing of combinations (Blumenthal, 1998). Similarly, analysis of specific products was outside the committee's charge—it was to focus instead on how to consider the safety of different dietary supplement ingredients and to note how to approach a product containing a combination of ingredients.

ATTRIBUTES OF AN IDEAL FRAMEWORK FOR EVALUATING DIETARY SUPPLEMENTS

There are numerous frameworks in place that FDA and other organizations can use to evaluate the safety of substances to which humans may be exposed. Assessment of the scope, characteristics, and processes used for other substances can aid in the development of a workable framework for dietary supplement safety evaluation. The committee considered frameworks FDA already had in place to evaluate food additives and pharmaceuticals, as well as the mechanisms other organizations use in working with FDA when considering the safety of cosmetic ingredients, food additives generally regarded as safe (GRAS), and nutrients. The Environmental Protection Agency has also developed a system for considering possible human and environmental impacts of toxic substances. Table 2–2 provides a brief summary of the nondietary supplement frameworks considered; more detailed summaries of the different approaches, as described by the organizations, are in Appendix B.

In considering frameworks used to evaluate the safety of substances other than dietary supplements, the committee developed an understanding of different types of "frameworks" and how they differed from other methods that might be used to evaluate dietary supplements. To this end, the committee developed a definition of a "framework" for safety evaluation of dietary supplement ingredients as follows: "The processes by which FDA can screen, categorize, and evaluate available information to make scientifically documented regulatory decisions regarding dietary supplement ingredients for consumers." In reviewing the methods used by other expert bodies to consider dietary supplements and in reviewing the discussions with the sponsors and other interested representatives, the following attributes of an ideal framework were identified:

- it must be workable and able to be integrated into the agency's program of work and resources available;
- it should provide guidance to organizing diverse information already available;
- it should categorize the diverse substances classified as dietary supplements based on a scientifically valid metric;
- it should establish a database for collection of information regarding potential safety concerns that can be updated as new information is available;

TABLE 2–2 Safety Review Systems for Nondietary Supplement Substances

Purpose of Review	Organization	Type of Organization	Endpoints
Premarket safety evaluation of food ingredients/food additives	Food and Drug Administration/ Center for Food Safety and Applied Nutrition	Government	Approved Approval with limitations Interim approval Disapproval
Safety evaluation of food additives/food ingredients generally recognized as safe (GRAS) in 1972	Select Committee on GRAS Substances[a]	Nongovernment/ nonindustry	Continue as GRAS Continue as GRAS with limitations Further testing required Evidence of adverse effects —may remove GRAS status if safety not established Remove GRAS status
Safety evaluation and determination of GRAS status of flavor ingredients	Flavor and Extract Manufacturers Association (FEMA) Expert Panel	Industry	GRAS status Not GRAS Insufficient data to determine GRAS status
Safety assessment of cosmetic ingredients	Cosmetics Ingredient Review Program	Industry	Safe as used Safe with qualifications Unsafe Insufficient data
Premarket evaluation and approval of new drugs	Food and Drug Administration/ Center for Drug Evaluation and Research	Government	Approved Not approved
Over-the-counter (OTC) Drug Review to establish conditions under which OTC drugs would be considered generally recognized as safe and effective (GRAS/E)	Food and Drug Administration	Government	Category I (GRAS/E) Category II (not GRAS/E or unacceptable indications) Category III (insufficient data)
Regulation of entry and use of new chemicals in the marketplace; assessment of human and environmental risk of new chemicals	Environmental Protection Agency New Chemicals Program	Government	No action taken to regulate the chemical More testing needed
Determination of the Tolerable Upper Intake Level (UL) for nutrients[b]	Institute of Medicine/Food and Nutrition Board	Nongovernment/ nonindustry	UL Scientific evidence insufficient to set UL

[a] Source: Select Committee on GRAS Substances (1982).

[b] Note that nutrients are in many cases dietary supplements or dietary supplement ingredients; this safety framework, however, only applies to nutrients and recognized food components thought to play a role in health.

- it should provide a method to integrate diverse information into a priority-setting scheme so that efforts and resources can be maximally directed toward those dietary supplement ingredients with the greatest safety concerns; and
- it should provide a mechanism for public input.

Once the definition and key attributes of a safety framework were understood and the committee had an understanding of approaches taken by other expert groups, the committee then developed a framework focused on the safety of dietary supplements. This approach is outlined briefly in the following chapter, with additional detail in succeeding chapters.

REFERENCES

AHP (American Herbal Pharmacopoeia). 2002. *American Herbal Pharmacopoeia and Therapeutic Compendium: Standards of Analysis, Quality Control, and Therapeutics.* Online. Available at http://www.herbal-ahp.org/. Accessed June 19, 2002.

AHRQ (Agency for Healthcare Research and Quality). 2002. *Evidence-based Practice Centers.* Online. Available at http://www.ahrq.gov/clinic/epc/. Accessed June 17, 2002.

Blumenthal M, ed. 1998. *Therapeutic Guide to Herbal Medicines. The Complete German Commission E Monographs.* Austin, TX: American Botanical Council.

Chopra A, Doiphode VV. 2002. Ayurvedic medicine. Core concept, therapeutic principles, and current relevance. *Med Clin North Am* 86:75–89, vii.

CRN (Council for Responsible Nutrition). 1998. *Reference on Evaluating Botanicals.* Washington, DC: CRN.

Department of Health. 2001. Natural health products regulations. *Canada Gazette, Part I* 135:4912–4981.

ESCOP (The European Scientific Cooperative on Phytotherapy). 2001. *Publications. ESCOP Monographs.* Online. Available at http://www.escop.com/publications.htm. Accessed November 12, 2001.

Foster S, Tyler VE. 1999. *Tyler's Honest Herbal. A Sensible Guide to the Use of Herbs and Related Remedies.* 4th ed. New York: Haworth Herbal Press.

Grieve M. 1996. *A Modern Herbal.* New York: Barnes and Noble.

McGuffin M, Hobbs C, Upton R, Goldberg A. 1997. *American Herbal Product Association's Botanical Safety Handbook.* Boca Raton, FL: CRC Press.

NMCD (Natural Medicines Comprehensive Database). 2002. *About the Database.* Online. Available at http://www.naturaldatabase.com/aboutdb.asp. Accessed January 7, 2002.

Select Committee on GRAS Substances. 1982. *Insights on Food Safety Evaluation.* Rockville, MD: Life Sciences Research Office.

USP (The United States Pharmacopeia). 2001. *USP Board of Trustees Agrees to Continue Proceeding with Pilot Program for Dietary Supplement Verification.* Online. Available at http://www.usp.org. Accessed October 31, 2001.

USP. 2002a. *USP 25-NF 20.* Rockville, MD: United States Pharmacopeial Convention, Inc.

USP. 2002b. *USP Fact Sheet.* Online. Available at http://www.usp.org. Accessed June 18, 2002.

WHO (World Health Organization). 1999. *WHO Monographs on Selected Medicinal Plants, Volume I.* Geneva: WHO.

3

Outline of the Overall Process for Evaluation of Dietary Supplement Ingredients

PROPOSED FRAMEWORK FOR EVALUATION OF DIETARY SUPPLEMENT INGREDIENTS

The Food and Drug Administration (FDA) asked the Institute of Medicine to propose a safety framework that would assist it in overseeing the safety of dietary supplement ingredients. In an ideal situation, FDA would be able to immediately undertake a full safety evaluation for every supplement ingredient. Since this is not possible, a process must be implemented to determine which supplement ingredients warrant the highest priority for review.

This report outlines a three-step framework for considering the safety of dietary supplement ingredients. The first two steps in the process, "screening/flagging" and "priority setting," are designed to categorize dietary supplement ingredients based on theoretical or possible concern, and therefore the immediacy of the need for in-depth evaluation of safety, the third step of the process.

For the purposes of describing the proposed process, it is convenient to think of the overall framework as three distinct phases, separating the screening and priority-setting phases into two distinct steps in the framework, with the third step being a critical in-depth review. The first step in the process, screening/flagging, is essentially a beginning point that incorporates the factors that will bring an ingredient to the attention of FDA and will indicate whether the material should immediately be examined more closely. This step is important because it is not feasible initially to research the information necessary for priority setting for the entire universe of dietary supplement ingredients. Over time, it is likely that steps one and two will be viewed as one ongoing system. The priority-setting system will determine which ingredients require a full safety evaluation first and can be done on an on-going basis once an ingredient is flagged in the screening step. After dividing flagged ingredients into priority categories for further evaluation, the third step—in-depth safety evaluations of highest priority ingredients—can be completed.

Ingredients versus Products

It is important to note that although dietary supplement *products* are the substances sold on the market, this framework is designed to consider the safety of dietary supplement *ingredients.* For the purpose of this framework, botanical ingredients are defined as the plant parts (e.g., seed, root, leaf) rather than the many individual chemical compounds contained in a plant. Although this framework focuses on identifying and reviewing ingredients with inherent safety concerns, it is very important to remember that all products containing a particular ingredient are not likely to

have equivalent safety profiles. As discussed in the following paragraphs, differences in safety profiles may exist because the products contain different amounts of an ingredient, there are differences in bioavailability (the degree to which a substance becomes available to the target tissue after administration), there are differences in the amounts or presence of other substances (including contaminants), or the products are sold in combination with different ingredients.

Substantial variation can exist among the different brands of products purportedly containing a given dietary supplement ingredient (Foreman, 2000; Howe, 2000) due to lack of standardization. Products labels may claim that products are standardized to contain a particular amount of a substance. Several reports of product analyses, however, suggest that product labels may be inaccurate—that products may contain significantly higher or lower amounts of substances than indicated on the label (Green et al., 2001; Hamilton-Miller et al., 1999; Kamber et al., 2001). While a number of reports have suggested that substances do not contain the substances purported on the label, reports of labeling discrepancies with several botanicals have been disputed on the basis that laboratories used different analytical methods or measured different chemical markers that may not be relevant (Betz et al., 1995; Marrone, 1999). The eventual development of standards may address this problem.

In addition to differences in the amount of a substance contained in a product, significant variation may exist in bioavailability. Variability in bioavailability may result from differences in manufacturing and formulation that affect how much of a substance is absorbed. For example, dissolution maybe incomplete, or even if the ingredient's dissolution is complete, absorption may be incomplete if it is degraded in the intestinal fluid or it does not undergo active or passive transportation out of the intestinal mucosa. Dietary supplements may be delivered in matrices (tablets, capsules, etc.) that impact dissolution and absorption, or they may contain ingredients that change absorption and other aspects of bioavailability (Chambliss, 2001).

Quality control guidelines for many ingested substances are described by current Good Manufacturing Practices (GMPs). As described in Chapter 1, FDA has not yet published proposed or final GMPs for the dietary supplement industry. Quality control variables that can impact the safety of dietary supplement products include, but are not limited to, contamination by heavy metals, contamination by harmful microorganisms, contamination by pesticides, misidentification of raw plant ingredients, and improper storage. GMPs should provide guidance in a number of these areas (CFSAN, 2000; FDA, 1997).

In addition to variations in products containing a particular supplement ingredient, many products sold today are “combination products” that are mixtures of more than one dietary supplement ingredient. These products raise another set of safety concerns because mixtures can have safety profiles different than the summed effect of discrete ingredients. There is a potential for interaction among ingredients, and even mixtures containing the same dietary supplements may differ in dose and ratio of components. Although combination products can produce effects distinct from the individual ingredients, a first approximation of a combination product's safety can come from examining the safety of the component ingredients. A combination product containing ingredients that individually are not considered safe is likely to demonstrate some of the same safety concerns as the individual ingredients.

Even if no single ingredient raises safety concerns, MedWatch and other information sources should be monitored for clusters of serious adverse events and other possible indicators of problems related to specific combination products. For example, when data suggest that interactions between individual supplement ingredients may be associated with adverse effects, combination products that contain these interacting ingredients warrant particular attention. If

potential interactions or clusters of serious adverse events from particular combinations come to FDA's attention, then the combination product itself should undergo the screening/flagging and priority-setting steps.

In the case of most combinations, it is expected that more data will be available about the safety of the individual ingredients than about the safety of the combination. If a review raised questions about the combination of kava kava, Saint John's wort, and passionflower, for example, the initial approach would be to consider the safety of kava kava, Saint John's wort, and passionflower individually to determine if any of these three ingredients were individually thought to be of potential concern from a safety perspective. If any of these individual botanicals were considered unsafe, then the combination product should also be considered unsafe. If none of the three ingredients alone had raised safety concerns, then it would be appropriate to monitor the literature, the MedWatch database, and other sources of information for clusters of adverse events or other indications that harmful effects might be associated with the combination. In the case of popular combinations of substances, it is possible that a significant amount of data about the safety of the combination will be available, perhaps even more than is available on the safety of the individual substances (the combination of glucosamine and chondroitin sulfate maybe such an example). In this case, it may be appropriate to consider the safety of the combination itself, in addition to the safety of the individual ingredients. If safety concerns have been raised for an individual ingredient, then these concerns should generally not be considered as mitigated when the ingredient is combined or used in combination with another ingredient.

In summary, this framework focuses on ingredients rather than products, but the variability among products necessitates that FDA consider the safety of products as well. Regular monitoring of MedWatch and other information sources will be necessary to detect indications of serious adverse events possibly related to specific brands of products.

Initiation of the Process

The three steps of the proposed framework are outlined in Table 3–1 and Figure 3–1. Step One is the initial screening/flagging process; Step Two, the priority-setting process; and Step Three, the evaluation process. The stepwise framework is important, but it is recognized that before FDA can get started with the framework, it needs an initiation process to start screening the large list of dietary supplement ingredients currently on the market. Several options for this initiation point were considered. It is possible to start by examining:

- *The number of serious adverse events reported.* MedWatch is a system for collecting adverse events. While anyone is free to file a MedWatch report, a sizeable portion of contributors to MedWatch are members of the medical community. The MedWatch system could therefore form the basis for concern about the safety of particular ingredients (or products). That is, the framework process could be initiated by first considering ingredients with a greater number of reported serious adverse events. The major disadvantage of this approach is the incomplete nature of the reports and the limited number of reports to MedWatch (GAO, 1997).
- *A priority list prepared by experts.* A group of several experts in the field could, within a day, provide a list of the top ingredients causing the most concern in their opinion. It is proposed that one expert would have a background in botanicals (e.g., a pharmacognosist), one would be a physician practicing alternative medicine, and one would be a nutritional pharmacologist or toxicologist. A key advantage of this method is that it would have a high probability of identifying most ingredients with any significant concern prior to collection and review of

TABLE 3–1 Overall Framework

Step in the Process	Step One: Screening/Flagging	Step Two: Priority Setting	Step Three, Part A: Draft Monograph Preparation and Monograph Review by the Food and Drug Administration (FDA)	Step Three, Part B: Critical Safety Evaluation
Which ingredients	All ingredients are considered "New" ingredients are automatically flagged	Ingredients flagged in screening step	Ingredients with highest priority based on Step Two ranking	Monographed ingredients for which a decision is not clear cut or for which further input is desired
Completed by	FDA	FDA	FDA or contractor	External advisory committee
Factors and modifiers used	Human data: serious adverse events only Other concerns,[a] as they come to FDA's attention	Human data Animal data Biological activity of structurally related and taxonomically related substances In vitro data Vulnerable group use (modifies other factors) Prevalence of use (modifies priority ranking)	Human data Animal data Biological activity of structurally related and taxonomically related substances In vitro data Vulnerable group use considered with other factors	Human data Animal data Biological activity of structurally related and taxonomically related substances In vitro data Vulnerable group use (considered with other factors)
Level of information search	Easily obtainable information (see Table 4–1)	Literature search is more comprehensive	Comprehensive Request industry data and data from other stakeholders	Comprehensive Public input
Depth of evaluation	Low level evaluation: is there evidence suggesting a concern *may* exist?	Weighting based on evidence of possible risk, potential seriousness of harm, and relative importance of factor	Comprehensive: totality of evidence is considered, including data requested from industry and other stakeholders	Totality of evidence; monograph reviewed and revised
Goal	Ingredients warranting further investigation are flagged	Table of ingredients sorted into priority groups for further evaluation	Monograph *AND* FDA decision for action/inaction *OR* Referral to external advisory committee	Monograph with conclusions of external advisory committee

[a] The term, "other concerns," as described in Chapter 3, encompasses concerns FDA becomes aware of without extensive information searching. These may include concerns expressed by other regulatory agencies, concerns expressed in secondary literature, or concerns expressed by other organizations.

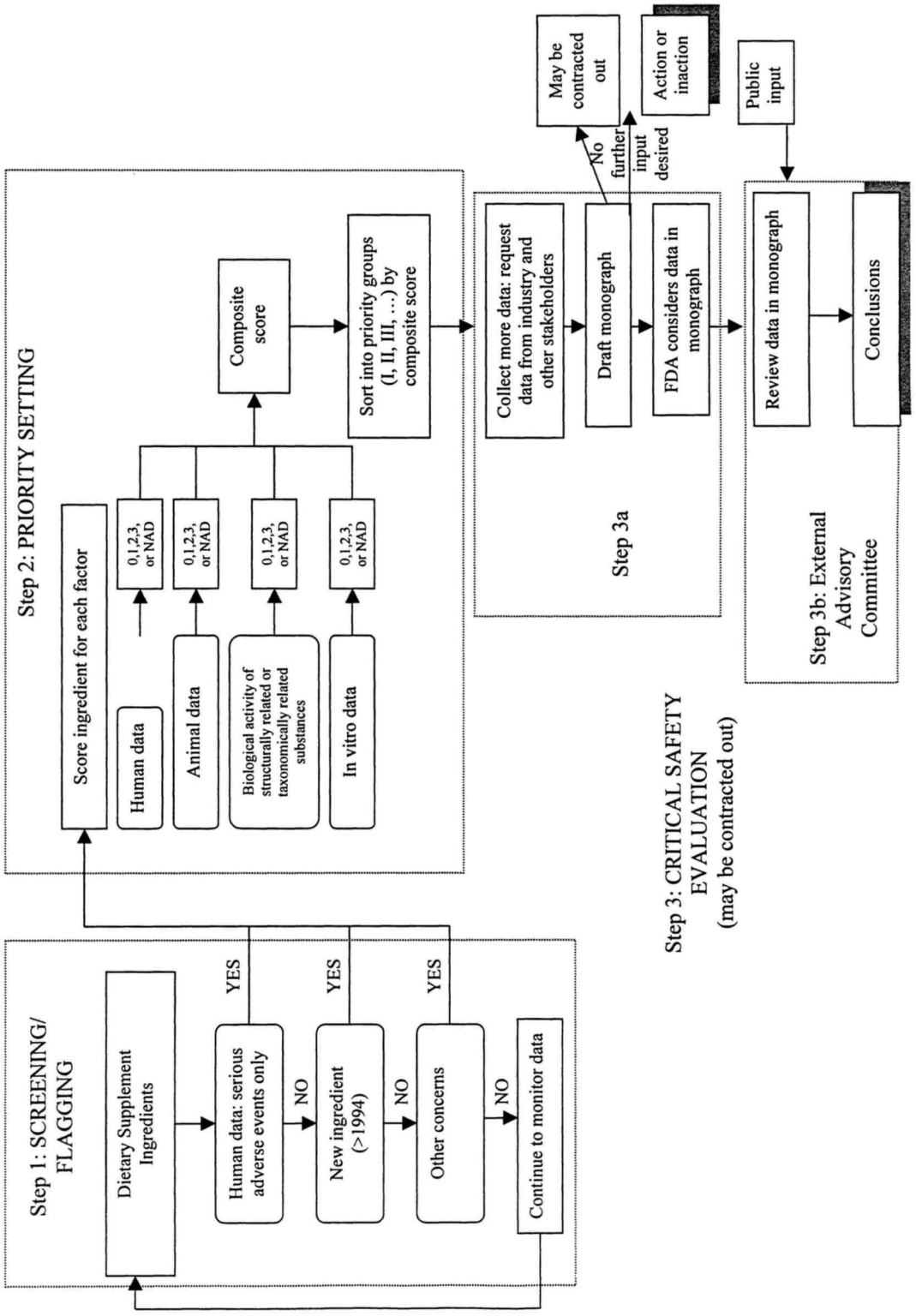

FIGURE 3–1 Flowchart of Overall Framework

available data. However, this method is not transparent, could be biased, and the exact ranking of the ingredients may tend to be somewhat arbitrary.

- *Sales volume.* On the basis (that an unsafe product would do the most harm if it reaches a large number of people, ingredients could be sorted by sales volume and those with the highest sales volume sent first through the screening/flagging and priority-setting steps. The major disadvantage of this system is that sales volumes are not static and sales figures serve only as proxy estimates of use. Another problem with this system is that as a class, vitamins will have the highest sales volume although their safety has been more thoroughly monitored than other classes of dietary supplements. It might therefore be appropriate to begin with the top sellers in the different classes of substances (e.g., the top 10 to 20 percent of hormones, of botanicals, of animal products, of vitamins, and so on).
- *Randomly, in no particular order.* The advantage of a random approach, rather than a systematic one, is that initiation of the process will not require additional resources and time investment.

One of these methods, or a combination of them, may be an effective way for FDA to initiate the screening process of ingredients described in this report.

Description of the Process

The first two steps in the process, screening/flagging and priority setting, are organized to categorize dietary supplement ingredients based on concern and therefore immediacy of need for subsequent in-depth evaluation of safety, the third step of the process. All three steps of this proposed framework are described in detail in Chapter 5 and briefly below.

Information or Factors Used to Identify or Flag Ingredients for Further Evaluation

Several types of readily available information, or "factors," are used to identify ingredients warranting farther consideration, as outlined in Table 3–1 and Figure 3–1, and described in more detail in Chapters 4 and 5. The first factor considered is the ingredient status; ingredients introduced to the market as dietary supplements after 1994 are automatically flagged in Step One to be reviewed in Step Two, priority setting. For pre-1994 ingredients, evidence of serious adverse events in humans is considered. If there is evidence of serious adverse events that may be related to a specific dietary supplement ingredient, that ingredient is flagged. The next consideration is "other information" available to FDA. This other information factor encompasses a broad range of potential concerns. Information that may make FDA aware of potential problems ranges from materials prepared by other groups that have evaluated the safety of dietary supplements, to expressions of concern from consumer protection or advocacy organizations. All flagged ingredients enter the priority-setting step of the framework (Step Two).

Evaluation and Weighting of Available Information

In Step Two, the priority-setting step, several key types of information about each flagged ingredient are considered. These types of information, or factors, are described in Chapter 4. They include human data, animal data, bioactivity of related substances, and in vitro data.

Information about each of these primary factors is retrieved and four key aspects of these data are considered:

- the relevance of the information to safe use by consumers;
- the potential seriousness of the harm reported;
- the methodological quality of the evidence; and
- the quantity of the evidence.

These aspects are used to give each ingredient a score for each of the four factors. The information for each factor in also considered in terms of how it might suggest possible susceptibility of particular subpopulations. After the scores are tabulated, they are sorted into several priority groups based on the scores, the hierarchy of the different types of data, and the estimated prevalence of use of the ingredient. This sorting process allows FDA to consider the different factors independently and individually for each ingredient.

Monograph Preparation, Internal Review, and In-Depth Safety Evaluation

As high priority ingredients are identified, safety review monographs will be compiled (Step Three) as described in Chapter 6. In this step, industry and other stakeholders are invited to bring forward information relevant to the safety of the ingredients being reviewed. Monographs will then be drafted. Monographs will include comprehensive reviews of human data, animal data, other different types of evidence about the ingredients' safety, and notations of where information is lacking. The monograph preparation may be done by FDA or may be contracted out. Once the monographs are prepared, FDA will decide whether to turn them over to an external advisory committee for further attention, to take action without further input from an external advisory committee, or to take no action at the current time. If FDA decides not to take immediate action, it could choose to make the monographs available as draft monographs. FDA may later decide to take action or to refer the ingredient to an external advisory committee, especially if additional information becomes available. A decision not to take further action does not indicate that the product is safe, and FDA may choose not to make a statement about the safety of the product.

If the data do not lead to a clear-cut FDA decision, then the ingredient and its draft monograph are referred to an external advisory committee for analysis and advice, and the draft monograph is made public. The external advisory committee will review the draft monograph, collect additional information as needed, and provide opportunity for public input on the ingredient's inherent safety. The external advisory committee will review the science base for the monograph and revise it as necessary. Finally, the committee will summarize the science relevant to assessing safety of the ingredient and provide opinions on the possible risks associated with the ingredient, including risks that may be specific to particularly vulnerable subpopulations. The committee will also outline where additional research may help resolve safety questions. The revised monograph and the committee's comments will be made available to the general public, so that the expert opinions of scientists are known even if no action is taken.

Ongoing Review and Reassessment

As new information becomes available to FDA, re-evaluation of internal draft monographs and monographs revised by an external advisory committee may be necessary. Such new information should be considered as described in the priority-setting step to determine if there is sufficient substantive new information to review and possibly revise the monograph.

REFERENCES

Betz JM, White KD, der Marderosian AH. 1995. Gas chromatographic determination of yohimbine in commercial yohimbe products. *J AOAC Int* 78:1189–1194.

CFSAN (Center for Food Safety and Applied Nutrition). 2000. *Dietary Supplement Strategy (Ten Year Plan).* Online. Food and Drug Administration. Available at http://vm.cfsan.fda.gov/~dms/ds-strat.html. Accessed March 5, 2002.

Chambliss WG. 2001. Nutraceutical formulations: Impact on bioavailability. In: *Examining the Science Behind Nutraceuticals: Proceedings of the AAPS Dietary Supplements Forum.* Arlington, VA: AAPS Press. Pp. 367–380.

FDA (Food and Drug Administration). 1997. Current good manufacturing practice in manufacturing, packaging, or holding dietary supplements; Proposed rule. *Fed Regis* 62:5699–5709.

Foreman J. 2000. St. John's wort: Less than meets the eye. Online. *The Boston Globe.* Available at http://www.boston.com/globe/search/stories/health/health_sense/011000.htm. Accessed March 5, 2002.

GAO (General Accounting Office). 1997. *Medical Device Reporting: Improvements Needed in FDA's System for Monitoring Problems with Approved Devices.* HEHS-97–21. Washington, DC: U.S. Government Printing Office.

Green GA, Catlin DH, Starcevic B. 2001. Analysis of over-the-counter dietary supplements. *Clin J Sport Med* 11:254–259.

Hamilton-Miller JM, Shah S, Winkler JT. 1999. Public health issues arising from microbiological and labeling quality of foods and supplements containing probiotic microorganisms. *Public Health Nutr* 2:223–229.

Howe K. 2000. Herb Remedies: Panacea or Problem? Online. *San Francisco Chronicle.* Available at http://www.sfgate.com/cgibin/article.cgi?file=/chronicle/archive/2000/06/02/MN75760.DTL. Accessed March 5, 2002.

Kamber M, Baume N, Saugy M, Rivier L. 2001. Nutritional supplements as a source for positive doping cases? *Int J Sport Nutr Exer Metab* 11:25 8–263.

Marrone CM. 1999. Safety issues with herbal products. *Ann Pharmacother* 33:1359–1362.

4

Factors Considered in Screening, Setting Priorities, and Safety Evaluation

In any scientific evaluation there are different categories of data that are useful and that could be termed as key factors to consider. It is helpful to collect and sort relevant information according to these categories. This chapter describes the different types of scientific evidence and other information, herein termed "factors," thought to be most useful when screening, setting priorities, and conducting a critical safety evaluation of a dietary supplement ingredient. Different factors contribute to each step of the framework process to a different degree, and different sources of information are necessary to examine and evaluate the factors in the various steps of the process.

DESCRIPTION AND USE OF KEY FACTORS

This chapter includes a description of each factor, limitations when considering the different types of information grouped under the factor, and suggestions for how each factor is used in each step of the process. In addition, the different sources of information for each factor are outlined in Table 4–1. These sources of information may change over time and new sources may be added. It is likely that, with use, the systematic approach described in this report will eventually evolve into an increasingly efficient and effective system as experience and an accumulating database inform and organize the process.

Of the key factors described below (human data, animal data, biological activity of related substances, and in vitro data), the primary factor that contributes to decision making at all steps of the framework is the evidence of harm in humans. This is provided by data collected in observational studies and clinical trials, spontaneously reported adverse events, and other sources of information about the consequences of use in humans. Whether or not the ingredient is new, and thus safety cannot be ascertained as readily, is also considered in the screening/flagging step. This is classified as the "new ingredient status" question.

In the descriptions below, each factor is defined, a rationale for its use provided, and limitations in the use of these types of data are described. A general description of how each factor can be used at each step of the process is then outlined, including a description of the appropriate information sources to consider at each step in the process—ranging from easily obtainable information for the screening/flagging step to an increasingly comprehensive information collection for the priority-setting and critical safety evaluation steps. Finally,

TABLE 4–1 Sources of Information for Key Factors and Modifiers[a]

Key Factors and Modifiers	Screening/Flagging	Priority Setting	Monograph/Critical Evaluation
Key factors			
Human data	Serious adverse events: MedWatch Poison Control Center Cursory search in scientific and medical literature including IBIDS, Medline, Toxline Letters to the Center for Food Safety and Applied Nutrition	Sources listed at left Secondary reviews	Sources listed at left All available sources, including: Published case reports—available through MedLine or other literature Unpublished safety information requested from published clinical studies Unpublished safety information requested from manufacturers Prepublication safety information requested from clinical trials Discovery materials from tort litigation
Animal data	Consider under "Other Concerns"	Literature searches (e.g., IBIDS, MedLine, Toxline, Embase) Database searches (e.g., NAPRALERT, Poisindex, Naurac) Secondary reviews[b]	Sources listed at left Data voluntarily provided by industry Data provided by animal poison control centers[c]
Biological activity of structurally related or taxonomically related substances	Consider under "Other Concerns"	Poisonous plants (Kingsbury, 1964) NAPRALERT	Sources listed at left Data voluntarily provided by industry
In vitro data	Consider under "Other Concerns"	Literature searches (e.g., IBIDS, MedLine, Toxline, Embase) Database searches (e.g., NAPRALERT, Poisindex, Naurac) Secondary reviews	Sources listed at left Data voluntarily provided by industry

Modifiers			
Prevalence of use	Industry estimates of production and sales (e.g., U.S. Consumer [2000]) Surveys describing supplement use Large-scale, cross-sectional data collection (e.g., the National Health and Nutrition Examination Survey, the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, the Continuing Survey of Food Intakes by Individuals, the Food and Drug Administration)	Sources listed at left	Not applicable
Vulnerable groups	Same sources as key factors (human data, animal data, structure/chemotaxonomy, in vitro)	Same sources as key factors	Same sources as key factors
New ingredient status	75-day advance notifications	Not applicable	Not applicable

[a]These information sources are likely to change over time.

[b] Secondary reviews include Commission E monographs, Agency for Healthcare Research and Quality evidence-based reports, American Herbal Products Association monographs, Natural Medicine Comprehensive Database, World Health Organization monographs, Dietary Reference Intakes by the Institute of Medicine, and National Toxicology Program reviews.

[c] The Animal Poison Control Center of the American Society for the Prevention of Cruelty to Animals (ASPCA) will provide database information on its cases if requested by the Food and Drug Administration (Personal communication, S. Hanson, ASPCA Animal Poison Control Center, May 17, 2002).

overarching guiding principles are presented to explain the scientific basis for the suggested use of each factor throughout the framework. These guiding principles will again be emphasized in the critical safety evaluation process described in Chapter 6.

Key Factor: Data from Humans and Clinical Evidence of Harm

To identify possible concerns regarding safety, it is essential to examine data and information on undesired effects that may have occurred in humans. These undesired effects are referred to as adverse events, a term that does not imply that a particular substance caused the event, but simply indicates that the untoward effects observed were associated with its use and *might* be related to the ingested substance (ICH, 1996). Information about the occurrence of adverse events in humans is obviously the data most relevant to the supplement ingredient in other humans. Information about adverse event occurrence in humans has its own limitations, however, and must therefore be interpreted carefully. This section describes different sources of information about data on adverse effects of dietary supplement ingredients in humans and considerations for using the different types of available information.

When human data suggest risk, these are the most relevant data for consideration of human safety. However, it is anticipated that applicable human data from experimental studies, observational studies, spontaneous reports, and historical use sources often will not be available. As discussed below, the limitations in using available human data often lead to its value only as a signal generator, but even weak data may be useful in this capacity.

Information about untoward effects associated with the use of supplement ingredients may come from experimental studies designed to examine the efficacy or safety of a substance, epidemiological studies, case reports or series, spontaneous adverse event reports to the Food and Drug Administration (FDA) or to poison control centers, or anecdotal reports in the history of the substance's use. Each of these sources provides a different type of potentially valuable information.

Clinical Trials

It is helpful to first consider the ideal source of data and then consider limitations of other sources of data. If available, the “gold standard” for determining the safety of an ingested substance is considered by many to be the randomized, controlled clinical trial (RCT) that is designed to assess safety as well as efficacy.

The ideal RCT would enroll a sufficient number of subjects who are systematically monitored for a sufficient amount of time to detect a wide array of adverse effects or physiological changes that might warrant concern. It is the usual practice in an RCT to query subjects for possible adverse events at defined intervals and to record and evaluate these events as “definitely,” “probably,” “possibly,” or “not” related to the ingested substance (ICH, 1995). The use of randomization and control groups enables scientists to determine the likelihood that adverse effects are actually due to the substance rather than to confounding factors. Limits to the generalizability of the study include the statistical power of the study to detect adverse events, differences between the study and target populations, and differences between how a substance is administered during the RCT and its actual use by the general population.

Most RCTs are designed to assess beneficial effects. Thus, in general, efficacy results are more reliably reported than safety data (Ioannidis and Lau, 2001). Although those conducting efficacy trials are expected to observe and report adverse reactions, the extent and detail of this

reporting is highly variable (Ioannidis and Lau, 2001). In some cases, however, investigators may be able to supply unpublished data useful in the safety evaluation, even if the published results do not contain all the available information about adverse events (Ioannidis et al., 2002).

While investigators may be able to provide unpublished additional data, characteristics of the study design itself may limit usefulness in predicting safety because even large studies may lack sufficient statistical power to detect adverse events of low incidence. Adverse events generally occur at rates much lower than desired effects (FDA, 1995). Clinical trials generally are designed to detect one primary endpoint, thus secondary events, such as adverse effects, will typically be inadequately reported (Ioannidis and Lau, 2001). A major cause of an incomplete safety evaluation is that the unexpected adverse events may not be noticed by the subject or detected by the investigator if they fall outside the investigator protocol.

For these reasons, a study to test the effects of a supplement ingredient on mood, for example, may not detect potentially dangerous cardiovascular effects if heart function is not monitored. Even if investigators are alert for adverse effects, the limited number of subjects, the limited duration, and the unrepresentative nature of populations studied limit the sensitivity in detecting adverse events that would occur infrequently, after extended exposure, or in subpopulations. For example, events that occur at the rate of 1 in 1,000 would require a study with at least 3,000 subjects at risk to have a 95 percent chance of being detected (Lewis, 1981).

Although RCTs can be limited in their sensitivity, they do provide valuable information when adverse events are detected. Information from clinical studies is strengthened by the following information (Counsell, 1997; ICH, 1995; Moher et al., 2001):

- demographic information on the study population;
- inclusion and exclusion criteria to determine if the results are generalizable;
- description of the condition or disease and comorbidities of the study population;
- description of the intervention (supplement ingredient [composition], dose, and duration of exposure);
- list of prior and concomitant ingested substances, including dietary supplements and drugs; and
- description of the adverse event including temporal relationship to ingestion of supplement ingredient (response to discontinuation or rechallenge).

Observational Epidemiological Research

As discussed above, a limitation inherent to many RCTs is that size and duration limit sensitivity to detect adverse events (FDA, 1995). Latent or delayed effects that occur long after exposure may not be detected. Information about these latent and infrequent effects often comes from observational or epidemiological studies that retrospectively or prospectively examine the effects of ingested substances on large populations. Like RCTs, the value of observational studies also depends on the endpoints examined. For example, if a study evaluates the incidence of cancer, death, or liver damage but does not evaluate anemia, the study is unlikely to detect interference with iron absorption.

For the endpoints examined, cohort studies using registries and other sources of information about large populations are a valuable source of safety information about ingested substances such as pharmaceutical drugs. These types of studies would likely be informative about the safety of particular dietary supplement ingredients, but unfortunately there are few studies of

this type conducted on them. The type of information needed to conduct such studies is rarely available for supplement ingredients because their use is not systematically tracked in a manner similar to use of prescription drugs.

Non-Study Information: Spontaneously Reported Adverse Events

Adverse events that are spontaneously reported to FDA, poison control centers, or as case reports or case series in the medical literature are also important sources of information. Generally, these voluntary spontaneous reports are made by consumers, physicians, or pharmacists who notice an untoward effect following ingestion of a substance. It is assumed that adverse effects most likely to be attributed to the ingested substance are unusual, persistent, or severe, and occur shortly following ingestion. Thus, effects that are not noticeable enough to garner attention are unlikely to be associated with the ingestion of the ingredient and thus unlikely to be reported to FDA or another data-collecting entity. Given these limitations, it is not surprising that the total rate of spontaneous adverse-event reporting is very low (OIG, 2001), and that even fewer reports are made to FDA (Chyka and McCommon, 2000).

It has been estimated that adverse events spontaneously reported to FDA account for only 1 percent of serious drug reactions that occur outside the parameters of clinical studies (Scott et al., 1987). It is unknown if spontaneous adverse event reporting may be even less frequent with dietary supplements, because it is unknown if consumers are less likely to associate dietary supplements with untoward effects than to associate drugs with untoward effects.Unlike drugs, supplement manufacturers and distributors are not required to share with FDA the adverse event reports they receive (CFSAN, 2001a; OIG, 2001). Nonetheless, MedWatch and other sources of reported serious adverse effects will often be the first line of evidence that indicates a substance might warrant a higher priority review. Even when reports are inadequately documented and causation difficult to assess, the reports should serve as sentinel events that alert regulators and the medical community to potential adverse effects of a product.

In summary, when they exist, spontaneous reports of adverse events and published case reports are useful for generating hypotheses about relationships between supplement ingredients and untoward effects. However, due to the nature of adverse event reporting, especially for dietary supplement ingredients, a lack of reports does not imply that a dietary supplement ingredient is safe. Similarly, the existence of adverse event reports does not, without extensive critical evaluation of the reports, establish a causal relationship between the adverse event and the ingredient.

Non-Study Information: Historical Use

Experience from generations of use in humans is often referred to as evidence of safety for modern day supplements that bear resemblance to substances used historically. Some botanicals, for example, have had a long history of medicinal use in many cultures.

Historical use is of less importance when relevant clinical, epidemiological, or animal toxicity data exist. For many supplements, however, the amount of scientific and experimental data that exists ranges from scant to nil. Recognizing that a full range of data is unlikely to be available for many dietary supplement ingredients, historical use may be taken into account as a limited surrogate measure for toxicity in the absence of relevant scientific and experimental data. In doing so, it is important to consider the relevance of the traditional use to the current use. Historical information is only useful if the product in question is not so far removed from

the original plant use as to constitute a distinct entity. For example, a whole root extract that was traditionally used for three days to treat a cold is not comparable to a fraction of a leaf extract promoted for long-term use to treat cancer. The discussion in this section focuses on questions to help assess how to consider the relevance of information about traditional use. These questions are listed in Box 4–1 and are explained in more detail below.

BOX 4–1 QUESTIONS TO BE ANSWERED WHEN CONSIDERING RELEVANCE OF INFORMATION ABOUT HISTORICAL USE

- Is the supplement ingredient one that was commonly used within the context of a traditional medical system?
- If the supplement ingredient is a botanical, is the part of the plant marketed the same as the part that was traditionally used?
- Is the preparation a crude preparation, extract, or concentrate; a selected fraction; an isolated compound; or a mixture of these? How similar is the current preparation to that used traditionally?
- Are current intake levels or recommended intake levels clearly different from traditional use?
- Is the modern duration of use consistent with historical use?
- Is the modern indication consistent with historical use?
- If there are traditional cautions in the use of the supplement ingredient, are these cautions typically heeded?
- Are there other reasons to expect a different toxicity profile for the modern formulation than for the traditional preparations?

If the supplement ingredient is a botanical, is the part of the plant marketed the same as the part that was traditionally used? Safety comparisons for botanicals can only be made when the same plant part used in traditional preparations is used in the modern preparation. Seeds, roots, leaves, and other parts may have distinct safety profiles due to different composition. For this reason, this report defines the specific plant part as the ingredient under question. Indication of safe use of one plant part should not be used as prima facie evidence that other plant parts might also be used safely.

Is the preparation a crude preparation, extract, or concentrate; a selected fraction; an isolated compound; or a mixture of these? The method of preparation can have an impact on an ingredient's safety. This is most clearly illustrated in botanicals with traditional medicinal uses. Traditionally, most orally ingested medicinal herbs were administered as crude aqueous extractions of plant parts that were soaked, steeped, or boiled in water. Today's supplements are often sold in a different form—as encapsulated dried herbs, fluid extracts, solid extracts (such as capsules or tablets), or foodstuffs containing herbal extracts. While these modem formulations are not equivalent to traditional preparations and may not have exactly the same effect as teas and infusions, they could have safety profiles similar to traditional preparations. A botanical with a history of benign use in infusions may or may not manifest new toxic effects when concentrated, lyophilized, or encapsulated. Teas (infusions) are typically extracts prepared from dried plant materials, while lyophilized plants are made from whole fresh materials. The chemical composition and concentrations could be sufficiently different between the two forms to result in different safety profiles. Even if dried and lyophilized materials were identical in all respects, an infusion of a botanical should not be thought of as necessarily comparable to whole

dried botanicals because the chemistry of the extract (tea) may be different. Differences in safety profiles could also be expected for alcoholic extracts of plants with known toxic components. Alcohol draws out different compounds, so alcohol extracts may contain a higher concentration of toxic compounds than aqueous extracts. An example is wormwood *(Artemisia absinthium),* which in an aqueous extract contains little thujone (a neurotoxin) (Tegtmeier and Harnischfeger, 1994), but may contain substantial amounts of thujone in alcohol extracts. Additionally, isolated compounds may be dissimilar to traditional plant extracts in safety, as could extracts to which isolated compounds (e.g., yohimbine, ephedrine, hypericin) have been added.

Are current intake levels or recommended intake levels clearly different from traditional use? A frequently quoted axiom of toxicology from Paracelcus is that "dose makes the poison." Unfortunately, differences in traditional and modern formulations render dose comparisons difficult or even impossible. In the rare cases where active compounds or groups of compounds are known and have been quantified (e.g., kavalactones in kava *[Piper methysticum],* ephedrine alkaloids in *Ephedra sinica*), doses can be compared. In most cases, however, dosing comparisons are so imprecise that it should probably only be attempted in cases where the modern formulation is clearly providing doses that are orders of magnitude higher than traditional doses. For example, consumption of a culinary herb in small amounts in cooked food may have different effects than medicinal consumption of large amounts of the same herb, rendering a safety extrapolation from culinary to supplemental use inappropriate.

Is the modern duration of use consistent with historical use? Is the modern indication consistent with historical use? The duration of use is another component of dosage that should be considered. Acute, short-term, and long-term intakes all have different safety implications. A lack of adverse events reported for an herb traditionally used only for a few days has little relevance to safety of the same herb chronically ingested. When considering how the current duration of use compares to traditional duration of use, it may be helpful to also consider whether the modern day indication is consistent with traditional indications. The modern uses of some botanicals, especially for nonmedical indications such as memory enhancement and ergogenics, for example, might lead consumers to use supplements chronically that were never used chronically in traditional medicine.

If there are traditional cautions in the use of the supplement ingredient, are these cautions typically heeded? Some dietary supplement ingredients, such as some botanicals, were traditionally prescribed by practitioners knowledgeable about contraindications to their use. It is scientifically appropriate to take contraindications in traditional use into account when considering the safety of the ingredient. If, for example, an ingredient traditionally contraindicated for pregnant women is currently being marketed to pregnant women or frequently consumed by pregnant women due to its expected effects, then FDA should be more concerned about the safety of this ingredient.

In summary, it is clear from these questions that historical use, even widespread historical use, is no guarantor of long-term safety. Historical use information is very useful when it describes a relationship between untoward effects and an ingested substance. It is less useful in predicting harmful effects, especially those effects that do not occur immediately following exposure. However, in the absence of scientific or experimental data, historical use may provide indirect evidence for lack of serious acute harmful effects, and it may be useful to compare with current cautions and exposures (intake levels and duration). Because little other data may be

available for many ingredients, it is important to judge the relevance of traditional use information to current use conditions.

Causation in the Consideration of Adverse Events

For adverse events from any type of study or nonstudy source, ascertaining whether or not a causal relationship exists between the adverse events and the ingestion of the ingredient is likely to be a challenging aspect of considering human data. At the screening/flagging step of the process, ingredients should be flagged without a burdensome evaluation of actual causation. At the priority-setting step to a limited degree, and in the critical evaluation step to a much greater degree, the evidence should be evaluated for causation. Generally accepted causation criteria for assessing the relationship between adverse events and drugs are outlined by Sackett and colleagues (1991). These criteria, listed below, should generally be applicable to other ingested substances as well, including dietary supplement ingredients.

- The adverse effect is well accepted as an adverse reaction.
- There is no good alternative candidate (unexplained exacerbation or recurrence of underlying illness).
- The timing is as expected for an adverse reaction to this compound.
- The blood level or other biomarker provides unequivocal evidence of overdose.
- The adverse effect improves suitably if the individual is not rechallenged with the compound.
- The adverse effect unequivocally recurs or is exacerbated on rechallenge.

These causation criteria and the quality and documentation of the data will be helpful in weighting the information collected about adverse events reported, but it is not necessary for causation to be clearly demonstrated or refuted during any step of the process.

The different types of human data discussed in the sections above are considered in all steps of the framework, but the degree to which the data are evaluated varies significantly with each step. The differences are summarized below and discussed further in Chapters 5 and 6.

Use of Human Data in the Screening/Flagging and Priority-Setting Steps

There are several primary differences in how human data are considered at each step. The first difference is that in the screening/flagging step, the occurrence of serious adverse events, rather than all adverse events, is used to flag ingredients that should be considered in the priority-setting step. This distinction is made because including nonserious adverse events in the screening could serve to dilute the efforts with untoward consequences that are nuisances or inconveniences (flatulence or halitosis, for example), but do not cause morbidity or mortality. Serious adverse events are defined in the *Guideline for Good Clinical Practice* issued by the International Committee on Harmonization (ICH, 1996) and endorsed by FDA (FDA, 2002). A serious adverse event is an untoward effect that is a death, life-threatening event, initial or prolonged hospitalization, disability, congenital anomaly, birth defect, or other important medical event (ICH, 1996). In contrast to the screening/flagging step, serious and nonserious adverse events are considered in the priority-setting and critical safety evaluation steps.

The second difference in how human data are considered at the screening/flagging and priority-setting steps is the degree to which causation is considered. As described above, the

term adverse event encompasses all untoward effects that may be associated with the supplement ingredient, even if the ingredient has not been demonstrated to actually cause the effect. At the screening/flagging step, the relationship of the adverse event and the ingredient (i.e., the causality) is considered to some degree, but it is considered less at this step than in the priority-setting and critical safety evaluation steps when more information and resources are available to examine causality. That is, ingredients are flagged in the screening/flagging step if a causative relationship between the ingredient and the adverse event cannot easily be ruled out.

The level of information gathering at each step also varies. For the screening/flagging step, readily or easily obtainable sources of information about serious adverse events should be explored. Data sources could include MedWatch and the Poison Control Center database that collect adverse event reports from consumers, pharmacists, physicians, and hospitals. A cursory search of the medical literature should also be conducted to determine if there are any reports of serious adverse events associated with supplement ingredients.[10]

At the priority-setting step, FDA should invest additional effort into weighing the strength of the evidence that a relationship exists between the supplement ingredient and the adverse event. Although the consideration of causation at this stage is not comprehensive, the reviewer makes some judgments about the strength of the evidence.

Historical use information may also be used in the screening/flagging and priority-setting steps. The screening/flagging step is focused on responding to indicators of concern, rather than on considering information that may suggest an ingredient is safe. To the degree that historical use information provides insight into possible concerns or subpopulations that may be harmed by the ingredient, it would be considered in these two steps of the process. As stated above, historical use information can be considered as a surrogate indicator that acute serious toxic effects are unlikely when other, more relevant safety information is not available. During the priority-setting step, it therefore may be appropriate for the reviewer to consider relevant historical use information to determine if it provides insight into areas of concern; such consideration may influence the priority score (see Chapter 5 for the proposed scoring system).

Use of Human Data in the Critical Safety Evaluation Step

The purpose of the critical safety evaluation step is to consider all of the available and relevant information about possible effects of the ingredient on humans, and to consider these data in the context of other types of data collected (e.g., animal or in vitro). Available information should be collected, which includes published case reports available through the National Library of Medicine databases and other sources. Also, clinical investigators may have adverse event information that was not published. This information should be solicited, as well as adverse event information from federal agency-sponsored studies in progress and materials discovered by plaintiff lawyers in tort litigation. Importantly, the manufacturers and distributors of ingredients that reach the critical safety evaluation stage should also be asked to provide data voluntarily on adverse events reported to them or other relevant evidence they have regarding safety evaluation.[11]

[10] For example, the National Library of Medicine's PubMed, available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi; TOXNET, available at http://toxnet.nlm.nih.gov/; and EMBASE, available at http://www.embase.com/.

[11] Manufacturers and distributors are always welcome to submit adverse event reports and other safety information. They are specifically requested to submit data after the priority-setting step because at this step additional effort can be expended to request information about specific ingredients in the *Federal Register* and/or via letters to individual manufacturers and distributors, if they are known.

In the critical safety evaluation step, experts will weigh the evidence and consider the likelihood that a substance poses a risk to human health. At this point, consideration of human adverse event data in relation to the other factors, such as animal, in vitro, and biological activity of related substances, will provide an overall picture of what is known about the ingredient's safety and may provide plausible biological explanations for reported human adverse events for which causation is not clear.

While it is hoped that eventually all dietary supplement ingredients will reach the critical safety evaluation step, given the large number of dietary supplement ingredients, it is unlikely that those ingredients for which significant safety concerns have not been raised will reach this step in the near future. Thus, ingredients that have been safely used historically are unlikely to be reviewed unless other information leads to questions about their safety.

Information about the historical use of an ingredient will be the most useful during the critical safety evaluation step, when it can be considered along with the in-depth analysis of potential for harm derived from other information. In this step, historical use information will be considered to the degree that the historical use is similar to current use. The historical use information should not be considered as more important than the scientific evidence, but it may be appropriate to take information about the history of use into account if it is relevant to understanding the likelihood of the potential harm being considered and it is relevant to current use conditions. For example, it would be important to determine whether the potential harm being considered would be expected to have been detected during years of previous use. In such cases, historical use information may mitigate concerns to some degree.

GUIDING PRINCIPLE FOR HUMAN DATA

A credible report of a serious adverse event in humans that is associated with use of a dietary supplement ingredient raises concern about the ingredient's safety and requires further information gathering and evaluation. A final judgment about the safety of the supplement ingredient, however, will require consideration of the totality of the evidence. Historical use should not be used as prima facie evidence that the ingredient does not cause harm. It may be appropriate, however, to give considerable weight to a lack of adverse events in large, high-quality, randomized clinical trials or retrospective or prospective cohort studies that are adequately powered and designed to detect adverse effects.

Key Factor: Animal Data

Animal testing provides invaluable evidence about the potential for ingested substances to cause harm in humans. Thus, studies on animals are regularly employed as an important step in attempting to predict untoward effects of these substances on humans (see, for example, Redbook 2000 [CFSAN, 200 1b] or guidance documents for new drugs [CDER, 2002). They are powerful because controlled studies can be conducted to predict effects that might not be detectable with customary use by humans until they lead to harmful results. Animal studies serve as important signal generators and, in some cases, may stand alone as indicators of unreasonable risk.

Different types of animal studies provide different types of information relevant to considering the safety of a dietary supplement ingredient and can be classified as either traditional toxicology data or safety pharmacology studies. FDA's Redbook II describes several different types of toxicology studies that are typically conducted in assessing the safety of food additives and other ingested substances (see Table 4–2) (CFSAN, 1993). These studies are applicable to evaluating most ingested substances, including dietary supplement ingredients, irrespective of what is known about their biological activities. It is not anticipated that animal data of each type will be available for each dietary supplement ingredient. However, consideration of the typical study protocols enables the animal data that is available to be placed in perspective regarding the type of information gleaned from the different study designs and the types of data that are often available for other ingested substances.

One type of animal study is the acute toxicity study.[12] In acute (single dose) and subacute (repeated doses) toxicity testing, animals are treated with increasing amounts of the test substance to determine the dose that induces overt abnormalities (i.e., toxic effects). The resulting abnormalities might be at the level of organs (detected by gross examination or by observing behavioral changes), cells (detected by histological examination such as light or electron microscope analysis of fixed tissue samples), or subcellular structures (detected in biochemical studies such as enzyme assays or protein analysis). In another example, chronic toxicity testing (and in subchronic toxicity testing, which is not as lengthy as chronic toxicity testing), the test substance is typically administered to animals on a daily basis for 3 to 24 months (depending on the species) to characterize possible longer-term toxicity.

When conducting animal studies, blood levels of the test substance and its active metabolites are often determined. These blood levels are used to provide evidence that the test substance was absorbed, to describe the dose-response curve, and to determine whether the metabolites formed in the test animal are qualitatively and quantitatively similar to those formed in humans. If the metabolites formed in the animals are not the same as those formed in humans, the results may be less meaningful and testing with other species should be considered.

Genetic, reproductive, developmental, and behavioral toxicity studies, as well as other types of studies provide further information regarding the toxicity of the test substance.

In addition to traditional animal toxicity testing, safety pharmacology testing is also conducted in various animal species in order to detect alterations in physiological functions at doses lower than those used to elicit overt toxic effects detected in animal toxicity testing. The *S7A Safety Pharmacology Studies for Human Pharmaceuticals* issued by FDA defines safety pharmacology studies as “those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above” (ICH, 2001). Safety pharmacology testing generally focuses on endpoints that differ from those examined in classic toxicity testing. It is designed to detect harmful effects in a “core battery” of vital organ systems, which include the cardiovascular, central nervous, and respiratory systems.

Safety pharmacology studies may detect potentially harmful physiological responses such as arrhythmias, blood pressure changes, and alterations in blood gases in nonrodent species—changes that would be difficult to observe in rodent species. When appropriate, supplemental safety pharmacology studies beyond the core battery is used to evaluate potential adverse effects in the renal/urinary, autonomic nervous, gastrointestinal, immune, skeletal muscle, and endocrine systems.

[12] See descriptions of acute, short-term, subchronic, one-year, and chronic toxicity tests in Table 4–2.

TABLE 4–2 Toxicity Studies in Laboratory Animals

Types of Studies	Protocols Typically Used in Studies	Purpose of Study/Information Gleaned
Acute Toxicity Tests Species used: typically rat	Single dose (limit test, up to 5 g/kg body weight or 5 m1/kg body weight) followed by 14-day observation period Estimate acute lethality, if appropriate, for test substance Monitor food consumption, weight change, lethargy, changes in behavior	Main focus: observe the symptoms and recovery of test animals Identify possible target organs Estimate dose range for other studies
Short-Term Toxicity Tests Species used: usually rat but other species such as mouse, dog, or miniature swine may be used	Daily dosing regimen is repeated for 14 or 28 days At least three and up to five different doses are used Observe general signs of toxicity: change in consumption of diet or water, change in body weight; hematology, clinical chemistry and limited urinalysis (prestudy and at termination); neurotoxicity and immunotoxicity studies, as appropriate; gross necropsy findings and microscopic findings	Identify target organs Refine dose range for further studies Establish the no-observed-adverse-effect level (NOAEL) for some endpoints
Subchronic Toxicity Tests Species used: usually rat, mouse, or dog	Daily dosing regimen is repeated for longer period, typically 90 days (up to 12 months, depending on species) Observations: same as for short-term tests described above	Identify target organs Refine dose range for further studies Establish NOAEL for additional endpoints
One-Year Toxicity Tests (nonrodent) Species used: usually dog	Similar to subchronic studies extended to 12 months At least three dose levels are used Observe general signs of toxicity: change in consumption of diet or water, change in body weight; hematology, clinical chemistry, and urinalysis (prestudy, at 3-month intervals, and at termination); gross necropsy and microscopic findings Observe specific signs of toxicity, if appropriate	Characterize possible toxicity of the test substance in a nonrodent species Establish NOAEL in a nonrodent species
Chronic Toxicity Tests (rodent) Species used: two rodents, usually rat and mouse At least 25 female and male surviving to the end of the study	Similar to subchronic studies extended up to 24 months, depending on species At least three dose levels are used; the high dose should be the maximum tolerated dose (MTD) Observe general signs of toxicity, as described above Observe specific signs of toxicity, if appropriate	Characterize possible long-term toxicity of the test substance in rodents Determine whether test substance is toxic when administered to rodents in regularly repeated oral doses for the major portion of the lifetime of the test animal

SOURCE: Center for Food Safety and Applied Nutrition (CFSAN, 1993, 200 1b).

In addition to information provided by laboratory animal studies, veterinary toxicology information may also prove useful in examining the potential effect of an ingredient on humans. Information is available on the effects of veterinary intoxication, similar to human adverse event reports. Serious adverse events reported in animals, such as livestock, may provide helpful information. For example, effects associated with ingestion of several plants were reported in livestock many years ago. Animal poison control centers, as well as a search of the veterinary literature, may provide this type of information.

Importance of Quality Data

While all animal experiments may be informative, the nature of the experimental design, the quality of the methodology, and the statistical significance of the results need to be taken into consideration in weighting the evidence. Recommendations for well-designed safety tests using animals are described in the FDA Redbook (CFSAN, 1993, 2001b). Specifically, the most ideal information will come from animal studies that are consistent with the guidelines listed in Box 4–2, recognizing that other data may be valuable as well.

Extrapolations from Animal Studies

Several considerations are important when extrapolating from animal data to predict effects on humans. Factors that can affect interpretation include interspecies physiological variability and differences in routes of exposure, dose levels, animal health, nutrition, and treatment. Testing substances in more than one species increases the likelihood that information related to effects in humans will be identified, and the more genetically diverse the examined species (e.g., one rodent and one nonrodent study), the more likely at least one of these will model human physiology.

The relevance of animal studies to human safety is also improved when treatment of the animal most closely resembles conditions experienced by humans and does not result in excessive stress. A healthy, inbred animal species is most likely to result in data that are

BOX 4–2 CHARACTERISTICS OF GOOD ANIMAL STUDIES

A good animal study is one that:

- uses Good Laboratory Practices;
- is specifically designed as a toxicity, safety pharmacology, or safety study and includes sufficiently large doses to detect toxicity;
- uses unanesthetized, unrestrained animals on a semipurified diet;
- fully characterizes the composition and formulation of the test substance;
- uses a species that has pharmacodynamics similar to humans (bioavailability, distribution, metabolism, excretion);
- estimates blood or other tissue levels to assure absorption;
- conducts clinical chemistry, blood, and urine analysis;
- uses more than a single species (that might respond differently than humans); and
- administers the test substance orally.

reproducible and reliable. Accreditation of laboratory facilities provides reasonable assurance that the animals are being treated according to established guidelines (ILAR, 1996).

In considering animal data generated in other countries, it is important to recognize that animal care accreditation is not globally harmonized. Animal data derived from studies in nonaccredited laboratories that do not follow good laboratory practices may be difficult to interpret or reproduce, possibly because animals are housed under stressful conditions, fed nonstandard diets, or have parasites or diseases that may confound the data interpretation.

Finally, the amount administered and tissue levels of a substance in test animals are important to consider when assessing the relevance of animal studies to human safety. One of the unique and powerful approaches of animal testing is the system of administering high amounts of a substance over a short time period. This allows the prediction of possible effects following prolonged human exposure and prediction of possible effects on particularly sensitive subpopulations. Many studies focused on toxicity will evaluate increasing doses until signs of toxicity are seen. While the amount administered may not appear relevant at first glance, organ toxicities at elevated intake levels in acute or subchronic studies can be indicative of toxicities that may develop at lower doses during chronic use of the ingredient.

Studies carried out using very different amounts or formulations from those being marketed must be carefully interpreted. High-dose effects can be useful in predicting potential for similar low-dose effects in humans, but these studies serve as indicators of risk or concern that should be considered in the context of other data when possible. Finally, animals that are given substances using intragastric or oral administration provide the ideal model to predict human toxicity or harm associated with a dietary component, but data following administration by other routes should not be disregarded.

As with any type of scientific study, it is important to remember that a lack of observed or reported detrimental effects in an animal study does not indicate that a particular substance is safe. Animal data should only be used to predict human effects that are relevant to the endpoints examined in the animals. For example, if an animal study only reported how many animals died or exhibited gross toxic effects following short-term administration of an ingredient, it is not acceptable to conclude that this ingredient does not cause cancer following chronic intake by humans. In summary, the sensitivity of the animal experiments to detect particular effects is of utmost importance to consider when extrapolating from animal studies to humans.

Use of Animal Data in the Screening/Flagging Step

In order to create a rapid review system and to avoid lengthy data searches during the screening/flagging step, animal and other nonclinical data are not designated as a separate, independent factor for this step. These data are considered in this step to the extent that they come to FDA's attention under the umbrella of “other concerns,” that is, without overt information-seeking action on the part of FDA.

Use of Animal Data in the Priority-Setting Step

The goal in considering animal data at this step is to set a higher priority on flagged ingredients for which animal data suggest there may be safety concerns. In this step, the scientific literature should be systematically searched for evidence of harmful effects in animals for all flagged ingredients (including ingredients flagged for other reasons). Sources for primary scientific literature include IBIDS, MedLine, Toxline, AGRICOLA, and other scientific

literature databases. Other databases, such as NAPRALERT, focus on natural products and also may be useful for searching for evidence of adverse effects observed in animal studies. Finally, it is important to consult several secondary or tertiary reviews that may cite older (pre-1960s) or foreign data not found in the main database.

After gathering information, the evaluation of animal data should be focused on two aspects: the evidence of possible risk, of which the quality and quantity of the data are components, and the seriousness of the potential harm suggested by the data. Points to consider when assessing the quality of the data are outlined above. The data are more meaningful when the dose and ingested form can appropriately be extrapolated from animal data to human effects, as outlined above.

In addition to assessing the evidence of possible risk, it is very important to consider the seriousness of effects suggested by the animal studies. Clearly, animal studies that predict serious harm or death warrant more attention than those that predict mild, self-limiting effects on humans. Certain chronic animal toxicity or biological activity data should be considered as immediate cause for high priority, regardless of the presence of high-quality human data suggesting no acute toxicity. This is because human exposure may need to be prolonged before such toxicities would be detected without the benefit of animal data, or the source of such detrimental effects may very difficult to detect except with animal studies. Animal studies that warrant special concern are those that indicate the following potential effects in humans:

- evidence of cancer;
- reproductive system effects;
- developmental toxicity effects, including teratology;
- acute organ toxicities; and
- cardiovascular, respiratory, and central nervous system effects.

Use of Animal Data in the Critical Safety Evaluation Step

The goal of the critical safety evaluation step is to conduct an in-depth consideration of the value of the available animal data in predicting harm to humans in the context of data from other factors. If animal data are a central focus of the in-depth safety evaluation, expert opinion in the interpretation of animal data will be sought. Such expert opinion will help ensure that the data are appropriately reviewed in the context of all information available regarding the ingredient.

Industry and the other public communities should be invited to submit animal study information for ingredients that reach the critical safety evaluation stage. If manufacturers or distributors have conducted animal studies on their products, these data should be made available on a voluntary basis by manufacturers at this stage, if not before. Veterinary toxicology information may also provide useful information; cases reported to the animal poison control centers should also be solicited.

GUIDING PRINCIPLE FOR ANIMAL DATA

Even in the absence of human adverse events, evidence of harm from laboratory animal studies can be indicative of potential harm to humans. This indication may assume greater importance if the route of exposure is similar (e.g., oral), the formulation is similar, and more than one species shows the same toxicity.

Key Factor: Bioactivity of Structurally Related and Taxonomically Related Substances

Complete information on safety-related effects of each dietary supplement ingredient will not be available. Consideration of risk may therefore be facilitated by understanding the biological activity of related substances. It is not possible to define all the different ways that substances may be "related." Substances with similar chemical structures, such as ephedrine and amphetamine, are structurally related, as are substances that stimulate or inhibit activity at the same cellular receptors or other biological targets, even if their chemical structures are not obviously similar in the strictest sense. Similarity of dietary supplement ingredients to biologically active metabolic intermediates such as cytokines or hormones may also be important if the actions of metabolic intermediates provide clues about the activity of the dietary supplement ingredients. Finally, it is possible to gain insight into the activity of a plant-derived substance by considering the activity of other plants in the same plant family or genus.

For some dietary supplement ingredients, reviewing the biological activity of individual chemical components or related chemicals will be straightforward and will lead easily to hypotheses about the action of the dietary supplement ingredient being considered. If the biological activity of related substances suggests concern that the dietary supplement ingredient may be harmful, these concerns should be considered.

In other cases it may be more difficult to identify substances related to the dietary supplement ingredient that could be used to predict biological activities. In these cases, if an ingredient's chemical components are known, it may be useful to employ systematic computational approaches to formulate hypotheses about biological activities of the chemical constituents, as described below. In the case of botanical ingredients, it is appropriate to review information about the individual chemical components to determine if any of the constituents raise concerns and to review information about taxonomically related plants. These approaches are described in the next few paragraphs.

Systematically Considering Biological Activity of Structurally Related Substances

The physical-chemical properties and biological effects of a substance are derived from its chemical structure. If the chemical structure of a dietary supplement is known, but additional insight into the biological activity is needed, then it may be helpful to consider the information about the biological activity of structurally related substances. It is assumed that the biological effects of chemicals, including toxic effects, are implicit in their molecular structures. On this basis, computational programs have been developed to predict the biological activity of chemicals by comparing their chemical structures with other well-characterized compounds.

Computer programs designed to assist in predictive toxicology are useful in predicting a chemical's potential propensity for causing particular effects. For example, The Open Practical Knowledge Acquisition Toolkit program (AIAI, 2002) uses chemical structures and a variety of models to estimate carcinogenicity and teratogenicity, among other toxicological endpoints, and is used by the Cosmetic Industry Review in setting priorities for review. An endorsement or comparative evaluation of individual programs is beyond the scope of this report, but these programs in general are believed to have value in providing insight into the potential for a dietary supplement ingredient to demonstrate toxicological outcomes not adequately addressed by available experimental data. Computational prediction is most useful for predicting biological activities of pure compounds.

Considering the Chemical Composition of Botanical Ingredients

As discussed in Chapter 3, for the purposes of this framework, a plant part (e.g., fruit, root) is considered as one dietary supplement ingredient, but of course this one ingredient is composed of many individual phytochemicals. It is well known that biological effects are tied to specific pharmacophores, or chemical structures, and that certain chemical structures are known to trigger a toxicological response. For this reason, it is helpful in predicting the toxicity of botanical ingredients to know if they contain such compounds. Thus, documentation of the chemical constituents known to be present in a botanical ingredient may enable safety predictions to be made based the presence of compounds known to be hazardous. For example, the presence of certain compounds, such as those listed in Box 4–3, can often point to a potential toxicity of a specific botanical product.

In addition to examining chemical composition profiles of botanical ingredients for the presence of chemicals associated with harm, much information can also be gained by reviewing what is known about plants that are taxonomically related to the dietary supplement ingredient under consideration. A number of genera of plants are often associated with toxic compounds (e.g., *Liliaceae* are known to contain cardiac glycosides, *Euphorbiaceae* are known to contain phorbol esters and toxic diterpenes). The ability to anticipate the presence of specific classes of compounds based on plant family or genus may be helpful in predicting potential toxicity. For example, if the botanical belongs to a genus known to contain certain compounds for which there is a toxic potential, one could presume that the same compounds might exist and pose a problem in the ingredient under question, unless there is reason to think otherwise.

The utilization of taxonomic relationships to predict composition and potential toxicity has its limitations. Not all genera of a given family will contain similar toxic components. Therefore, knowledge of taxonomy, phytochemistry, and pharmacognosy is ideally used as a tool to complement other data such as bioavailability, pharmacokinetics, and toxicological evaluation. Furthermore, the concentration of these compounds in the final product must be considered, as well as the plant part being utilized and the manner of preparation, processing, and formulation. The goal is to consider two likely scenarios that could provide some guidance regarding the possible toxicity a botanical dietary supplement ingredient: where a known constituent of the plant is structurally similar to a known toxic compound, and where a plant genus or species is (or is closely) related to a known toxic plant.

BOX 4–3 EXAMPLES OF POTENTIALLY HAZARDOUS COMPOUNDS

- alkaloids (usually active on the central nervous system as well as other organs or systems of the body)
- cardenolides/bufadienolides (usually cardiotoxic)
- colchicine-like compounds (toxic at very low doses)
- cyanide-containing compounds
- nitrophenathrenes (aristolochic acid, mutagens, carcinogens)
- nitrosamines (carcinogens)
- phorbol esters (irritants, tumor promoters)
- pyrrolizidines (liver toxins, carcinogens)
- urushiol-related compounds (poison ivy-type compounds, severe irritants)

Use of Bioactivity of Related Substances in the Screening/Flagging Step

Consideration of the bioactivity of related substances is not a separate, independent factor of the initial screening/flagging step. It is expected that ingredients that cause concern based on their structural or taxonomic similarity to harmful compounds or plants will come to FDA's attention through secondary reviews highlighting the potential for safety problems or through other mechanisms of expressed public concern.

Use of Bioactivity of Related Substances in the Priority-Setting Step

Information about the biological activity of related substances may be utilized as a predictor of possible harm, and therefore a reason for considering a supplement ingredient as higher priority. In gathering information for the priority-setting process, sources such as databases (e.g., the American Chemical Society's Chemical Abstracts Service) and texts with information about biological activities of phytochemicals and plants will be useful in examining whether the ingredient's chemical structure or plant's genus and species indicates a potential for harm. Computational approaches that predict possible toxicological endpoints based on chemical structure may be used for dietary supplement ingredients with identified major chemical components.

When considering the potential for botanically-based supplement ingredients to cause concern, several key sources of information should be consulted in the priority-setting stage. Texts that list poisonous plants by plant family, genus, and species are helpful in identifying harmful ingredients. *Poisonous Plants of the United States and Canada* (Kingsbury, 1964) is a good example that lists examples of harmful plants and also contains information helpful in identifying related plants. Databases (e.g., NAPRALERT) provide pharmacological and toxicological information about plant compounds that is helpful in identifying potential toxic substances by the taxa of botanicals.

Use of Bioactivity of Related Substances in the Critical Safety Evaluation Step

In the critical safety evaluation, information derived from comparison to the biological activity of related substances should be considered as part of the totality of the evidence. For example, if the information suggests a plausible mechanism of harm and could explain the human adverse events reported, then it may be appropriate to find that the ingredient is not safe. If structure and taxonomic prediction data are a central focus of the critical safety evaluation, expert opinion in the interpretation of such information will be sought. Such expert opinion will help ensure that the data are appropriately reviewed in the context of all information available about the supplement ingredient.

GUIDING PRINCIPLE FOR STRUCTURALLY RELATED AND TAXONOMICALLY RELATED SUBSTANCES

The presence of a constituent that is structurally similar to known toxic or potentially harmful compounds or a plant that is taxonomically related to known toxic plants suggests increased risk, and therefore higher priority, unless there is evidence that the compound is not toxic or harmful, the compound is present in concentrations that will not lead to harm, or there is other evidence supporting the safety of the ingredient.

Key Factor: In Vitro Data

In vitro studies are defined here as studies not conducted in humans or other whole animals. A wide range of in vitro experimental systems are used to gain insight into the risk of adverse clinical effects of compounds. These systems include isolated cells, microorganisms, subcellular components, and isolated organs. In vitro assays often focus on measuring effects on cells and subcellular targets such as enzymes, receptors, and DNA. The primary advantage of conducting in vitro studies is that their reductionist approach allows insight into a compound's mechanisms of action that might be more difficult to obtain in a whole animal study, making in vitro studies useful screening tools. They are also generally more rapid and less expensive, leading to a greater amount of this type of data being available in the literature.

As mentioned above, it is the reductionist approach of in vitro studies that makes them powerful and inexpensive assays useful for learning about effects and mechanisms of actions of compounds. The reductionist approach of in vitro assays, however, requires that reviewers of these studies carefully consider their limitations and caveats. It is very important, for example, to consider whether the compound applied to the in vitro system is similar in identity and concentration to the compound that reaches the target (e.g., tissue, receptor, subcellular component) in the human. After a substance is ingested, the metabolic fate of the compound and the amount of the biologically active compound that actually reaches the target site is dependent on a multitude of processes including absorption, distribution within the body, metabolism by liver and intestinal enzymes, and rate of excretion. Knowledge of an ingredient's pharmacokinetics and in vivo metabolism will allow the most appropriate interpretation of the relevancy of the dose used in the in vitro tests.

Botanical extracts provide an example of how important it is to consider bioavailability of the ingested substances. When applied to cells in vitro, these extracts often contain polyphenolic compounds (e.g., tannins and related compounds) that may reversibly or irreversibly bind to subcellular components such as enzymes, signal transduction factors, and receptors where they cause effects. In a human, however, these compounds can bind to the food bolus or be metabolized by gastrointestinal enzymes, becoming unavailable for absorption, and therefore not exert the same effects on receptors and enzymes (Bravo, 1998; Yang et al., 2001). Another example of problematic interpretation can be in hepatocyte cultures that do not always support expression of metabolizing enzymes, causing some data to be misleading. In contrast, some cell cultures are established specifically to evaluate metabolism of substances and can provide useful information. All cell types do not respond similarly to a single substance, even when the cells originate from the same organ; one cell type may exclude or excrete a compound whereas another cell will not, and another may behave differently due to its unique biochemical pathways.

In the drug development world, results from some in vitro assays are considered predictive enough of toxicological problems that the assays are used to screen compounds in development and influence decisions about further development. For example, assays have been developed to identify compounds that may contribute to the development of *torsades depointes* cardiac arrhythmia by slowing cardiac repolarization. Drugs that may potentially contribute to this condition can be identified by in vitro experiments conducted with isolated organs and measurement of potassium channel activity in isolated cells (Liu et al., 1998; Wang et al., 1998; Zabel and Franz, 2000).

It is also possible to use in vitro assays to anticipate which dietary supplement ingredients may contribute to supplement-drug interactions by studying the effects of a dietary supplement

ingredient on cytochrome P450 enzymes, which are important in the liver metabolism of drugs and supplements (Budzinski et al., 2000; Obach, 2000; Piscitelli et al., 2000). In vitro assays that assess enzymes, receptors, tissues, or other biological endpoints that might provide useful information in the context of other data are listed in Box 4–4. As additional in vitro assays are developed and validated, they will be useful in identifying which dietary supplement ingredient may potentially be associated with risk.

BOX 4–4 USEFUL IN VITRO ASSAYS

- apoptosis induction
- ATP synthesis inhibition
- cell cycle effects
- cell proliferation effects
- cell transformation effects
- cholinergic effects
- cholinesterase inhibition or induction
- cytolytic effects
- cytotoxic effects
- detoxification enzyme inhibition or induction
- DNA damage
- Epstein-Barr virus activation
- histaminergic effects
- hormone receptor binding studies
- immunosuppressant effects
- mitochondrial respiration inhibition
- mitogenic effects
- parasympatholytic and parasympathomimetic effects
- pharmacokinetic alterations
- phototoxicity effects
- prooxidation effects
- sympatholytic/sympathomimetic effects

Because of the difficulties that often exist in their interpretation, it is often appropriate to use in vitro data as hypothesis generators or potential indicators of harmful health effects rather than as stand-alone demonstrated indicators that in themselves suggest possible risk. However, some in vitro assays, when carefully conducted and interpreted, provide valuable information beyond simply reinforcing observations from other systems or generating hypotheses. When the relationship between the results of an in vitro assay and actual clinical or animal outcomes has been demonstrated, thus validating the predictive value of the assay, then the in vitro assay warrants careful attention.

Use of In Vitro Data in the Screening/Flagging Step

In vitro data are not a separate, independent factor of the initial screening/flagging step. It is expected that in vitro data that raise concerns about the safety of a supplement ingredient will come to FDA's attention through secondary reviews or other outlets for expression of public concern.

Use of In Vitro Data in the Priority Setting Process

Information about in vitro effects can be obtained from many of the same sources used to locate animal data. These sources include literature databases and secondary and tertiary reviews. As with the other factors, at this step it is important to consider what the in vitro data suggest about the risk and seriousness of possible harm.

Use of In Vitro Data in the Critical Evaluation Step

The same information sources used for the priority-setting step should be searched in greater depth for the critical safety evaluation. In addition, industry and other public communities should specifically be queried for any in vitro data on the safety of the ingredient being evaluated.

As discussed above, some in vitro effects in themselves raise substantial concerns about potential for harm. These effects, as well as other in vitro assays with less clinical validation and independent predictive value, become very important in assessing biological plausibility of observations made or predicted by other systems, such as animal, human, or structural association. While it is not necessary to determine a rational mechanism of harm to determine that an ingredient is potentially unsafe, it is valuable to identify possible mechanisms that explain the totality of the data. In vitro studies can be very useful and irreplaceable in this regard. If in vitro data are a central focus of the critical safety evaluation, expert opinion in the extrapolation of in vitro data will be sought. Such expert opinion will help ensure that the data are appropriately reviewed in the context of all information available regarding the ingredient.

GUIDING PRINCIPLE FOR IN VITRO DATA

In vitro studies can serve as signals of potential harmful effects in humans, but not as independent indicators of risk unless an ingredient causes an effect that has been associated with harmful effects in animals or humans and there is evidence that the ingredient or its metabolites are present at physiological sites where they could cause harm. Alone, in vitro data should serve only as hypotheses generators and as indicators of possible mechanisms of harm when the totality of the data from the different factors is considered.

MODIFYING FACTORS

In addition to the key factors that explicitly contribute to the screening/flagging and priority-setting steps, prevalence of use and vulnerability of subpopulations are considered as modifying factors. These two factors must be considered when evaluating the different types of scientific evidence. Both are considered to some extent in the screening/flagging step and when setting priorities for evaluation. Prevalence of use in the general population, however, is not a factor considered during the critical safety evaluation.

Prevalence of Use in the Population

The number of individuals who could be at risk of harm due to overall use of the dietary ingredient in the United States (or "prevalence of use") can be estimated from various types of data that provide estimates of the relative popularity of different ingredients. Across the wide variety of dietary supplement ingredients that are currently available, there is a wide range of usage patterns in the population. Some ingredients are used only rarely or by a small fraction of the population, while others are used by a considerable fraction. Dietary supplements that are readily available or are consumed or marketed for common concerns and conditions are more likely to result in a high level of usage, while those that are less widely available, used only

rarely, or used by few consumers would be expected to result in a low level of exposure on a population basis.

Estimating prevalence of use allows a qualitative consideration of population exposure and therefore how much of the population may be at risk if an ingredient is harmful—a factor that is important in optimizing the impact of a rigorous safety evaluation on public health. That is, from a public health perspective, it is more logical to first allocate resources to evaluation of potentially harmful ingredients that have the potential to harm many people before evaluating those ingredients that may only affect a small fraction of the population (assuming other information is equivalent).

Relative consumption and prevalence of use of various dietary supplement ingredients in the general population can be estimated from two types of data. One type is industry estimates of production or sales. Dietary supplement industry publications such as the *Nutrition Business Journal* provide such data. Additionally, manufacturers and distributors collect production data, unit sales data, and total sales information in dollars as a normal component of business operations. The industry may be willing to make this information available.

Neither unit sales nor total sales data are ideal, but both can serve as proxy indicators useful in developing a qualitative understanding about prevalence of use. Unit sales data, especially, allow a rough comparison of relative potential use among different ingredients, serving as a surrogate marker of actual use of each ingredient —information that is usually not readily available. One limitation with the use of sales figures, however, is that these numbers are often collected and collated by methods that make cross-category comparisons difficult. This is important to keep in mind when estimating relative ingredient use.

The second type of data about prevalence of use is that collected in surveys about supplement use. Increasingly, national surveys that have traditionally collected information from a large number of persons regarding health issues and conventional food consumption information are also collecting valuable information about specific supplement use. An example is the expanded monitoring efforts of the National Health and Nutrition Examination Survey. Although it may be several years before this information is available, the expanded data collection will provide more detailed and useful information than is currently available.

Such surveys can provide data on prevalence of use in the general population as well as in specific population groups. Most surveys also ask subjects about patterns of use and other information that is helpful in estimating the effect of potential adverse effects on a population. Although some publications based on such surveys group supplement ingredients into broad categories (e.g., vitamins, botanicals) for the purpose of data analysis, other sources of information are likely to list specific ingredients or products. Even when data on specific ingredients are not included in the published articles, such data might have been collected and might be available from the investigators upon request.

One deficiency of older survey data sets is that frequency of use information was rarely collected (i.e., differentiating supplement use for only short intermittent periods versus chronic use). This type of information is important because it augments the evaluation of total sales figures. Some ingredients that are widely sold may be used less frequently than others. Whether a substance is used for short periods of time or chronically is particularly important in evaluation of safety, because a product or ingredient that is used intermittently will usually pose a smaller or different type of risk than one used chronically.

Another limitation of available information is in the collection and interpretation of data on combination products or ingredients that are typically used in combination products (in addition

to formulation and sales as a single-ingredient product). Obtaining reasonably accurate estimates of usage of ingredients that are largely consumed as components of combination products may be more difficult but may be available from manufacturers of raw ingredients or if registration procedures for dietary supplement ingredients, similar to that currently required for drugs, is implemented at some point in the future.

Prevalence of Use as a Modifying Factor in the Screening/Flagging Step

Information about prevalence of use is not considered as a key factor, but it is used as a modifying factor for human data. Prevalence of use is considered in the screening of human data in that it may mitigate or exacerbate concern. That is, if an ingredient is widely used but few adverse events are spontaneously reported, it is less likely to be flagged than a rarely used ingredient with a similar number of spontaneously reported adverse events.

Prevalence of Use as a Modifying Factor in the Priority-Setting Step

The prevalence of use is considered in the priority-setting step only in establishing relative rank within a Priority Group. Within each Priority Group (explained in Chapter 5), items that are widely used are moved to the top of that Priority Group.

Prevalence of Use as a Modifying Factor in the Critical Evaluation Step

Prevalence of use is not considered in the critical safety evaluation step.

GUIDING PRINCIPLE FOR PREVALENCE OF USE DATA

Ingredients that are widely used by the general population should be given higher priority for critical safety evaluation than less widely used ingredients with similar degrees of safety concerns. This is consistent with the public health goal of producing the most impact from limited resources.

Use by Vulnerable Subpopulations

When considering the safety of supplement ingredients or other substances, it is important to consider that some individuals may be particularly vulnerable to adverse effects from certain supplement ingredients. Vulnerable subpopulations can be defined as groups of individuals who are more likely to experience an adverse event related to the use of a particular dietary supplement ingredient, or individuals in whom such events are more likely to be serious in comparison with the general population. Characteristics that contribute to such vulnerability may be physiological, disease-related, or due to other aspects, such as therapeutic interventions that are commonly utilized by the subgroup.

An example of a physiological characteristic that results in an individual's increased susceptibility compared to the general population is the change in the capacity for metabolism of various dietary supplement ingredients across the lifespan. Changes in metabolism may lead to variable concentrations of active compounds at sites of action and result in different responses.

For example, elderly individuals are a potential vulnerable subpopulation for some ingredients in that aging is associated with changes in the ability to digest, metabolize, or excrete some ingested substances (Munro, 1989; Rosenberg et al., 1989). Supplement ingredients that are normally cleared by, or altered by, the kidney or liver may potentially pose a greater risk to this subgroup than to a younger population. This factor should be considered for supplements specifically directed toward an older population. Children also metabolize some chemical substances differently than do adults, which for certain supplement ingredients might make children more susceptible to adverse effects and should be taken into consideration for any supplements marketed toward children. Likewise, differences in metabolism between children and adults may make children more resistant to adverse effects of certain substances (Guzelian et al., 1992). Infants have limited hepatic function that may make them particularly susceptible to certain hepatotoxic substances. Other age-related changes may involve receptors or kinetic parameters such as the volume of distribution. Physiological changes that occur during pregnancy may also influence susceptibility to adverse effects associated with particular supplement ingredients.

In addition to life stages that may alter responses to ingested substances, the presence of disease may also result in enhanced susceptibility to adverse effects from particular ingredients. For example, hepatitis or renal disease can significantly alter xenobiotic clearance, allowing compounds that are normally cleared rapidly to accumulate to toxic levels. People who are prescribed critical medications to be used on a chronic basis may be at greater risk of harm from drug interactions with various supplement ingredients. For example, people living with HIV/AIDS or other chronic diseases may be taking drug combinations that may interact with supplement ingredients, such as St. John's Wort, that alter cytochrome P450 activity (Ernst, 1999; Piscitelli et al., 2000).

Interactions between drugs and dietary supplements may be of particular concern when both are recommended for the same pathology and are thus potentially taken at the same time. For example, vitamin E supplements, which are often recommended to patients with atherosclerotic vascular disease, may have an interaction with statin drugs (Brown et al., 2001).

Disease or pre-existing conditions, such as hypertension, cardiac arrhythmias, or other early stages of cardiovascular disease, can also be expected to exacerbate susceptibility to products that specifically affect the organ exhibiting the disease or condition. Another example is the potential for supplements that affect insulin and glucose regulation to affect persons with diabetes. Thus, factors such as age, disease, pre-existing conditions, ethnicity, gender, or history of specific xenobiotic exposure such as pesticides can alter supplement exposure by altering pharmacodynamics and clearance of a drug. Alternatively, these factors may alter the dose-response, causing certain individuals to be more sensitive to a specific supplement than the majority of the population.

The paragraphs above describe several general reasons for particular susceptibilities. In addition, special concerns are warranted for supplement ingredients that may have teratogenic effects. Fetuses may be harmed if exposed to dangerous substances in utero as may infants if exposed to substances released into human milk. A well-known example is the teratogenicity of high doses of vitamin A and related retinoids in the periconceptual period (Eckoff and Nau, 1990; Lammer et al., 1985; Rothman et al., 1995). Animal studies or chemical characteristics may provide clues that fetuses or infants are particularly susceptible to other supplement ingredients as well.

In summary, certain segments of the population may be particularly susceptible to the effects of some supplement ingredients for a variety of reasons. When reviewing data, it is important to ask if ingredients are more likely to cause harmful effects to particular subgroups of the population. In the proposed framework, "vulnerable groups" are described as a modifying factor, in that whether identifiable subpopulations are particularly susceptible to harm should always be taken into consideration when assigning screening and priority-setting scores (see Chapter 5 for more details).

Vulnerable Subpopulation Information as a Modifying Factor in the Screening/Flagging Step

In examining the human data used to screen/flag dietary supplement ingredients, the reviewer should consider if the dietary supplement ingredient is being used by subpopulations that are particularly susceptible to serious adverse effects.

Vulnerable Subpopulation Information as a Modifying Factor in the Priority-Setting and Critical Safety Evaluation Steps

Particular susceptibility of identifiable subgroups of the population is taken into account when considering the scientific evidence (human, animal, structure/chemotaxonomy, and in vitro evidence) in this step, as noted in the description of scoring provided in Chapter 5.

GUIDING PRINCIPLE FOR VULNERABLE SUBPOPULATION DATA

When data indicate that an identifiable Subpopulation may be especially sensitive to adverse effects from a certain supplement ingredient, then this higher level of concern should be taken into account when scoring the ingredient.

New Ingredient Status

A new dietary supplement ingredient is one that was introduced to the U.S. market after October 1994, when the Dietary Supplement and Health Education Act was implemented. In this proposed framework, the notification of intent to market a new dietary supplement ingredient by a manufacturer automatically moves the ingredient through the screening/flagging step and on to the priority-setting step. Noting new ingredient status allows the ingredient to be considered during the priority-setting process in relation to other new ingredients and other ingredients flagged in the first step of the process.

If the new ingredient has been used in other countries there may be a considerable amount of clinical, animal, and in vitro data; data on serious adverse events; or data on usage patterns. If this type of information is not available, it is expected that considering the biological activity of related substances will be helpful in setting priorities in Step Two of the process. If the new dietary supplement ingredient is marketed after the 75-day notification period, more data may become available, and the priority level of the ingredient may change.

The rationale behind channeling all new ingredients directly into the priority-setting process is that the limited information on the other factors, especially human data, is no indication of

safety because the ingredient has not been marketed in the United States. Thus, the direct channeling of all new products to the priority-setting step assures that scientific data and theoretical prediction of harm are considered by the framework to some degree.

Use of New Ingredient Status in the Screening/Flagging Step

Consideration of new ingredient status in the screening/flagging step does not require that FDA actively collect information. The 75-day notification, which comes to FDA directly from the manufacturer, indicates that the item should be flagged and moved forward to the priority-setting step, simply by virtue of being a new ingredient about to enter the market.

Use of New Ingredient Status in the Priority-Setting and Critical Safety Evaluation Steps

New ingredient status is not considered in the priority-setting step or in the critical safety evaluation of an ingredient. The new ingredient status simply moves it into the priority-setting process, where the evaluation of evidence of the other key factors occurs.

SUMMARY

In summary, several different key factors and modifying factors should be taken into consideration when evaluating the safety of dietary supplement ingredients. The four primary key factors (data from humans and clinical evidence of harm, animal data, bioactivity of structurally related and taxonomically related substances, and in vitro data) contribute to different extents in the two first steps of the proposed process, screening/flagging and priority-setting, as compared to their contribution to the third step, the critical safety evaluation. The same holds true for the two modifying factors (prevalence of use in the population and use by vulnerable subpopulations). In Chapter 5, the processes for screening/flagging and priority-setting are described, with more suggestions about how different types of data are appropriately weighted when setting priorities. A systematic approach to this weighting process is described. After ingredients are categorized and prioritized, in-depth safety evaluations should be conducted for the ingredients with the greatest safety concerns (and which thus have the highest priority scores). Chapter 6 outlines a system for conducting these reviews and also revisits the guiding principles underlying the consideration of different types of data that were first outlined in this chapter.

REFERENCES

AIAI (Artificial Intelligence Applications Institute). 2002. *TOPKAT—The Open Practical Knowledge Acquisition Toolkit.* Online. University of Edinburgh. Available at http://www.aiai.ed.ac.uk/-jkk/topkat.html. Accessed June 19, 2002.

Bravo L. 1998. Polyphenols: Chemistry, dietary sources, metabolism, and nutritional significance. *Nutr Rev* 56:317–333.

Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ. 2001. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 345: 1583–1592.

Budzinski JW, Foster BC, Vandenhoek S, Arnason JT. 2000. An in vitro of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. *Phytomedicine* 7:273–282.

CDER (Center for Drug Evaluation and Research). 2002. *Guidance Documents.* Online. Food and Drug Administration. Available at http://www.fda.gov/cder/guidance/index.htm. Accessed May 2, 2002.

CFSAN (Center for Food Safety and Applied Nutrition). 1993. *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food. Draft Redbook II.* Washington, DC: CFSAN, Food and Drug Administration.

CFSAN. 2001a. *Overview of Dietary Supplements.* Online. Food and Drug Administration. Available at http://www.cfsan.fda.gov/-dms/ds-oview.html. Accessed February 22, 2002.

CFSAN. 2001b. *Toxicological Principles for the Safety of Food Ingredients. Redbook 2000.* Online. Food and Drug Administration. Available at http://www.cfsan.fda.gov/-redbook/red-toca.html. Accessed June 19, 2002.

Chyka PA, McCommon SW. 2000. Reporting of adverse drug reactions by poison control centers in the US. *Drug Safety* 23:87–93.

Counsell C. 1997. Formulating questions and locating primary studies for inclusion in systematic reviews. *Ann Intern Med* 127:380–387.

Eckhoff C, Nau H. 1990. Vitamin A supplementation increases levels of retinoic acid compounds in human plasma: Possible implications for teratogenesis. *Arch Toxicol* 64:502–503.

Ernst E. 1999. Second thoughts about safety of St John's wort. *Lancet* 354:2014–2016.

FDA (Food and Drug Administration). 1995. *Clinical Therapeutics and the Recognition of Drug-Induced Disease. A MedWatch Continuing Education Article.* Online. Available at http://www.fda.gov/medwatch/articles/dig/rcontent.htm. Accessed February 25, 2002.

FDA. 2002. *Good Clinical Practice in FDA-Regulated Clinical Trials.* Online. Available at http://www.fda.gov/oc/gcp/guidance.html. Accessed February 25, 2002.

Guzelian PS, Henry CJ, Olin SS, eds. 1992. *Similarities and Differences Between Children and Adults: Implications for Risk Assessment.* Washington, DC: ILSI Press.

ICH (International Conference on Harmonisation). 1995. *Guidance for Industry. E3. Structure and Content of Clinical Study Reports.* Rockville, MD: Drug Information Branch, CDER, FDA.

ICH. 1996. *Guidance for Industry. E6. Good Clinical Practice: Consolidated Guidance.* Rockville, MD: CDER, FDA.

ICH. 2001. *Guidance for Industry. S7A. Safety Pharmacology Studies for Human Pharmaceuticals.* Rockville, MD: Division of Drug Information, CDER, FDA.

ILAR (Institute of Laboratory Animal Research). 1996. *Guide for the Care and Use of Laboratory Animals.* Washington, DC: National Academy Press,

Ioannidis JPA, Lau J. 2001. Reporting of the safety of medications in randomized trials in neglected: An evaluation of 7 medical areas. *J Am Med Assoc* 285:437–443.

Ioannidis JPA, Chew P, Lau J. 2002. Standardized retrieval of side effects data for meta-analysis of safety outcomes: A feasibility study in acute sinusitis. *J Clin Epidemiol* 55:619–626.

Kingsbury JM. 1964. *Poisonous Plants of the United States and Canada.* Englewood Cliffs, NJ: Prentice Hall.

Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, Curry CJ, Fernhoff PM, Grix AW Jr, Lott IT, Richard JM, Sun SC. 1985. Retinoic acid embryopathy. *N Engl J Med* 313:837–841.

Lewis JA. 1981. Post-marketing surveillance: How many patients? *Trends Pharmacol* 2:93–94.

Liu XK, Katchman A, Ebert SN, Woosley RL. 1998. The antiestrogen tamoxifen blocks the delayed rectifier potassium current, IKr, in rabbit ventricular myocytes. *J Pharmacol Exp* Ther 287:877–883.

Moher D, Schulz KF, Altman DG. 2001. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Med Res Methodol* 1:2–8.

Munro HN. 1989. The challenges of research into nutrition and aging. Introduction to a multifaceted problem. In: Munro HN, Danford DE, eds. *Nutrition, Aging, and the Elderly.* New York: Plenum. Pp. 1–21.

Obach RS. 2000. Inhibition of human cytochrome P450 enzymes by constituents of St. John's Wort, an herbal preparation used in the treatment of depression. *J Pharmacol Exp Ther* 294:88–95.

OIG (Office of Inspector General). 2001. *Adverse Event Reporting for Dietary Supplements. An Inadequate Safety Valve.* OEI-01–00–00180. Boston, MA: OIG, Food and Drug Administration.

Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. 2000. Indinavir concentrations and St John's wort. *Lancet* 355:547–548.

Prevention Magazine. 2001. *Consumer Use of Dietary Supplements.* Emmaus, PA: Rodale.

Rosenberg IH, Russell RM, Bowman BB. 1989. Aging and the digestive system. In: Munro HN, Danford DE, eds. *Nutrition, Aging, and the Elderly.* New York: Plenum. Pp. 43–60.

Rothman KJ, Moore LL, Singer MR, Nguygen UDT, Mannino S, Milunsky B. 1995. Teratogenicity of high vitamin A intake. *N Engl J Med* 333:1369–1373.

Sackett DL, Haynes BR, Tugwell P. 1991. *Clinical Epidemiology: A Basic Science for Clinical Medicine.* Boston: Little, Brown. Pp. 283–302.

Scott HD, Rosenbaum SE, Waters WJ, Colt AM, Andrews LG, Juergens JP, Faich GA. 1987. Rhode Island physicians' recognition and reporting of adverse drug reactions. *Rhode Island Med J* 70:311–316.

Tegtmeier M, Harnischfeger G. 1994. Methods for the reduction of thujone content in pharmaceutical preparations of Artemisia, Salvia and Thuja. *Eur J Pharm Biopharm* 40:337–340.

U.S. Consumer Supplement Use Summary 1999. 2000. Online. *Nutrition Business Journal.* Available at http://www.nutritionbusiness.com/sub/consume.xls. Accessed March 1, 2002.

Wang WX, Ebert SN, Liu XK, Chen YW, Drici MD, Woosley RL. 1998. "Conventional" antihistamines slow cardiac repolarization in isolated perfused (Langendorff) feline hearts. *J Cardiovasc Pharmacol* 32:123–128.

Yang CS, Landau JM, Huang MT, Newmark HL. 2001. Inhibition of carcinogenesis by dietary polyphenolic compounds. *Annu Rev Nutr* 21:381–406.

Zabel M, Franz MR. 2000. The electrophysiological basis of QT dispersion: Global or local repolarization? *Circulation* 101:E235–E236.

5

Framework Steps One and Two: Screening/Flagging and Priority Setting

The proposed framework begins the evaluation of the safety of dietary supplement ingredients with a process of screening each ingredient and then flagging those that should receive highest priority for an in-depth critical safety evaluation. Using the factors described in Chapter 4, it is possible to utilize readily available information resources to aid in identifying those dietary supplement ingredients that warrant further evaluation and to prioritize them for the evaluation process. In this chapter the proposed general approach to setting priorities for review is described, followed by a discussion of how screening and priority setting can be done. It is assumed that the screening/flagging and priority-setting steps will be completed by Food and Drug Administration (FDA) staff, but FDA may instead choose to contract these processes out to a suitable scientifically based organization.

GENERAL APPROACH

The initial goal of the framework is to organize the factors described in chapter 4 into a structure that enables regulators to focus on the supplement ingredients that require the most attention. A three-step framework is proposed to focus such efforts. The three-step process consists of (1) screening and flagging based on readily available information, (2) priority setting based on analysis of available information, and (3) critically evaluating the data regarding safety of supplement ingredients. It is designed to help FDA first make initial judgments that reduce the large number of ingredients currently in the U.S. marketplace to a manageable number. The ingredients are then categorized by priority based on the greatest likelihood of potential harm. This will allow FDA to focus on conducting in-depth critical safety assessments for ingredients determined to be of high priority (Step 3, described in Chapter 6).

As was discussed in Chapter 4, data regarding key factors are used in one or more of the steps of the framework, but there are differences in how the different factors, modifiers, and new ingredient status are considered in each of the three steps. For example, new ingredient status is assigned an integral place in the screening/flagging step, but it plays no role in the subsequent safety assessment. In contrast, there are also factors that are not explicitly considered as discrete factors in the screening/flagging step but which may play an integral role in the priority-setting or critical safety evaluation steps.

In summary, the goal of Step One, screening/flagging, is to identify those supplement ingredients that could possibly cause harm. The goal of Step Two, priority setting, is to determine which of the ingredients identified in the screening/flagging step are of the highest concern and should therefore be placed at highest priority for a full evaluation. The goal of Step Three, critical safety evaluation (discussed in Chapter 6), is to provide a detailed review of what is known about the theoretical and demonstrated safety of a dietary supplement ingredient that would allow FDA to determine if further action is needed in regulating the ingredient in the marketplace.

STEP ONE: SCREENING/FLAGGING

The screening/flagging step was developed on the premise that it is not feasible for FDA to immediately search extensively for information about every dietary supplement ingredient. Readily available information can be used to flag substances that warrant further attention while maintaining enough sensitivity to minimize false negatives and not omit any items with potential safety concerns.

To flag substances warranting some level of attention, “yes or no” questions were developed to identify ingredients that should move forward to Step Two, the priority- setting step. A “yes” answer to any of the following questions flags the dietary supplement ingredient and moves it on to Step Two.

1. Has a 75-day new ingredient notification been filed with FDA?
2. Are there serious adverse events reported through MedWatch, poison control centers, or clinical studies that illustrate a pattern in terms of the type of incident reported, that are well-documented in the medical literature, or that may be plausibly linked to the dietary supplement ingredient? Or, does the number of serious adverse events reported appear high compared to the ingredient's prevalence of use? Or, does it seem plausible that particular subpopulations are particularly susceptible to serious adverse events reported for this dietary supplement ingredient?
3. Has the ingredient been brought to FDA's attention because of concerns other than new ingredient status or human adverse event data described above? (A preliminary evaluation of concerns that have come to FDA's attention will allow PDA to determine which of these ingredients should move into the priority setting process.)

The following are examples of “other concerns” that may bring an ingredient to FDA's attention for screening and possibly flagging, but this list is by no means exhaustive:

- Safety concerns from other groups or organizations that have evaluated substances currently on the market as dietary supplement ingredients. Examples of such safety concerns include compounds previously evaluated as drugs (including over-the-counter drugs), regulatory actions from other governments (e.g., Commission E), usage levels greater than the tolerable upper intake level values set by the Dietary Reference Intakes process (IOM, 1998), and information released by the Office of Dietary Supplements, National Institutes of Health.
- Strong evidence of serious interactions with prescription drugs.
- Evidence that the ingredient mimics hormonally active compounds.

- Communications, such as letters describing potential public health problems associated with a particular ingredient, brought to FDA's attention via consumers, consumer representative organizations, or scientific organizations. Likewise, this type of concern may come to FDA's attention through media coverage of a public health problem or new experimental data.

In some cases, reports coming to FDA through any of these mechanisms may indicate that contamination or adulteration of a dietary supplement ingredient may be associated with serious adverse events. Such cases should be directed to the section of FDA handling Good Manufacturing Practice issues for dietary supplement ingredients, rather than moving the ingredient forward to the priority-setting process in this framework.

In keeping with the philosophy that the screening/flagging step should be relatively simple and straightforward, answering the three screening questions does not involve evaluation or weighting of the evidence. A "yes" to any of the questions is sufficient to move the ingredient to the next step. The rationale for the questions is explained below.

New Ingredient Status

New ingredient status is the most straightforward of the screening questions. The reviewer asks if the ingredient is a new ingredient, marketed after the Dietary Supplement Health and Education Act (DSHEA) was enacted (after October 1994). According to DSHEA (see Chapter 1), FDA is to be notified of all ingredients *new* to the United States 75 days before they are marketed, so this information is readily available. As described in Chapter 4, the rationale for flagging all new ingredients and moving them to the priority-setting process is that (1) they are less likely to be associated with a history of safe use, and (2) there has been little opportunity for serious adverse events to surface, at least in the United States. There is also likely to be less scientific research on these ingredients, although this may not always be the case.

Human Data

Human data is the first key factor considered. In the screening/flagging step, upon learning of serious adverse events from a number of sources such as FDA's MedWatch reporting system, poison control center databases, published clinical studies and case reports, or secondary reviews of safety information, FDA flags the dietary supplement ingredient involved and moves it forward to the priority-setting process. Adverse events that warrant consideration are those that are "serious," as defined in Chapter 4. FDA makes an initial judgment about the reported events, but does not attempt to determine if there is causation or to validate the reports at this stage in the framework. To determine which ingredients are moved forward to the priority-setting step, FDA looks *tor possible* patterns in the type of events reported, for well-documented reports, and for reports that suggest a linkage between the ingredient and the event is at least plausible. Importantly, at this screening step, the reviewer asks whether the data suggest a *possible* problem rather than focusing on making a definitive judgment. While this strategy has the potential to overestimate ingredients causing possible harm, it is important to be inclusive at this point in the process.

In this preliminary evaluation of human data on serious adverse events, some consideration should be given to the usage patterns of the ingredient in question. Ingredients for which the number of serious adverse events relative to the prevalence of use seems high should be moved

forward. Likewise, the pattern of vulnerable group use should also be considered if data regarding their use come forward. If an ingredient is particularly marketed to, or preferentially used by, a particular subpopulation, and human data suggest particular susceptibility of this subpopulation to the biological action of the ingredient, it should be moved forward to the priority-setting step.

Other Concerns

The third screening category, "other concerns," recognizes that information regarding safety will come to FDA's attention for reasons other than new ingredient status or serious adverse events in humans. As discussed earlier, it is important for FDA to take advantage of sources of information that do not require detailed and time-consuming searches. Consumer protection organizations and the media bring forward information that they believe warrants FDA attention. This screening question allows FDA to consider this input and other concerns that come to its attention without judging the quality until it is examined more thoroughly in the priority-setting step.

FDA may also learn about other possible safety problems by perusing the safety concerns of other evaluative groups. For example, information can be gleaned about ingredients previously considered by other governments (e.g., Commission E in Germany), organizations conducting secondary reviews (e.g., the World Health Organization [WHO, 1999]), and texts describing historical patterns of use. The accuracy and reliability of the different secondary sources as arbiters of safety information may vary considerably, but when concerns are raised they warrant consideration.

It is not possible to list all the possible concerns that warrant moving an ingredient forward for consideration in the priority-setting step, but there are a number of concerns that definitely should flag a dietary supplement ingredient when FDA becomes aware of them. These include ingredients that mimic hormonally active compounds and ingredients that may interact with prescription drugs.

In summary, the screening questions given above are designed to use readily available information sources to flag ingredients for consideration in the priority-setting step. Information pertaining to serious adverse events in humans will require FDA to actively and regularly search primary information sources, but new ingredients and other concerns will either come to FDA's attention directly or will require only minimal information-gathering activities.

STEP TWO: PRIORITY-SETTING PROCESS

The goal of the priority-setting process is to identify those dietary supplement ingredients that require the most immediate attention of FDA for a more in-depth safety evaluation. The priority-setting process differs from the initial screening process in four fundamental ways:

- additional factors are considered;
- additional information about each factor is obtained through more active searching;
- a more evaluative judgment about the strength of the evidence and the level of potential harm is made; and
- the different factors are weighted differently, based on their comparative importance.

Thus, the most fundamental difference is that as a dietary supplement advances at each step in the process, it requires more information and there must necessarily be more evaluative input.

The factors to be used in the priority-setting process include:

- human data;
- animal data;
- biological activity of structurally related and taxonomically related substances;
- in vitro data suggesting potential risk of harmful effects; and
- prevalence of use.

It is assumed that FDA staff with enough experience to make initial judgments regarding the level of evidence of possible risk and seriousness of potential effects will conduct this activity. It is possible, however, that FDA may want to contract with a suitable scientifically based organization to conduct the priority-setting process.

General Description of How to Score Information

In the priority-setting process (Step Two), a sorting matrix can be used to categorize the variety of dissimilar ingredients according to their relative priority for review. For each of the supplement ingredients flagged in the screening process, the information for each of the four key factors (human data, animal data, data about the bioactivity of related substances, and in vitro data) is reviewed and assigned a score. These scores are 0, 1, 2, 3, or NAD when no appropriate data are available to evaluate the information. The four scores (one for each factor) for each ingredient are entered into a matrix (see Table 5–1).

The numerical scores are designed to reflect a judgment of the potential *seriousness,* and therefore *relevance,* of the physiological effect and the evidence of possible risk, which is derived from both the quantity and quality of the evidence reviewed. Specific guidelines are outlined for each factor later in the following section, but in general, the following scoring guidelines are employed, as illustrated in Figure 5–1:

- **A score of 3 is assigned for each factor where the data suggest both a potentially serious and very relevant harm and where there is a strong evidence of possible risk, or there is strong evidence suggesting a possible serious drug interaction.**

	Evidence of Possible Risk	
Potential Seriousness	High	Low
High	3	2
Low	1	1
None	0	

FIGURE 5–1 Scoring system.

- **A score of 0 is assigned when there is strong evidence that there is no *serious* harm.**
- **A score of NAD is assigned when no appropriate data are available.**

Scores of 1 and 2 are not explicitly defined but result from a judgment of the potential seriousness of the physiological effect and the evidence of possible risk. This is illustrated in Figure 5–1. For background information on each of the factors, including discussions of what constitutes strong evidence of possible risk, see Chapter 4.

As the information about a number of ingredients is scored, more cells of the priority-setting matrix are filled, as shown in Table 5–1 for fictitious ingredients. The matrix serves as an increasingly useful informational database for classifying information about the different ingredients. The matrix structure also enables the ingredients to be sorted based on their relative priority for further in-depth review. This sorting is described below, following the description of the relative priority of scores for each factor.

TABLE 5–1 Matrix of Scores Used in Establishing Relative Priority Among Dietary Supplements

Ingredient Name	Human Data	Animal Data	Biological Activity of Structurally Related or Taxonomically Related Substances	In Vitro Data
Yellow plant extract	3	1	2	2
Vitamin X	2	NAD	2	NAD[a]
Animal tissue	2	1	1	1

[a] NAD=no appropriate data.

Which Scores Indicate Higher Priority

A number of different sorting schemes could be developed to produce a ranking of ingredients categorized in order of priority for a full safety evaluation. The committee, recognizing that weights assigned to different factors could easily be arbitrary, deliberately chose not to assign explicit quantitative weights to the factors other than hierarchical ranking. In the proposed scheme, ingredients are ranked and categorized into priority groups by a sorting mechanism that reflects the hierarchical value of the different key factors. When available, concerns raised by human data are weighted more heavily than animal data, and are thus given higher priority. Concerns raised by either human or animal data are given greater weight than concerns raised by bioactivity of related substances or in vitro data, which are weighted equally.

Scores of 3 represent greater concern and therefore rank higher than scores of 2, 1, or 0. NAD scores always rank higher than 0. Because a score of 0 indicates that there is evidence suggesting no serious harm, and a NAD score indicates that there is no evidence, it is clear that NAD scores represent more reason for concern than scores of 0.

Does an NAD score cause more concern than some evidence of harm, as would be indicated by a score of 2 or 1? In the model presented here, a score of NAD is sorted as warranting more concern than a score of 1, but less concern than a score of 2 (e.g., as if it is assigned a value of 1.5). There are two exceptions to this rule: if either the data about bioactivity of related substances or animal data are scored as a 3, then a NAD score for human data is sorted as if it falls between scores of 2 and 3 (e.g., as if it is assigned a value of 2.5). How NAD scores are sorted compared to the numerical scores is summarized here:

- human data: 3, 2, NAD, 1, 0 if neither animal data nor bioactivity of related substances are scored as 3; or 3, NAD, 2, 1, 0 if either animal data or bioactivity of related substances are scored as 3
- animal data: 3, 2, NAD, 1, 0
- bioactivity of structurally related or taxonomically related substances: 3, 2, NAD, 1, 0
- in vitro evidence: 3, 2, NAD, 1, 0.

The sorting methodology can be further illustrated with examples. The following list indicates how an ingredient with a score of NAD in animal data would be sorted in comparison to three other ingredients. The ingredient with a score of NAD is sorted as if the NAD had a value of 1.5:

2–2–2–3
2–2–2–3
2-NAD-2–3
2–1–2–3

The following list illustrates how an ingredient with a score of NAD for human data and a 3 for animal data is sorted compared to three other ingredients. Because the animal data is a 3, the NAD value is given more weight and the ingredient with a score of NAD is sorted as if the NAD had a value of 2.5:

2–3–3–3
2-NAD-3–3
2–2–3–3
2–1–3–3

To further illustrate the sorting methodology, all possible scoring combinations are listed in order of priority in Appendix C.

Ranking Ingredients Within the Matrix: Using Scores to Sort Ingredients Into Priority Groups

The proposed mechanism for categorizing dietary supplement ingredients considers the scores for each factor to sort ingredients into priority categories named Priority Group I, Priority Group II, Priority Group III, and so on. These priority groups are illustrated in Table 5–2. The proposed sorting mechanism reflects the hierarchy of the different types of relevant scientific data reviewed (i.e., human data>animal data>data about bioactivity or structurally related and taxonomically related substances=in vitro data). It places highest priority on the ingredients for which there is strong human *and* animal evidence of possible risk of serious adverse events or serious drug interactions (i.e., scores of 3). Next priority is given to ingredients for which there is strong *human* data evidence of possible risk of serious adverse events or serious drug interactions, and then to ingredients for which there is strong evidence from *animal* studies of possible risk of serious adverse events or serious drug interactions, and so on.

This rationale is numerically reflected in the sorting of scores. First, dietary supplement ingredients with scores of 3 in the human data and animal data factors are grouped into Priority

Group I. There are 25 different score combinations that would be included in this priority group. Within Priority Group I, the 25 score combinations are ranked according to their scores in the bioactivity of related substances and in vitro data. These details are apparent in the in-depth scheme provided in Appendix C, which lists all possible combinations of scores and ranks them by priority.

TABLE 5–2 Matrix for Priority Establishment Based on Factor Analysis

Priority Group	Human Data	Animal Data	Bioactivity of Structurally Related or Taxonomically Related Substances	In Vitro Data	Number of Combinations (Total=625)	Characteristics of Priority Group
I	3	3			25	Two 3s in first two factors
II	3				100	3 in human data
III		3			100	3 in animal data
IV			3		144	One or two 3s in structure/ taxonomy or in vitro factors
				3		
V					256	No 3s in any key factor

Priority Group II includes ingredients with a score of 3 in the human data factor and less than 3 in the animal data factor. The 100 different score combinations within Priority Group II are sorted based on the scores in animal data, bioactivity of related substances, and in vitro data. Priority Group III includes ingredients that scored a 3 in the animal data section and less than 3 in the human data factor. Priority Group IV includes ingredients that have a score of 3 in the bioactivity of related substances factor *or* the in vitro factor. Finally, Priority Group V ingredients are ingredients that did not score a 3 in any of the categories. Within Priority Group V, ingredients are ranked as described above; that is, more weight is placed on human data, less on animal data, and even less on data about bioactivity of related substances and in vitro data. If, with use of this system, Priority Group V is found to encompass too many ingredients to be helpful, it could be further divided into subgroups V-1, V-2, and so on, following the pattern for defining the other priority groups.

All theoretically possible scores and how they fit into the different Priority Groups are listed in Appendix C. A number of these combinations of scores, or composite scores, are unlikely to occur because the combinations of data they represent are expected to occur infrequently, if at all. For example, the composite score of 0–0–0–3 (Priority Group IV) would be unlikely to occur very often, given the conflicting nature of the data that must exist to derive this score. That is, a 0–0–0–3 indicates that there are strong human data, animal data, and data about related substances, implying the ingredient causes *no* serious harm, but there is also strong in vitro evidence of harm in a highly predictive in vitro assay and evidence that harmful ingredients may reach sites of action where they can cause harm. At first glance the current approach might seem to inappropriately allow the in vitro data alone to place this theoretical ingredient in the Priority Group IV, but if this scenario does exist, the higher Priority Group IV classification provides an

opportunity for FDA to consider the disparity presented by the information before considering ingredients in Priority Group V with scores of 2s but no 3s.

Prevalence of Use: A Modifier of Sorting Within Priority Groups

Within each priority group, the prevalence of use is considered as a modifier of the available data. Ingredients with relatively high prevalence of use are shifted to the top of the ranked list within each priority group, so that they will receive attention first before those in the same priority group. "Relative prevalence of use" cannot be precisely defined, but it is suggested that lists of sales data and surveys about the use of particular ingredients be consulted, as described in Chapter 4.

Specifics on Assigning a Score for Each Factor

More information about assigning a score to each of the ingredients is provided below. Some examples for what is considered a higher priority (a score of 3) and what is considered a lower priority (a score of 1) are presented, recognizing that judgment comes into the process of scoring. Although judgment is important in setting scores, the scoring process enables the reviewers to consider the different factors independently and individually for each ingredient, taking advantage of all the data that are available. The system also enables FDA to develop an overall ranking for each ingredient—a ranking that is dynamic and can shift when more information becomes available. Finally, one could imagine that the composite scores of ingredients (such as 3–1–2–2 for the yellow plant extract in Table 5–1) might be used internally to summarize the preliminary information collected in the priority-setting step.

Scoring Human Data

Human data are considered from a different perspective in the priority-setting process, as compared to how human data are considered in the screening/flagging step. As with all the factors, the information is scored based on the potential seriousness of the harm and the evidence of possible risk. In the screening step, however, the effort is focused on examining evidence of only *serious* adverse events (as defined in Chapter 4), while in the priority-setting step all evidence of adverse events in humans is considered. Another difference is that in the priority-setting step, more time is invested in assessing the evidence that suggests adverse events. It will also be necessary to consider the human data for ingredients that were flagged for reasons other than evidence of serious adverse events in humans.

As shown in Figure 5–1, evidence of possible risk is considered in scoring human data. At this point in the framework, sufficient resources are unlikely to be available to determine causation, but the general guidelines outlined in Chapter 4 for considering causation should guide the judgment of the data quality and quantity.

The seriousness of the adverse effects or potential interactions is also important in scoring. In addition to considering the seriousness of potential harm to the general population and the strength of the data suggesting potential harm to the general population, it is also important to consider how particular subpopulations might be particularly vulnerable to adverse effects from the ingredient (as described in Chapter 4).

The following descriptions should be used as guidelines to score the human data, bearing in mind that some judgment is involved in scoring:

- A score of 3 should be given if there is strong evidence that there is a possible risk of potentially serious adverse effects or potentially serious drug interactions. *For example, well-documented cases of potentially serious adverse events in the medical literature, a strong pattern of similar potentially serious adverse events in MedWatch, action against a dietary supplement ingredient by another country's regulatory authority, clinical studies indicating potentially serious drug interactions, or multiple -well-documented case reports of potentially serious drug interactions.*
- Scores of 1 and 2 fall between 3 and 0 and thus are notably more subjective. Using Figure 5–1 as a guide, a score of 2 would be appropriate in a situation where the evidence of possible risk is limited but the potential harm is serious. Likewise, a score of 1 might be appropriate in situations when there is some evidence of possible risk, but the potential risk does not appear to be very serious.
- A score of 0 should be given if there is strong evidence suggesting no potential *serious* harm and no potential *serious* drug interactions (in most cases it is not anticipated that information about historical use would provide strong enough evidence to warrant a score of0).
- A score of NAD should be given if there is no appropriate data available to evaluate.

Scoring Animal Data

The consideration of animal data in the priority-setting step is very different from the consideration of animal data in the screening/flagging step. In the screening/flagging step, animal data are only considered if they come to FDA's attention. In contrast, FDA needs to actively look for the data in the priority-setting step. In this step, the scientific literature should be systematically searched for evidence of harmful effects in animal studies for all flagged ingredients. Sources for primary scientific literature include IBIDS, MedLine, Toxline, and other scientific literature databases. Other databases that focus particularly on natural ingredients (e.g., NAPRALERT) may also be useful for searching for evidence of adverse effects in animals. Finally, it is important to consult secondary or tertiary reviews that may cite older or foreign data that might otherwise be difficult to uncover using databases that do not capture pre-1960s or non-English literature. Reviews that may be helpful include those listed in Table 4–1.

After gathering information, the evaluation of animal data should be concerned with the same two components considered for human data: the evidence of possible risk, of which the quality and quantity of the data are components, and the seriousness of the harm. While all whole animal experiments may be informative, the nature of the experimental design, the quality of the methodology, and the statistical significance of the results need to be taken into consideration in scoring the evidence. When considering seriousness of harm, animal studies that predict serious harm or death warrant more attention, and thus higher scores, than those that predict mild, self-limiting effects on humans. It is not practical to list all animal data that predict serious effects in humans, but it is important to note that certain types of animal data should be considered serious because associations between these effects and consumption of particular ingredients are likely to be much more evident in animals than in humans. These effects include evidence of cancer, reproductive system effects, or developmental toxicity effects, including teratogenicity or other harm to fetuses.

Ingredients for which data indicate serious effects are scored higher than those with potentially less serious effects. Likewise, ingredients for which the evidence of risk is stronger

are scored higher than those with weaker evidence of possible risk. As discussed in Chapter 4, the strongest animal data result from experiments in which the ingredient is orally administered in a form similar to that used by humans. This characteristic is reflected in the scoring definitions below. As with human data, it is also important to consider how vulnerable subpopulations may be particularly susceptible to adverse effects observed in animals. The scoring guidelines outlined for animal data are analogous to those given for scoring human data:

- A score of 3 should be given if there is strong evidence that there is a possible risk of potentially serious adverse effects or potentially serious drug interactions. *Strong evidence is generated by experiments in which the ingredient is orally administered in a form similar to that used by humans. Serious harm includes effects that would eventually be reported as serious adverse events in humans and those effects that would not be readily detected from general human use or clinical trials.*
- As outlined earlier for human data. Figure 5–1 provides general guidance in judging whether a score of 2 or 1 is appropriate. A score of 2 would be appropriate in a situation where the evidence of potential risk is limited but the potential harm is serious.
- A score of 0 should be given if there is strong evidence suggesting no potential *serious* harm and no potential *serious* drug interactions.
- A score of NAD should be given if there are no appropriate data available to evaluate.

Scoring Data on the Biological Activity of Structurally Related and Taxonomically Related Substances

A dietary supplement ingredient may be structurally related or taxonomically related to substances with biological activity that cause concern. As with animal data, this type of data will be considered in the screening/flagging step if it comes to FDA's attention. In the priority-setting step, if the chemical structure of a dietary supplement ingredient or its component chemical compounds is known, FDA should actively look for information to determine if structurally related or taxonomically related substances are of known toxicological concern. This type of information can be gathered from sources such as *Medicinal Chemistry Reviews* or other journals. Chemicals that act as agonists or antagonists at the same receptors or other biological targets are likely to produce similar effects and should be considered as related chemicals, even if they are not structurally related in the strictest sense.

As described in Chapter 4, the plant genus itself may also provide clues about adverse effects. In the case of botanical dietary supplement ingredients, several key sources of information about plants should be consulted in the priority-setting stage. Texts that list poisonous plants by plant family, genus, and species are helpful in identifying harmful ingredients. *Poisonous Plants of the United States and Canada* (Kingsbury, 1964) lists egregious examples of harmful plants and also contains information helpful in identifying related plants. Additionally, several databases (e.g., NAPRALERT) provide pharmacological and toxicological information about plant compounds, which is helpful in identifying potentially dangerous substances by the taxa of botanicals.

When scoring information about the biological activity of structurally related or taxonomically related substances, several considerations are important:

- the ingredient's similarity in structure or taxonomic relatedness to a known harmful substance;
- the seriousness of harm caused by ingesting related substances; and
- the strength of the evidence suggesting that the related substance does cause harm.

Taken together, these components allow the data about the biological activity of related substances to be scored (see below). As in the case of other factors, scoring of this factor should take into account if and how a predicted adverse effect might particularly affect vulnerable subpopulations.

Scoring for the biological activity of related substances is analogous to the scoring schemes outlined for the factors above:

- *A score of 3 should be given if the ingredient has the same or similar structure, or putative biological target (e.g., receptor) as a known compound that causes potentially serious adverse effects or potentially serious drug interactions. Or, the plant-derived dietary supplement ingredient is of a related species and same genus as a plant for which there is strong evidence of possible risk for potentially serious adverse effects or potentially serious drug interactions.*
- As outlined earlier for human and animal data, Figure 5–1 provides general guidance in judging whether a score of 2 or 1 is appropriate. A score of 2 would be appropriate in a situation where the evidence that a related structure or plant causes harm is limited, but the potential harm is serious. Likewise, a score of 1 might be appropriate in situations when there is some evidence of possible risk, but the risk does not appear to be potentially very serious.
- A score of 0 should be given if there is strong evidence suggesting no structurally related or taxonomically related ingredient that causes serious adverse events or drug interactions.
- A score of NAD should be given if there is no available evidence about the structure of the substance or its taxonomy, or the biological activity of structurally related or taxonomically related substances.

Scoring In Vitro Data

In vitro data collected on flagged ingredients are scored in the priority-setting step in the same manner as the other factors described above. Information about in vitro effects can be obtained from the same sources as those for animal data (see Table 4–1). These sources include literature databases, other databases, and secondary and tertiary reviews.

In vitro data are considered in terms of the evidence of possible risk and the potential seriousness of harm suggested by the data. Predictive value is also considered for in vitro data; assays that strongly correlate with animal or human outcomes that are very harmful or serious are scored higher.

Scoring for in vitro data is as follows:

- A score of 3 should be given if there is strong in vitro evidence that there is a possible risk of potentially serious adverse effects or potentially serious drug interactions. *Strong in vitro evidence consists of (a) data from a validated assay that strongly predicts in vivo*

outcomes that are potentially serious or predictive of potentially serious drug interactions and (b) evidence that the potentially harmful substances are bioavailable. Examples of results from validated assays may include inhibition of mitochondrial oxidative phosphorylation, substantial cytochrome P450 inhibition, and evidence of slowed cardiac repolarization.

- As outlined for human and animal data, Figure 5–1 provides general guidance in judging whether a score of 2 or 1 is appropriate. A score of 2 might be appropriate when the evidence of possible risk is limited but the potential harm is serious. Similarly, a score of 1 might be appropriate in situations where there is some evidence of possible risk, but the potential harm does not appear to be serious.
- A score of 0 should be given if there is strong evidence suggesting no potentially *serious* harm and no potentially *serious* drug interactions.
- A score of NAD should be given if there is no appropriate data available related to in vitro assessment.

SUMMARY

In summary, each type of information available (human data, animal data, data about the biological activity of structurally related or taxonomically related substances, and in vitro data) is scored. These scores are derived by considering what the available information reveals about both the evidence of possible risk and the potential seriousness of harm. These scores are used to sort the dietary supplement ingredients into priority categories based on their priority for further safety evaluation. The result of the priority sorting may be modified by information on the prevalence of use.

REFERENCES

IOM (Institute of Medicine). 1998. *Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients.* Washington, DC:National Academy Press.

Kingsbury JM. 1964. *Poisonous Plants of the United States and Canada.* Englewood Cliffs, NJ: Prentice-Hall.

WHO (World Health Organization). 1999. *WHO Monographs on Selected Medicinal Plants, Volume I.* Geneva: WHO.

6

Framework Step Three: Critical Safety Evaluation of Dietary Supplement Ingredients

The screening/flagging and priority-setting steps outlined in the previous chapters will result in the identification of a group of dietary supplement ingredients that are of highest priority for further evaluation. This further evaluation requires the collection of additional information and critical analysis of the available safety data by the Food and Drug Administration (FDA) (Step 3 A), and then, if appropriate, analysis by an advisory committee (Step 3B). The process for this evaluation is described in this chapter. As with the two earlier steps of the process, these two steps may be organized by FDA or contracted out to an appropriate scientifically based organization.

STEP 3A: DRAFT MONOGRAPH PREPARATION AND REVIEW BY THE FOOD AND DRUG ADMINISTRATION

Step 3 A includes the preparation of a draft monograph and review of this monograph by FDA to determine if further input should be solicited. It is assumed that resources will initially be allocated to preparing monographs for substances ranked as higher priority in Step Two.

The process for Step 3A begins with completing the data collection (see Figure 3–1). Data will already have been obtained during the priority-setting step, but efforts should now be expanded to more comprehensively and systematically search for relevant information. The general types of information to be collected are listed in Box 6–1 (the monograph format) and include a description of the ingredient (e.g., constituents, different types of preparations, active components, traditional indications) and available information about toxicities and safety (human data, animal data, data describing the biological activity of structurally related or taxonomically related substances, in vitro data, and questions raised about the safety of the ingredient). Table 4–1 in Chapter 4 describes resources to be consulted in gathering safety information for this step, but this description is not exhaustive. For example,' additional information may be obtained by requesting information from clinical investigators who have published reports about the particular ingredient. Additional information may also be obtained from industry (e.g., distributors and manufacturers). At this stage in the review, there is sufficient concern about the safety of the ingredient to justify FDA's requesting that more safety data information be volunteered by industry. This request may be made through notice in the *Federal Register* and through the FDA website as a means to make the need for more information widely known to the

public. FDA should also directly request information from the manufacturers and distributors of the ingredient under consideration to the extent that manufacturers and distributors are known.

BOX 6–1 SAFETY REVIEW: MONOGRAPH FORMAT

I. INGREDIENT NAME
II. DESCRIPTION OF THE INGREDIENT, which includes the following:

- Constituents as appropriate: chemical structure; for a botanical ingredient, genus, species, part of plant
- Examples of products known to contain the ingredient
- Descriptions of different preparations (include U.S. Pharmacopeia process if available; country of origin, if known)
- Range of typical intake levels (where known, this will include recommended intake levels and data on actual intake)
- Description of active components, if known
- Traditional indications, if applicable
- Claim (label or other marketing information)
- Usage patterns (prevalence of use in the general population, use by vulnerable groups, use in combination with other ingredients)

III. AVAILABLE SAFETY INFORMATION AND EVALUATION

- Human data (serious and nonserious adverse effects)
- Animal studies
- Biological activity of structurally related and taxonomically related substances
- In vitro studies

IV. RESEARCH NEEDS
V. CONCLUSIONS

- Unresolved issues and uncertainties in the available data
- Recommendations and conclusions about the safety of the ingredient, based on the strength of the scientific evidence

VI. CITATIONS (including citations and hard copies of references used)

The collected information should be collated into a "draft dietary supplement ingredient safety review monograph," or simply "draft monograph." The monograph should be prepared using a standard format to summarize all the data collected on the ingredient (see Box 6–1 for an outline of the monograph structure).

After the draft monograph is prepared, FDA should consider the totality of the scientific evidence obtained. FDA should decide, based on the weight of the evidence, if the evidence is sufficiently clear to allow the product to remain on the market or if it is sufficiently clear to take action to limit marketing the ingredient. The guiding principles in Box 6–2, summarized from Chapter 4, should be followed for assessing and weighting the different types of evidence that enter into the decision.

BOX 6–2 GUIDING PRINCIPLES FOR CONSIDERING THE RELATIVE VALUE OF DIFFERENT TYPES OF INFORMATION

- **A credible report of a serious adverse event in humans that is associated with use of a dietary supplement ingredient raises concern about the ingredient's safety and requires further information gathering and evaluation. A final judgment about the safety of the supplement ingredient, however, will require consideration of the totality of the evidence. Historical use should not be used as prima facie evidence that the ingredient does not cause harm. It may be appropriate, however, to give considerable weight to a lack of adverse events in large, high-quality, randomized clinical trials or retrospective or prospective cohort studies that are adequately powered and designed to detect adverse effects.** The rationale for this statement is that adverse events might only be detected if readily apparent or specifically searched for. A study that does not systematically examine participants for adverse events and then publish this information is therefore of little value. In addition, some studies have insufficient statistical power to detect adverse events of low incidence.
- **Even in the absence of human adverse events, evidence of harm from laboratory animal studies can be indicative of potential harm to humans. This indication may assume greater importance if the route of exposure is similar (e.g., oral), the formulation is similar, and more than one species shows the same toxicity.** Particular weight is placed on evidence of certain types of delayed effects that are less likely to be detected in humans; these effects include cancer, teratogenicity, developmental toxicity, and reproductive toxicity. This evidence warrants particular attention as these nonacute effects are often only detectable in animals (as opposed to humans) because large doses can be administered subchronically or chronically to predict delayed effects following chronic exposure in humans.
- **The presence of a constituent that is structurally similar to known toxic or potentially harmful compounds or a plant that is taxonomically related to known toxic plants suggests increased risk, and therefore higher priority, unless there is evidence that the compound is not toxic or harmful, the compound is present in concentrations that will not lead to harm, or there is other evidence supporting the safety of the ingredient.**
- **In vitro studies can serve as signals of potential harmful effects in humans, but not as independent indicators of risk unless an ingredient causes an effect that has been associated with harmful effects in animals or humans and there is evidence that the ingredient or its metabolites are present at physiological sites where they could cause harm. Alone, in vitro data should serve only as hypotheses generators and as indicators of possible mechanisms of harm when the totality of the data from the different factors is considered.**

After considering the draft monograph and the totality of the evidence in the context of the guiding principles outlined above, FDA should either make a decision to take regulatory action, not to take regulatory action, or to refer the dietary supplement ingredient to an advisory committee of multidisciplinary expe rts for a safety review. Because only high-priority ingredients with significant potential for concern are likely to reach this evaluation stage, it is expected that FDA may want further input from an advisory committee on a number of dietary supplement ingredients.

STEP 3B: CRITICAL EVALUATION BY AN EXTERNAL ADVISORY COMMITTEE

Unless FDA has internal scientists with the appropriate expertise, it may be cost-effective to create an external advisory committee to provide further input on the safety of the dietary supplement ingredient. FDA may choose to have external advisors participate for one of a myriad of reasons, including,

- There is credible evidence that the ingredient may cause harm, but further review is needed by consultants with specific knowledge about the ingredient to interpret the totality of the data and derive conclusions and recommendations.
- Available evidence is of questionable scientific basis or difficult to interpret.
- Insufficient data are available to make decision-making obvious.
- A mechanism for public input is needed.

These reasons are only examples, as many other circumstances may trigger the decision for external advisory committee review. The decision to refer a dietary supplement ingredient to an external advisory committee rests with FDA and may be made for any reason that external expert opinion is deemed necessary or cost effective. The external advisory committee opinions or conclusions should be based on the information and data presented, but the decision on the regulatory consequences of the external advisory committee determinations must rest with FDA.

The decision to refer an ingredient for external review requires that a standing external advisory committee be established. To ensure that the critical evaluation of the monograph and related information is as free of conflict of interest and as objective as possible, the external advisory committee should be composed of expert scientists who, by training, education, and experience, constitute the most appropriate body to advise FDA. Box 6–3 lists several types of expertise that should be included. Importantly, external advisory committee members should be selected based on their disciplinary expertise rather than as representatives of stakeholder viewpoints. Advisory committee members should not have a financial stake in the outcome of the process or otherwise have a real or perceived conflict of interest. The external advisory committee should explicitly exclude representatives of the dietary supplement industry and its trade organizations. It is assumed that the organization assembling the external advisory committee will use standard practices to identify and avoid other types of conflict of interest as well.

The composition of the external advisory committee needs to include expertise in critical key disciplines, but still be small enough to be effective. One approach would be to have the external advisory committee be a standing committee of about seven persons, with the option to add one or two scientists with special expertise as needed for the review of individual substances. A second option would be to have a standing committee of five scientists representing the core disciplines, and the addition of three or four special experts depending on the nature of the substance and/or the data to be evaluated.

After the external advisory committee is assembled, it will assume responsibility for further refining the monograph drafted by FDA or the contractor. At this point, a draft monograph should be released, and the public should be provided with an opportunity to comment on the completeness of the data included, as well as the strength and relevance to humans of the different types of evidence. Industry and other stakeholders should be given time during meetings of the external advisory committee to provide input into the process.

BOX 6–3 ADVISORY COMMITTEE EXPERTISE

The Advisory Committee, either one constituted by FDA or by contracting with a scientifically based, nonprofit organization, should include individuals with the following expertise:

- toxicology, preferably with expertise in safety evaluation
- pharmacognosy
- clinical pharmacology
- nutritional science
- epidemiology
- biostatistics
- clinical trials
- medicinal chemistry and structure-activity relationships
- bioavailability
- pharmacokinetics
- consumer behavior related to dietary supplement use
- public health
- ad hoc consultants with expertise in specific fields on an as-needed basis (e.g., specialists needed to evaluate particular ingredients such as experts on oriental medicine, herbalists, clinicians with relevant experience).

After reviewing the information collected in the draft monograph and in the public information sessions, the external advisory committee should revise the draft monograph as needed to create as complete a picture of the scientific information available on safety as possible within the resources available to FDA. The advisory committee should evaluate this information and reach conclusions where possible, describing what is known about the safety of the ingredient based on the weight of the scientific evidence. The conclusions should describe

- the relevance of the evidence;
- the seriousness of the potential harm suggested by the evidence; and
- the quality and quantity of the evidence.

The advisory committee's conclusions should include comments about the risks and hazards that may be associated with use by the general population, as well as risks that may be particular to subgroups of the population. As much as possible, the advisory committee should describe how its conclusions may be dependent on how the ingredient is used—that is, the dose, manner, and form.

The advisory committee may conclude that there is little or no substantial evidence within the available information to suspect a hazard to the public when the ingredient is used at the recommended levels on the label, or at levels that might reasonably be expected. If current use does not demonstrate a hazard, the advisory committee may decide to comment on if it is possible to foresee whether a significant increase in consumption would constitute a hazard. If there is not enough information available to conduct a scientific evaluation of the safety of the dietary supplement, the advisory committee should indicate this. All conclusions should also be

accompanied by a description of additional research needed. If uncertainties exist that could be addressed by further study, the advisory committee should identify in detail what the uncertainties are and what types of studies could help resolve them.

After the advisory committee's conclusions are shared with FDA, the revised monograph and the advisory committee's conclusions should be posted on FDA's website. One of the important components of the Dietary Supplement Health and Education Act of 1994 was that the public should be educated about dietary supplements. FDA thus has a responsibility to educate consumers about the safety of supplement ingredients, and the public availability of the revised monographs can be an important aspect of the educational process. The monographs will provide the public with a reputable summary of the available information and scientific uncertainties about the inherent safety of the supplement ingredient. Importantly, public access to information from an advisory committee that is free of direct conflicts of interest will add to the quality and quantity of the available scientific literature.

An added benefit of making monographs easily available to the public is that industry and publicly funded scientists may choose to conduct studies that address the concerns raised, increasing the knowledge base of dietary supplement safety. The general public, as well as industry, pharmacists, health care providers, and distributors will benefit from the publicly available information and individually can decide whether to use, sell, or recommend the dietary supplement ingredient, even if FDA decides not to take action.

The monographs developed should not be considered static documents. New information should be added as it becomes available, and an organized process for adding information should be developed. The process should also include periodic reviews of monographs to determine if additional external reviews are appropriate.

OVERSIGHT OF MONOGRAPH PREPARATION AND REVIEW

Preparation of Draft Monographs

Collecting descriptive and safety information and organizing and summarizing the information into a draft safety monograph will require significant expertise and resources. Time and other resources required to complete the draft monographs are likely to vary, as some draft monographs will be extensive and others will be brief, depending largely on the amount of relative safety information available for the dietary supplement ingredient being considered. FDA may choose to prepare monographs internally, or it may choose to contract the work out to organizations, individuals, or both.

There are a number of academic, nonprofit, and for-profit organizations that have the resident expertise and administrative abilities to prepare monographs as directed by FDA. It is also possible that unbiased individuals without conflicts of interest could be identified to prepare draft monographs, but organizations are probably a more objective resource for monograph preparation. In addition, if FDA aims to obtain as many monographs as possible in the shortest timeframe acceptable, organizations rather than individuals may be more qualified.

The extent of time and effort devoted to preparation of monographs on dietary supplement ingredients will depend on FDA's prioritization of need. FDA could screen, set priorities, and then develop a complete list of substances warranting monographs first. Alternatively, FDA could retain one or more individuals or groups to develop monographs and determine the need for individual monographs on an ongoing basis as priority setting proceeds or as new needs emerge. The former approach may be more cost effective to implement, given that the latter

approach might not provide continuity in workload. However, preparing a list of priority substances to be monographed under contract will require more resources up front and will be dependent on information available at the time the list is prepared.

Assuming that draft monographs are prepared under contract, FDA may choose to directly monitor the monograph preparation done by individuals. Otherwise, it may choose to contract with an outside organization to administer and manage the monograph preparation process. The first approach involves direct control of the activities of the individuals preparing the monographs by FDA staff monitoring the contract deliverables, while the second delegates that responsibility to an outside organization.

Depending upon the type and expertise of the contracting organization, it is possible that additional aspects of the critical evaluation step could be carried out by the organization. The critical safety evaluation process described in this chapter includes provision for additional data and input to be provided by industry and other stakeholders. Typically, this input process involves announcement of the request for data and information, submission of written materials, and oral testimony at a public meeting. If FDA contracts with organizations that do not have the capability to conduct such activities, FDA would have to undertake these information gathering and collation activities itself for the contracting organization. However, if FDA contracts with an external scientifically based, nonprofit organization, this organization could administer and manage the monograph preparation process with the assistance of one or more individuals whose sole responsibility would be monograph preparation. This organization would conduct the public information gathering process, and monitor the preparation, publication, and dissemination of the draft monographs for review and submittal to FDA.

Additional advantages of this approach include relieving FDA of administrative management and increased public assurance that the draft monograph is as complete and as objective as possible. In addition, if FDA first develops an extensive list of substances warranting monographs, contracting with an external scientific organization would be an efficient method of managing the entire process and the simultaneous development of several monographs; such processes have been employed in the past.

The disadvantages of this tiered approach include the necessity for fiscal resources from FDA to support the ongoing administrative and monograph preparation processes. However, the absence of direct governmental control of the information gathering and expert evaluation process suggests this latter approach should be given serious consideration.

Management of the External Advisory Committee

As discussed above, FDA should consider each draft monograph developed either internally or by a scientifically based organization and decide if additional expert opinion would be helpful in evaluating the evidence. Therefore, in addition to determining who will be responsible for preparing draft monographs, FDA will also need to decide whether to establish or contract to have established an external advisory committee to develop conclusions and research needs and provide further input on the draft monograph.

If an external, as opposed to internal (i.e., made up of FDA scientists with appropriate backgrounds), advisory committee is established, several options for administrative management of the external advisory committee could be considered. One option is for the external advisory committee to be a standing subcommittee of the Center for Food Safety and Applied Nutrition's existing Dietary Supplements Committee, which is itself a subcommittee of the Food Advisory Committee. As such, external advisory committee members would be aware of ongoing issues of

wider interest regarding dietary supplements. However, the affiliations of persons on the Dietary Supplements Committee might make this approach difficult to carry out while assembling a group as free as possible from conflicts of interest. Time commitment might be a consideration in whether to include one or more members of the Dietary Supplement Committee. To be effective over time, the external advisory committee members should anticipate tenure of at least three years with at least four meetings per year. Administratively, the external advisory committee might have a workload analogous to the former Life Sciences Research Office Select Committee on GRAS Substances or a National Institutes of Health Study Section.

Another option is for the external advisory committee to be either a free-standing entity or to be an activity conducted by an external scientific organization under contract to FDA. If the external advisory committee were a free-standing entity that is disassociated from the monograph preparation process, there would be an increased burden of cost for its management. If the external advisory committee management and the monograph preparation are subsumed under one contract with a nonprofit, scientifically based organization, then administration and management might be less costly and have greater continuity. One advantage of separating management of the external advisory committee from FDA is that this approach would provide greater assurance to the public of the external advisory committee's independence and objectivity. The proposed process regarding development of the draft monograph and public input does not include consensus conclusions, but if FDA determines that consensus conclusions about the safety of dietary supplement ingredients are necessary, then there are additional advantages to contracting with an outside organization to facilitate the development of them. In this case, it would be necessary to identify an organization that has adequately experienced and knowledgeable scientific and administrative staff to manage both the monograph preparation process and the conduct of objective scientific evaluations. A limited number of scientific organizations have the capabilities to meet the administrative, managerial, and scientific requirements required for this approach.

SUMMARY

In summary, this chapter outlines a system for preparing monographs and conducting reviews of dietary supplement ingredient safety. FDA or a contractor of FDA would prepare the initial draft monograph that is a collection and review of available safety information. FDA would then determine whether additional input to the draft monograph would be helpful. If the data are not sufficiently clear for FDA to make a decision about whether to take action, or for any other reason, an advisory committee could be requested to review the information. An external advisory committee could be established to accomplish this task. The external advisory committee would review the draft monograph, determine if additional information should be collected, and hold sessions for input from the public. It would then modify the draft monograph as appropriate and make conclusions based on the evidence. The revised monograph, along with the external advisory committee conclusions, would be made public in an easily accessible format.

7

Attributes and Limitations of the Proposed Framework

The previous chapters propose a framework for screening/flagging, priority setting, and conducting a full safety evaluation for dietary supplement ingredients. This framework was drafted after considering systems used by other organizations for reviewing the safety and effectiveness of dietary supplement ingredients, and after considering frameworks that have been established to evaluate the safety of other types of substances, as described in Chapter 2.

ATTRIBUTES OF THE PROPOSED FRAMEWORK

There are a number of attributes of the proposed framework, and there are also a few limitations. This framework integrates the variety of available evidence about safety, balancing the value of different types of evidence and also integrating prevalence of use information to enhance the public health impact of the process. Using the framework, FDA can be both proactive and reactive, as well as provide an open and transparent process helpful to the general public and industry.

First and foremost, it is important to note that this framework focuses on how to consider the *safety* of dietary supplement ingredients rather than offering guidance on how to consider their *benefits and role in health.* This was a key point of the request to the Institute of Medicine from FDA, as is appropriate since dietary supplements are regulated as foods that are assumed to be safe, rather than as drugs requiring a risk-benefit analysis.

As mentioned above, a strength of the proposed framework is that it incorporates several different types of data that may be available, providing a mechanism to evaluate the totality of the available data—not just relying on one type, such as human data. Utilizing the diverse types of data available (i.e., the different "factors") is especially important because the extent of the types of data available are vastly different from one dietary supplement ingredient to another. Since FDA has no authority to require specific types of studies or data in advance of marketing, it is not possible to have available for safety review the same types of information regardless of the ingredient. Thus the integrative approach proposed is more useful than centering a framework on one type of data in establishing priorities and subsequently reviewing safety.

A somewhat distinct aspect of this framework, compared to the approaches taken by other organizations, is that it reflects a public health perspective that a supplement ingredient used by more individuals warrants greater attention, given similar safety concerns. The framework

reflects this perspective by integrating estimates of prevalence of use with the available safety information as part of the priority-setting step.

In addition to providing a method for integrating various types of information, the framework is also practical in that it allows FDA to be both proactive and reactive. The screening/flagging and priority-setting steps are reactive in nature, providing a mechanism for FDA to integrate new safety concerns into the existing priority scheme. The priority-setting mechanism can be initiated with limited information, but as additional resources are devoted to proactively searching for data, the level of concern characterized by the priority group to which a dietary supplement ingredient is assigned becomes increasingly accurate. As additional information about flagged ingredients becomes available, the information is used to update "scores" of dietary supplement ingredients that have not yet reached Step Three (the critical safety evaluation), easily updating and thus revising the ingredient's priority ranking. For example, it is easy to envision that a new clinical study may report serious adverse events for an ingredient, changing its score for human data from an NAD (no appropriate data) to a 3. The priority ranking of this ingredient relative to the others is easily adjusted to reflect this new information.

The practical nature of the framework is also reflected in the fact that it allows FDA to score each ingredient one factor at a time. Relative priorities can be set without having to simultaneously consider the entire array of each ingredient's safety concerns.

The critical safety evaluation step is designed to be as open and transparent as possible, so a mechanism for the public and the relevant industry to provide data and other input is provided. Keeping the activity open and transparent also allows the general public to be able to access safety conclusions made by scientists devoid of conflicts of interest. For this reason, the framework stresses the value of making safety reviews readily available to the public.

LIMITATIONS OF THE PROPOSED FRAMEWORK

In addition to the framework's attributes outlined above, there are also limitations inherent to the framework. By definition, the framework cannot be used to consider the possible benefits of consuming dietary supplement ingredients. Another limitation is that, as with any evaluation of dietary supplement ingredients under the current regulatory scheme, the framework's evaluation of safety depends on publicly available data or data voluntarily made available by industry and other groups. Another limitation of this framework is that a major component of it is human data, which unfortunately can be highly variable in quality and quantity.

The framework, especially through the priority-setting scoring process, seeks to evaluate explicitly the different components of the data—considering the evidence or possible risk, seriousness of harm, the hierarchy of data types, and the potential public health impact as distinct variables. This approach attempts to guide judgments made at the screening/flagging and priority-setting steps, but judgment of safety is in the end a subjective determination dependent upon expert interpretation of the totality of evidence.

The use of expert judgment via an external advisory committee may itself be another limitation, in that the number of qualified experts not associated with industry or the regulatory agency may be limited.

An additional limitation of the framework is the extent to which evaluation of the safety of any combination of dietary supplement ingredients can be conducted when the review is limited to available data. In the absence of having the authority to require manufacturers to present specific evidence of safety, the burden of conducting studies to ascertain adverse effects is

placed on FDA, which has limited resources compared to the number of the dietary supplements currently marketed.

SUMMARY

While the framework approach outlined here is not based entirely on empirical data, it should provide a mechanism for FDA to accomplish its goal of using a science-based approach to set priorities for evaluating the safety of dietary supplement ingredients given its available resources and the legislative authority under which it regulates the industry.

8

Dietary Supplement Ingredients Selected for Prototype Safety Monographs

The second phase of the Food and Drug Administration's (FDA) charge to the Committee on the Framework for Evaluating the Safety of Dietary Supplements is to, after proposing a framework for the safety evaluation of dietary supplement ingredients, develop at least six monographs as prototypes for the system outlined in the framework. Based on this experience and on comments received by industry and other stakeholders about the proposed process, the framework will be revised and included in a final report along with the prototype monographs.

These monographs are referred to as "prototypes" for several reasons. Because the six monographs are simultaneously being prepared within the timelines of the overall IOM project, the information collected is not expected to be as complete as what might be collected if FDA or another organization was specifically charged to undertake only the monograph generation. For example, the timeline of this project requires that industry and other stakeholders volunteer data within one month after the time the dietary supplement ingredients under consideration are announced. The sources of and process for systematically collecting information is also being considered during this process and is likely to be refined with experience.

CHOICE OF INGREDIENTS FOR PROTOTYPE MONOGRAPH DEVELOPMENT

The six supplement ingredients selected by the committee as the subject of prototype monographs are (in no particular order other than alphabetical): chaparral, chromium picolinate, glucosamine, melatonin, saw palmetto, and shark cartilage.

These six ingredients were selected to fulfill several criteria. One criterion, for example, is that the selections include at least one botanical, one vitamin or mineral, one animal product, and one hormonal product. Another criterion is that the selected ingredients include substances for which a range of different types of available information and a range in the quality of available information are anticipated. Finally, selected ingredients should not be undergoing safety research by committee members so as to possibly bias the review or interpretation.

The ingredients chosen for monograph development would be expected to be flagged in the screening/ flagging step and would therefore enter the priority-setting step. The selected ingredients would not necessarily be expected to be at the top of the priority list of all flagged ingredients, but a few are. The selected ingredients might have been flagged in Step One for a

variety of reasons, many of which fall under "other concerns." Chaparral has raised safety concerns from authoritative sources. In 1992 FDA issued a press release warning of a potential relationship between its use and liver toxicity (FDA, 1992), the MedWatch System has documented several adverse event reports (CFSAN, 1993; OSN, 2002), and the American Herbal Products Association's *Botanical Safety Handbook* (McGuffin et al., 1997) noted that Health Canada did not allow chaparral as an orally-administered, nonmedicinal ingredient. Possible liver problems were also mentioned in several other secondary sources of information (Foster and Tyler, 1999; NMCD, 2002). Glucosamine was flagged because secondary sources raised concerns about its use by persons with diabetes (Hendler and Rorvik, 2001, NMCD, 2002). Melatonin was flagged because of serious adverse events reported to the MedWatch system (OSN, 2002). Shark cartilage was flagged because the Committee was aware of a case report of hepatitis following ingestion (Ashar and Vargo, 1996), and it was selected to allow the committee to consider an animal product at this phase of the review. Saw palmetto was flagged because of two serious cardiac events reported to the Medwatch system (OSN, 2002). Finally, chromium picolinate was flagged because secondary sources mentioned that its use has been reported in renal toxicity cases (Hendler and Rorvik, 2001), and because secondary sources discussed its purported effect on insulin regulation and use by persons with diabetes (NMCD, 2002).

NEXT STEP

The next step of this IOM project is to collect safety-related data on these six ingredients from industry, consumer groups, and other interested parties, as described in Chapter 6. These data should be provided to IOM no later than one month after the proposed framework is released for public comment. The draft monographs summarizing the collected data and other available data will then be released for additional public input, with comments due in a short period of time.

Industry representatives, consumer protection advocates, and other stakeholder representatives will be invited to provide oral and written input at open sessions to be held in Washington, D.C. It is expected that these open sessions will be held in August and September 2002. The committee, with input from working groups and consultants on each ingredient, will release prototype monographs with conclusions about safety concerns and further research needed as part of the final revised framework report.

REFERENCES

Ashar B, Vargo E. 1996. Shark cartilage-induced hepatitis. *Ann Intern Med* 125:780–781.

CFSAN (Center for Food Safety and Applied Nutrition). 1993. *Illnesses and Injuries Associated with the Use of Selected Dietary Supplements.* Online. Food and Drug Administration. Available at http://vm.cfsan.fda.gov/~dms/ds-ill.html. Accessed July 9, 2002.

FDA (Food and Drug Administration). 1992. *Chapparal Warning.* P92–38. December 10. Press Release.

Foster S, Tyler VE. 1999. *Tyler's Honest Herbal. A Sensible Guide to the Use of Herbs and Related Remedies.* 4th ed. New York: Haworth Herbal Press.

Hendler SS, Rorvik D, eds. 2001. *Physician's Desk Reference for Nutritional Supplements.* Montvale, NJ: Thomson Medical Economics Company.

McGuffin M, Hobbs C, Upton R, Goldberg A. 1997. *American Herbal Product Association's Botanical Safety Handbook.* Boca Raton, FL: CRC Press.

NMCD (Natural Medicines Comprehensive Database). 2002. *Products.* Online. Available at http://www.naturaldatabase.com/products.asp?1tr=c. Accessed July 10, 2002.

OSN (Office of Special Nutritionals). 2002. *The Special Nutritionals Adverse Event Monitoring System.* Online. Center for Food Safety and Applied Nutrition, Food and Drug Administration. Available at http://www.cfsan.fda.gov/~dms/aems.html. Accessed July 11, 2002.

Appendix A

Other Approaches to Considering the Safety of Dietary Supplements

The following text provides an overview of the different approaches taken by other groups to consider the safety of dietary supplements. Please note that the summaries reflect information published or provided by the organizations involved, and do not reflect judgments or endorsements of the committee.

AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

The Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services aims to sponsor, conduct, and disseminate research to improve the quality and effectiveness of health care. Other federal agencies, private sector agencies, and Congress have asked AHRQ to review and evaluate the scientific information on specified topics to be used as the basis for clinical guidelines, performance measures, and other quality improvement tools. This AHRQ program is referred to as the Evidence-based Practice Centers, and it has produced "evidence reports" requested by other federal agencies on the effectiveness and safety of a limited number of dietary supplements. The San Antonio Evidence-based Practice Center (EPC) at the University of Texas Health Sciences Center, working under contract to AHRQ, has completed reports on garlic and milk thistle. In addition, the Southern California Evidence-based Practice Center/RAND is developing an evidence report on the clinical efficacy and side effects of ephedra.

The EPC evidence reports are based on a systematic analysis of the relevant scientific data. Other groups, such as the well-known Cochrane Collaboration, prepare and maintain similar evidence-based reviews. These reviews are based on a weighting/ranking methodology and are dependent on judgments that are based on well-defined criteria.

The first step of an AHRQ review is to identify relevant citations through what is intended to be an exhaustive search of the literature in a variety of electronic databases. Additional citations are identified from bibliographies, manufacturers, and technical experts. Both English and non-English references are included in the search. In general, only published full articles are used, but additional unpublished information provided by authors of published studies are also included.

Independent reviewers on the EPC staff read the titles and abstracts of all the identified citations and exclude those citations that do not meet certain selection criteria on types of participants, interventions, control groups, outcomes, and study designs. To assess adverse

clinical events, all types of human studies are used (e.g., randomized controlled trials, prospective trials, case-control, and cohort studies). Data are abstracted from the literature and analyzed by independent reviewers with clinical and methodological expertise. The analysis includes an assessment of the internal validity and quality of the studies. The data analysis includes generation of evidence tables, graphical summaries, statistical tests, and meta-analyses. The results and conclusions of the analyses are summarized in an evidence report that contains conclusions on the current knowledge on the efficacy and adverse effects of the substance and provides recommendations for future research. Reports are available on the AHRQ website (http://ahrq.gov).

Nominations for clinical topics to be reviewed by an Evidence-based Practice Center are solicited through notices in the *Federal Register.* Topics must meet specific selection criteria including high incidence; significance for the needs of Medicare, Medicaid, or other federal health programs; high cost; controversy about effectiveness; and availability of scientific data. Based on this process, the dietary supplements milk thistle and garlic, in addition to over 70 other nondietary supplement topics, have been reviewed (AHRQ, 2002).

U.S. PHARMACOPEIA-NATIONAL FORMULARY

The U.S. Pharmacopeia-National Formulary (USP-NF) develops and provides standards of identity, strength, quality, purity, packaging, and labeling of drugs sold in the United States in the form of standards monographs; these standards monographs do not consider the inherent safety of the substance. The USP standards are recognized by Congress in the Federal Food, Drug, and Cosmetic Act of 1938 (21 U.S.C. § 321 *et seq*.) as the official compendium of the United States, making its established standards for drugs essentially similar to federal regulations (USP, 2002a). From its first publication in 1820, the USP contained monographs for hundreds of botanicals; however, most of them were removed by the end of the 1930s due to the changes in medical practices and the arrival of synthetic organic medicinal compounds in the U.S. marketplace. In 1990, in response to a USP Convention Resolution, the USP Committee of Revision, an independent body of elected scientific experts representing industry, academia, and government agencies, established public standards for vitamins, minerals, and their combination products. These standards monographs, along with general chapters that include manufacturing practices for nutritional supplements, were grouped together and published within a separate section of the USP called *Nutritional Supplements.*

In 1995, after passage of the Dietary Supplement Health and Education Act (DSHEA), the USP Convention, in recognition of the resurgence in the use of botanicals by the American public, adopted a resolution that encouraged the USP Committee of Revision to establish public standards for botanical dietary supplements. In response to the Convention resolution, the USP Committee of Revision generated a list of approximately 20 widely used botanicals for public standards monographs. Criteria for identification of these botanicals included lack of safety risk, extent of use by consumers, interest from regulatory agencies, positive assessment by recognized pharmacognosists, and the ability of the botanical to meet typical requirements for USP monographs. History of traditional use and pharmacological action were also considered. Standards monographs are not developed for botanicals that the USP believes may be associated with a significant safety risk (USP, 2000a, 2002b).

Once a botanical has been approved for inclusion in the USP or NF[13], analytical methods are requested from several manufacturers and reviewed by the USP Expert Committee relating to dietary supplements. Before official adoption into USP-NF, public comment on proposed standards is generated by publicizing them in *Pharmacopoeia Forum* (Personal communication, V.S.Srinivasan, U.S. Pharmacopeia, February 11, 2001).

U.S. PHARMACOPEIA DIETARY SUPPLEMENT VERIFICATION PROGRAM

Distinct from its monograph development program, the USP launched its Dietary Supplement Verification Program (DSVP) in October 2001. This program's goal is to ensure that dietary supplement products contain the ingredients stated on the product label (Personal communication, V.S.Srinivasan, U.S. Pharmacopeia, February 11, 2001).

Dietary supplement manufacturers who pay to participate in the program will have their products reviewed by USP, and if the product meets the DSVP program requirements, the product will be granted a USP certification mark. This mark is intended to signify that the product contains the ingredients stated on the label in the declared amount and strength, meets stringent standards for product purity, meets specified limits on known contaminants, and has been manufactured under good manufacturing practices according to the USP-NF General Chapter on Manufacturing Practices for Nutritional Supplements and the FDA's Advance Notice of Proposed Rulemaking for good manufacturing practices (USP, 2001). Importantly, the DSVP certification mark is not intended to imply safety or efficacy of dietary supplement ingredients.

AMERICAN HERBAL PHARMACOPOEIA

The American Herbal Pharmacopoeia (AHP), a nonprofit organization, develops monographs on the quality, effectiveness, and safety of botanical medicines commonly used in the United States (Blumenthal, 1997). The monographs include botanicals with origins in Ayurvedic, Chinese, and Western traditions and includes information from both traditional and scientific sources (CRN, 1998; Upton, 1999). The monographs are intended to provide consumers, health professionals, and botanical manufacturers with the knowledge required for using and manufacturing botanical products safely and effectively, and to provide regulatory bodies and researchers with guidance for integrating botanical products into the health care system (AHP, 2001).

Selection of a botanical for monograph development can be made by three methods. A Prioritization Committee consisting of professional herbalists, botanical industry representatives, and herbal educators produces a list of priority botanicals based on the extent of their use or the unique value of the botanical. A second method is through monograph sponsorship. Because AHP seeks funding and technical support for development of monographs from interested organizations or companies, a sponsored botanical may be given higher priority than was assigned by the Prioritization Committee (AHP, 2001). Thirdly, AHP considers what other groups have done. If there is an existing monograph of a botanical on the prioritization list, AHP may use, with permission, relevant sections of that monograph as a starting point for its own monograph development (AHP, 2001).

[13] Whether a botanical monograph is admitted into the USP or its companion guide, the NF, currently depends on its approval status, as determined by the USP. If the botanical has an FDA- or USP-approved use, then standards are developed for it and it is published in the USP; otherwise, the standards for the botanical are published in the NF.

According to AHP, the first step in the development of an AHP monograph is a search of the primary literature. Primary literature is preferred, but secondary literature such as review articles may be used if considered acceptable or necessary. The search is not limited to English-language references. To address the safety of the botanical, a review of the toxicological literature is done and includes data on acute and chronic toxicity; use during pregnancy, lactation, fetal development, and driving; mutagenicity; teratogenicity; and carcinogenicity. All reported side effects, contraindications, and negative interactions are reviewed (AHP, 2001).

Next, each section of the monograph is assigned to a writer with expertise in that section area, and the writer is provided with the results of the literature search. Once the sections are drafted, the AHP editor and at least one other expert in the specific field reviews them. All the sections are then incorporated into an initial monograph draft. This draft is then circulated to a peer-review committee of botanists, chemists, herbalists, pharmacists, pharmacologists, pharmacognosists, and physicians (AHP, 2001). Reviewer comments are incorporated into the draft and the initial authors review and approve their sections. Before it is finalized for publication, the monograph is reviewed by an expert of either the botanical under review or the physiological system that the botanical affects (AHP, 2001).

AMERICAN HERBAL PRODUCTS ASSOCIATION

The American Herbal Products Association (AHPA) is a national trade association for the botanical products industry. In response to passage of DSHEA, AHPA convened a special subcommittee of their Standards Committee to address the need for a comprehensive review of safety data for botanical ingredients sold in North America. According to AHP A, the goal of this committee, which consisted of three natural product scientists and practicing herbalists, was to critically evaluate safety and categorize botanicals based on safety. These evaluations are published as *The Botanical Safety Handbook* (McGuffin et al., 1997).

The committee reviewed botanicals that were on the market in the United States, identified primarily by reviewing *Herbs of Commerce,* another AHPA publication (Foster et al., 1992). After identifying which botanicals to include, AHPA reported that its committee reviewed the available scientific literature for data on human and animal toxicity, traditional use, regulatory status in numerous countries, and current usage of herbs in the United States, China, India, Europe, and Australia. Notably, the committee also relied on its own and others' expertise and clinical experience for the evaluations.

There was no formal weighting of the data used for the evaluations; however, there were some exclusionary criteria. The monographs did not include the following data, conditions, or related products: excessive consumption, safety or toxicity concerns based on isolated constituents, toxicity data based solely on intravenous or intraperitoneal administration, traditional Chinese and Ayurvedic contraindications, gastrointestinal disturbances, potential drug interactions, idiosyncratic reactions in sensitive individuals, allergic reactions, contact dermatitis, well-known toxic plants that are not found in products on the market, homeopathic herbal preparations, essential oils, botanical products to which chemically-defined active substances had been added, or environmental factors, additives or contaminants.

The AHPA review committee followed guidance from the World Health Organization's (WHO) Programme on Traditional Medicines (WHO, 1991), which states that regulatory action is not necessary for traditionally used products that have not been shown to be harmful unless new evidence necessitates a risk-benefit assessment. The AHPA safety classification was based on an assumption of rational, informed use of botanicals and the committee stated that it

carefully considered the intended use of the substance within the historical context of that use (McGuffin et al., 1997). As listed in the exclusionary criteria above, the committee reported that it did not extrapolate toxicity data of isolated constituents and did not use data from studies that had excessive or irresponsible consumption patterns (McGuffin et al., 1997).

Once the committee reviewed all available information, the botanicals were assigned to one of four safety classes. Class 1 are botanicals that the AHPA committee believes can be used safely when used appropriately. Class 2 are botanicals for which certain restrictions apply (see subclasses) unless otherwise directed by an expert qualified in the use of the substance. Class 2a are botanicals only to be used externally. Class 2b are botanicals not to be used during pregnancy. Class 2c are botanicals not to be used while lactating. Class 2d are botanicals for which other use restrictions have been specified in the monograph. Class 3 are botanicals for which significant data exist to recommend special labeling: "to be used only under the supervision of an expert qualified in the appropriate use of this substance." Class 4 are botanicals for which the AHPC committee found insufficient data for classification.

NATURAL MEDICINES COMPREHENSIVE DATABASE

The publishers of *Pharmacist's Letter* and *Prescriber's Letter* created the Natural Medicines Comprehensive Database (NMCD) that is available online and in printed version (NMCD, 2002). The stated goal is to bring together in one place the consensus of the available data on natural medicines so that practitioners do not need to search multiple sources to find scientifically reliable and clinically practical information on botanical medicines and supplements for their patients. NMCD reports that it provides an assessment of the available data regarding safety and effectiveness of each natural medicine reviewed and that it covers nearly every natural medicine on the market in North America (NMCD, 2002). New product reviews are prioritized based on market saturation and requests by health professionals (Personal communication, P.Gregory, NMCD, February 21, 2002).

For each product that is reviewed, a research team of pharmacists, physicians, and pharmacologists begins the process with a literature search. Initially, when the database was first being developed, the research team consulted reference textbooks such as the *Commission E Report,* the *Physician's Desk Reference,* and AHPA's *Botanical Safety Handbook* for their evaluation of the literature. However, the research team soon turned to the primary literature using electronic databases such as Medline and Toxline to find the pertinent literature.

For the most part, the research team limited their search to English-language references. However, non-English articles of special significance are also included. For the safety evaluation, the team relied mainly on human data; animal data were rarely used (Personal communication, P.Gregory, NMCD, February 21, 2002).

After completion of the literature review, the information is evaluated and a consensus on any relevant issues is reached by the research team (NMCD, 2002), and then a single author drafts the reviews. The draft is then sent out for review to two or three pharmacists and physicians who were not on the research team. After this review, final drafts are added to the database (Personal communication, P.Gregory, NMCD, February 21, 2002).

Each product is rated according to specific criteria as: *likely safe., possibly safe, possibly unsafe, likely unsafe,* or *unsafe.* Natural products that are rated *likely safe* are those for which there is general agreement among reliable references that the product is safe when used appropriately or those for which a governmental body has approved their use. A product is rated *possibly safe* if the reputable references suggest that the product might be safe when used

appropriately or there are human studies that report no serious adverse effects. A rating of *possibly unsafe* requires that there is some data suggesting product use might be unsafe. *Likely unsafe* indicates agreement among reputable references that the product can be harmful or there are reliable reports of harm to product users. A rating of *unsafe* is based on finding general agreement among reliable references that the product should not be used, reliable reports of clinically significant harm to product users, or safety warnings issued by a reliable agency for the product. Special mention is made if use during pregnancy, lactation, or in children presents special concerns. Natural products that have different uses (e.g., oral versus topical use) may receive more than one rating (NMCD, 2002).

WORLD HEALTH ORGANIZATION

WHO has developed international specifications for medicinal plants that are the most widely used in an effort fill the need for current, authoritative information on their safety and efficacy. WHO has published the first volume of 28 monographs on selected medicinal plants (WHO, 1999). A second volume is in press, and a third volume has been approved and is in preparation. The medicinal plants and products in each volume of monographs were selected by a WHO advisory group based on the extent of each plant's use and importance throughout the world and on the sufficiency of the data available to evaluate safety and efficacy. The goal is to include information on safety, effectiveness, and quality control of botanical medicines. The monographs present descriptive information, purity tests, chemical constituents, medicinal uses, clinical studies, pharmacology, contraindications, warnings, precautions, adverse reactions, and posology.[14]

Each monograph was drafted under the direction of a team of experts in botanical medicines and medicinal plants. Information for the monographs was collected from a review of the literature, bibliographies, review articles, pharmacopoeias from several countries, reference books, and the NAPRALERT database. Once drafted, the monographs were reviewed by a large number of additional experts throughout the world with expertise in traditional medicine, drug regulation, drug evaluation, and pharmaceutical science. Finally, WHO convened a Consultation on Selected Medicinal Plants that consisted of 16 experts in medicinal plants and drug regulation to approve, modify, or reject the proposed monographs. WHO plans to periodically supplement and update the monographs as new data are made available (WHO, 1999).

COMMISSION E

In 1978 the Second Medicines Act in the Republic of Germany went into effect, requiring a scientific review of all medicines in the pharmaceutical market including conventional drugs and medicinal plants and phytomedicines. This resulted in the formation of a series of scientific commissions. Commission E was established by the German Minister of Health to review botanical drugs and preparations from medicinal plants. This 24-member committee was made up of physicians, pharmacists, nonmedical practitioners, pharmacologists, toxicologists, and biostatisticians (Blumenthal, 1998). According to the Commission E member consulted, at least 60 percent of the commission members had practical experience with phytomedicines (Personal communication, H.Schilcher, Commission E, March 19, 2002). The Commission completed its monograph work in 1994; however, it has met since 1994 to review drug registrations

[14] From the Greek, *posos,* (how much), representing the science or doctrine of dosing.

(Blumenthal, 1997). The monographs produced by Commission E have been compiled and published in English by the American Botanical Council (Blumenthal, 1998). This publication and input from Commission E also describes the process used by Commission E, in addition to input from a member of the Commission E as the basis for this summary (Personal communication, H.Schilcher, Commission E, March 19, 2002).

The stated objective of Commission E was to ensure that approved botanicals were reasonably safe when used according to the product label instructions and to remove unapproved botanicals from the market even if they only posed minor safety risks (Blumenthal, 1998). Commission E reviewed 378 botanicals used in German folk medicine for both safety and effectiveness (Blumenthal, 1997; Personal communication, H.Schilcher, Commission E, March 19, 2002). It was the manufacturer's responsibility to provide proof of quality (Blumenthal, 1998). Safety and effectiveness were assessed using the published scientific literature. Approximately 100 to 200 worldwide references were consulted for each botanical (Personal communication, H.Schilcher, Commission E, March 19, 2002).

The Commission considered data on traditional use, chemical composition, pharmacology, and toxicology and used data from clinical studies, in vitro and in vivo studies, field studies, epidemiological studies, case reports, and unpublished proprietary data submitted by manufacturers that included chemical, lexicological, pharmacological, and clinical testing data. The Commission also reviewed summaries produced by Kooperation Phytopharmaka (an umbrella organization of about 120 pharmaceutical manufacturers). These Kooperation Phytopharmaka summaries were based on literature reviews and clinical experience, but did not contain any recommendations about the product under review (Blumenthal, 1998).

According to the American Botanical Council's description, controlled clinical studies appear to have been considered the most useful type of data (Blumenthal, 1998). If no controlled studies were available, safety was evaluated based on other types of data such as well-documented review articles, older clinical trials, and well-documented knowledge of traditional usage. Blumenthal (1998) indicates that Commission E did not accept long-term therapeutic or traditional use as sufficient evidence of safety without additional data, and that field and case studies were only used when they had been evaluated according to scientific standards.

Once the Commission finished drafting a monograph for a botanical medicine, it was published and comments were solicited from scientists and other experts. The Commission then prepared a final draft of the monograph. Notably, the monographs do not include references. An unpublished justification with relevant references for the monographs are kept; however, these justifications cannot be accessed except in cases of legal disputes (Blumenthal, 1998).

Each substance was assigned one of three approval ratings: (1) positive (approved), (2) negative (unapproved), or (3) negative-null (unapproved). Positive/approved substances were considered reasonably safe when used according to the dosage, contraindications, and other warnings specified in the monograph. If safety concerns outweighed the potential benefits of a substance, the monograph was assigned a negative (unapproved rating). No dosage recommendations were provided for substances assigned a negative rating, and the intent of the Commission was the immediate withdrawal of these substances from the market. If no risk was found, but also no substantiated efficacy, the substance was designated as negative-null (unapproved). If manufacturers could later document the efficacy of such substances, the products could be approved; however, no new monographs would be produced (Blumenthal, 1998).

HEALTH CANADA NATURAL HEALTH PRODUCTS DIRECTORATE

In Canada vitamin and mineral supplements, herbal products, homeopathic preparations, and traditional Chinese, Ayurvedic, and native North American medicines are considered to be natural health products (NHPs). At present, there are no specific regulations for NHPs—they are regulated as either foods or drugs depending upon the active ingredient, the form of the product labeling, and the presence or absence of claims.

In 1997, in response to growing concerns about access to NHPs, the Minister of Health asked the Canadian House of Commons Standing Committee on Health to conduct a full review of how NHPs were regulated in Canada and how the government could better provide Canadians with the safety, quality, and freedom of choice that they were seeking. Following extensive consultation, the Standing Committee issued its report in November 1998. The report contained 53 recommendations, including the establishment of a new regulatory authority specifically for the regulation of NHPs.

In March 1999 the government accepted all of the recommendations of the Standing Committee and announced the creation of the Office of Natural Health Products (now the Natural Health Products Directorate) within Health Canada (the federal department of health) as the authority charged with developing and maintaining a regulatory framework for NHPs. An Expert Advisory Committee with expertise in medicine, biostatistics, nutrition, traditional medicines, herbs, aromatherapy, toxicology, biochemistry, botany, pharmacognosy, pharmacology, pharmacy, and homeopathy was appointed to support the work of the Directorate.

The Natural Health Products Directorate has proposed a regulatory framework for NHPs, which would be considered a subset of drugs under the Canadian Food and Drugs Act. The Natural Health Product Regulations were published in the *Canada Gazette, Part I*, for comment on December 22, 2001. One of the most complex issues in developing the regulatory framework has been defining what is and is not a natural health product (Personal communication, M. Cheney, Health Canada, June 11, 2002). The proposed definition of an NHP contains two parts: a function part and a substance part. The function part captures those substances that are manufactured, sold, or represented for use in the diagnosis, treatment, mitigation, or prevention of a disease, disorder, or abnormal physical state or its symptoms in humans; restoring or correcting organic functions in humans; or maintaining or promoting health or otherwise modifying organic function in humans. This part of the definition allows for the full range of claims normally associated with drugs.

The substance component of the definition is driven by the medicinal ingredient. There is an inclusion list of the substances that may be contained within NHPs and an exclusion list of substances that are not NHPs. The former list includes vitamins, minerals, amino acids and essential fatty acids, probiotics and plant or plant material alga, fungus or nonhuman animal material or an extract or isolate provided the primary molecular structure is not altered. Exclusions include antibiotics, biologies, and products administered by injection.

The main components of the proposed NHP Regulations are requirements for product licensing, site licensing, good manufacturing practices, clinical trials, packaging and labeling, and reporting of adverse reactions. Under product licensing, each NHP sold in Canada will undergo an assessment before it is authorized for sale. The application for a product license would be required to provide specific information about the NHP, including the quantity of medicinal ingredients it contains, the specifications, the intended use or purpose, and supporting safety and efficacy data. The Natural Health Products Directorate is developing standards of evidence that will indicate the type of information required to support various claims for NHPs.

In addition, the applicant for a product license would be required to show that the product will be manufactured, packaged, labeled, distributed, and imported in accordance with good manufacturing practices.

The regulatory framework proposed will provide for the conduct of clinical trials to allow the industry to test new products, including products that have not received market authorization, where no other data are available. The regulations would not place any requirements on the clinical trial investigator, who must be a health professional regulated by the laws of the province where the clinical trial site is located and whose scope of practice under those laws must be directly related to the subject matter of the clinical trial. The regulations do require, however, that one member of the Research Ethics Board of the study be knowledgeable in complementary or alternative health care. The regulations would require that the trial be conducted in accordance with good clinical practices and that adverse reactions be reported. Final regulations are expected by the end of 2002 (Personal communication, M.Cheney, Health Canada, June 11, 2002).

EUROPEAN SCIENTIFIC COOPERATIVE ON PHYTOTHERAPY

The European Scientific Cooperative on Phytotherapy (ESCOP) was created in 1989 to promote the scientific status of phytomedicines and the harmonization of their regulatory status in Europe. ESCOP is an umbrella organization of national associations for phytotherapy from countries both within and beyond the European Union. Monographs are produced by a Scientific Committee of ESCOP, a subgroup of delegates from participating member countries, with expertise in medicine, phytotherapy, pharmacognosy, pharmacology, and regulatory affairs (ESCOP, 2001). The goal is to compile monographs to provide information on the therapeutic uses and safety of botanicals that are widely used in European medicine and pharmacy (Blumenthal, 1997; ESCOP, 2001). Information on quality is not included in these monographs (Blumenthal, 1997).

The Scientific Committee, with assistance from researchers on specific plants, drafts the monographs by evaluating information from the published scientific literature (ESCOP, 2001). Once a monograph is drafted, it is reviewed by an independent board of supervising editors, consisting of academic experts in phytotherapy and medicinal plants. The monographs are then published as fascicules, each containing 10 monographs; 60 monographs have been published to date (ESCOP, 2001).

REFERENCES

AHP (The American Herbal Pharmacopoeia). 2001. *Monographs Defined. Developing Quality Control and Therapeutic Monographs: Monograph Prioritization, Development, Review, Finalization and the Value of Monographs to Health Professionals, Industry and Consumers.* Online. Available at http://www.herbal-ahp.org/mgdefine.html. Accessed November 12, 2001.

AHRQ (Agency for Healthcare Research and Quality). 2002. *Evidenced-based Practice Centers.* Online. Available at http://www.ahrq.gov/clinic/epc/. Accessed June 17, 2002.

Blumenthal M. 1997. Herbal monographs. *HerbalGram* 40:30–38.

Blumenthal M, ed. 1998. *Therapeutic Guide to Herbal Medicines. The Complete German Commission E Monographs* . Austin, TX: American Botanical Council.

CRN (Council for Responsible Nutrition). 1998. *Reference on Evaluating Botanicals.* Washington, DC: CRN.

ESCOP (The European Scientific Cooperative on Phytotherapy). *Publications. ESCOP Monographs.* Online. Available at http://www.escop.com/publications.htm. Accessed November 12, 2001.

Foster S, Moley T, Awang D. 1992. *Herbs of Commerce.* Austin, TX: American Herbal Products Association.

McGuffin M, Hobbs C, Upton R, Goldberg A. 1997. *American Herbal Product Association's Botanical Safety Handbook.* Boca Raton, FL: CRC Press.

NMCD (Natural Medicines Comprehensive Database). 2002. *About the Database.* Online. Available at http://www.naturaldatabase.com/aboutdb.asp. Accessed January 7, 2002.

Upton R, ed. 1999. *American Herbal Pharmacopoeia and Therapeutic Compendium.* Valerian Root, Valerian officinalis. Analytical, Quality Control, and Therapeutic Monograph. Santa Cruz, CA: American Herbal Pharmacopoeia.

USP (The United States Pharmacopeia). 2001. *USP Board of Trustees Agrees to Continue Proceeding with Pilot Program for Dietary Supplement Verification.* Online. Available at http://www.usp.org. Accessed October 31, 2001.

USP. 2002a. *USP 25-NF 20.* Rockville, MD: United States Pharmacopeial Convention, Inc.

USP. 2002b. *USP Fact Sheet.* Online. Available at http://www.usp.org. Accessed June 18, 2002.

WHO (World Health Organization). 1991. *Report of the Consultation to Review the Draft Guidelines for the Assessment of Herbal Remedies.* Munich, Germany, June 19–21, 1991. Geneva: WHO.

WHO. 1999. *WHO Monographs on Selected Medicinal Plants, Volume I.* Geneva: WHO.

Appendix B

Existing Frameworks or Systems for Evaluating the Safety of Other Substances

The following text provides an overview of existing safety frameworks that have been developed by federal agencies, industries, or other organizations. The descriptions are based on presentations to the committee and information provided by the organizations themselves; the descriptions are not the committee evaluations of the frameworks. These approaches are also listed in Table 2–2.

PREMARKET APPROVAL OF FOOD ADDITIVES

"Food additives" include an array of substances that accomplish a variety of technical effects in food. Included are direct food additives (e.g., artificial sweeteners), food-processing aides (e.g., antimicrobials), food contact substances (e.g., food packaging) and, by legal definition, sources of food irradiation. Under the 1958 Food Additives Amendment (FAA, P.L. 85–929), the Food and Drug Administration (FDA) has responsibility for the premarket approval of food additives.[15] The statute, as interpreted by FDA, establishes both the standard of data review (i.e., fair evaluation of the data of record), as well as the standard of safety (i.e., a reasonable certainty of no harm under the intended conditions of use). Notably, the statute exempts from premarket safety evaluation the use of substances in food that are "generally recognized as safe" (GRAS) by qualified experts in light of scientific procedures or, for substances used prior to 1958, in light of scientific procedures or experience based on common use in food. As discussed in the next section, FDA has in place a process for assessing the worthiness of claims of GRAS status.

FDA conducts safety assessments of new food additives under the principle of establishing a reasonable certainty of no harm by applying a decision framework. This framework uses a risk assessment approach that includes the compilation of available data and information, and the application of toxicological and other types of decision elements.

To assess safety, FDA first examines data on the additive's chemical identity and probable human exposure. The human exposure data yield the "estimated daily intake" (EDI) of the substance. This value is based on estimates of the probable intake of high-percentile eaters of the additive over a lifetime of exposure.

[15]In 1997 the Food, Drug, and Cosmetic Act (FDCA) was amended to provide for premarket notification, rather than premarket approval, for food contact substances.

FDA then reviews the available toxicology studies. It has developed guidelines (*Toxicological Principles for the Safety of Food Ingredients,* commonly known as The Redbook [FDA/CFSAN, 2001]) for food additive petitioners to use when assembling the required data in support of their petitioned use. The Redbook outlines the types of toxicological testing FDA normally expects to be provided in support of the food additive's safety, based initially on the additive's chemical structure and probable human exposure (The Redbook provides guidance and is not a requirement). Using this information, FDA assigns additives to initial "concern levels" (or "minimum testing levels") of I, II, or III. In its data review, FDA applies toxicological decision elements to further refine the scope of needed toxicological data.

From the animal studies FDA determines the highest level of intake associated with no adverse toxicological effects in the most sensitive, longest duration, most relevant animal study. This "highest no-effect level" is then divided by an "uncertainty factor" (or "safety factor"), often a factor of 100, to account for both intra- and interspecies variability. The resulting value is the acceptable daily intake (ADI) for the additive. The ADI is compared to the EDI to determine whether the proposed use of the additive is consistent with a reasonable certainty of no harm.

For some substances, the traditional risk assessment approach is not applicable. For example, an additive may be so toxicologically inactive that not enough of the additive can be orally ingested by the test animals to elicit a toxic response without perturbing normal nutrition. In such cases it is difficult to determine an ADI. FDA may then employ other types of decision elements. In these cases increased emphasis may be placed on, for example, chemical identity information and structure-activity relationships; data on absorption, distribution, metabolism, and excretion; and human tolerance studies (to look at physiological and nutritional responses).

Once all the information has been evaluated, FDA concludes whether the proposed use of a food additive is consistent with a reasonable certainty of no harm and can be safely marketed. After a new food additive is on the market, FDA may monitor the substance for safety through examination of available clinical studies and postmarket surveillance (Personal communication, A.Rulis, FDA, January 25, 2002).

SELECT COMMITTEE ON GRAS SUBSTANCES

Based on the 1958 FAA to the Federal Food, Drug, and Cosmetic Act, FDA developed specific processes to determine whether substances used in foods were safe for their intended use (see previous section). Food additives, as defined in the amendment, are subject to premarket approval by FDA unless they are GRAS or fall within another statutory exception (21 USC321(s)). Requirements for premarket approval are discussed in the previous section.

For about a dozen years after the passage of the FAA, FDA assumed a lenient approach to dealing with the GRAS exception. In the early 1970s however, in response to public concern about the apparent carcinogenicity of cyclamate, which FDA had listed as GRAS, FDA adopted a more rigorous approach (Degnan, 2000). In 1972 FDA contracted with the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology for assistance with a comprehensive review of GRAS substances. LSRO established a Select Committee on GRAS Substances that examined monographs on each substance that provided all known data on physical and chemical properties of the substance, human exposure data, animal and human toxicity data, and reports of special studies on mutagenicity, carcinogenicity, and teratogenicity of the substances. The Select Committee reached one of five conclusions on each GRAS substance reviewed: (1) continue as GRAS, (2) continue as GRAS with limitations, (3) uncertainties exist—issue interim food additive order requiring further testing, but continue as

GRAS until tests are evaluated, (4) evidence of adverse effects—establish conditions of safe use or remove GRAS status, or (5) inadequate data precludes evaluation—rescind GRAS status. The review was completed in 1982.

In 1972 FDA also established procedures for petitioning to affirm the GRAS status of a substance, which are still in use today. Currently, in order to achieve GRAS status for a substance not used in food prior to 1958, four key criteria must be met: (1) general recognition of safety by qualified experts, (2) the experts must have the scientific training and experience necessary to evaluate the safety of the substance, (3) experts must base their safety determination on scientific procedures, and (4) GRAS determination must fully consider the intended use of the substance (Hallagan and Hall, 1995).

In 1997 FDA proposed to replace the current GRAS affirmation petition scheme with one allowing any organization to notify FDA of a GRAS determination. The proposed rule would also clarify the types of evidence needed to establish GRAS status (Degnan, 2000).

GRAS DETERMINATION FOR FLAVOR INGREDIENTS: FEMA EXPERT PANEL

Because flavor ingredients are a type of food additive, the flavor industry has to adhere to the requirements laid out in the 1958 FAA. To determine GRAS status for flavoring substances, the Flavor and Extract Manufacturers Association (FEMA), the trade organization of the flavor ingredients industry, created its own independent expert panel. The FEMA Expert Panel, which has been reviewing flavoring substances since soon after the passage of the 1958 Amendments, includes qualified experts in toxicology, pharmacology, biostatistics, pharmacokinetics, biochemistry, pathology, nutrition, organic chemistry, medicinal chemistry, and metabolism (Woods and Doull, 1991). The panel evaluates the available data on safety and use of flavoring ingredients and assesses whether the ingredients meet the criteria for GRAS status.

The FEMA Expert Panel has developed a safety assessment evaluation process for determining GRAS status. Once an application for GRAS status is submitted to the panel with a complete literature search, the first step is preliminary assessment of the data for adequacy by FEMA staff. These data are then evaluated by the panel using the following criteria: (1) exposure to the substance in specific foods, (2) natural occurrence in foods, (3) chemical identity and chemical structure, (4) metabolic and pharmacokinetic characteristics, and (5) animal toxicity (Woods and Doull, 1991). The panel examines toxicity and metabolic data on structurally similar compounds (Hallagan and Hall, 1995) and considers the history of use of the substance (Hall, 2001).

Based on the weight of the evidence and expert judgment, the panel reaches one of three conclusions: (1) GRAS, (2) not GRAS, or (3) insufficient data to determine GRAS status. If data are insufficient, the panel will re-examine the substance after more data is available. The designation of GRAS status on a flavor ingredient must be based on a unanimous decision by the panel.

COSMETICS INGREDIENT REVIEW

As is the case for dietary supplements, there is also no premarket regulatory system for cosmetic ingredients other than color additives that are regulated directly by FDA. The Cosmetics Ingredient Review (CIR) Program was established in 1976 by the Cosmetic, Toiletry,

and Fragrance Association (CTFA) to review and assess the safety of cosmetic ingredients in the marketplace.

The CIR Program is funded by industry but its review process is independent and open to public and scientific scrutiny (Bergfeld and Andersen, 2000). Approximately 2,800 cosmetic ingredients were on the market in 1976 when the CIR Program was established. In response, the CIR Program developed a system to prioritize these ingredients before performing the safety review. First it excluded or deferred ingredients being reviewed by other groups, such as fragrances and ingredients being evaluated by FDA, including color additives and over-the-counter drug ingredients. The CIR Program then grouped the remaining ingredients into chemically-related families and prioritized based on the following factors: frequency of use, ingredient concentration in cosmetic products, area of human exposure, number of products containing the ingredient used by sensitive population subgroups (such as infants and the elderly), biological activity, frequency of consumer complaints, and skin penetration. Using a ranking methodology, ingredients were given a weighted score based on these factors and were then reviewed in priority order. Frequency of use and biological activity were given the most weight in the ranking. This priority listing and ranking methodology is updated periodically.

The safety review starts with a comprehensive literature search by CIR staff. The staff summarizes the available published data and publishes the summaries for public comment. During a 90-day period, interested parties may submit comments or additional data.

Following this comment period, a CIR Expert Panel begins its review of the collected data and determines whether more data are needed. The panel consists of seven scientists and physicians who serve as voting members and three nonvoting liaison members, representing the CTFA, FDA, and Consumer Federation of America. CIR emphasizes that voting members are careful to avoid any perceived or real conflicts of interest. Liaison members serve to keep consumer groups, FDA, and the industry informed of the panel's deliberations.

If additional data are required, an informal request is directed toward the cosmetic industry. If data are not forthcoming or are still inadequate for the safety assessment, a formal request is made. Once all the necessary data are received, the panel reviews them and produces a tentative report that is released for public comment. At the end of the comment period, comments are considered and the final report is written.

In determining safety for the final report, the panel looks at all the available data, considers structurally similar substances, and relies on panel members' experience and expertise. The data needed for the safety assessment are dependent on the particular ingredient under review. However, the panel usually considers chemical and physical properties, impurities, extent and type of use, concentration of use, subchronic or chronic toxicity, skin penetration, skin irritation, and skin sensitization.

In each final report, the CIR Expert Panel reaches one of four conclusions on the safety of a cosmetic ingredient: (1) safe as currently used, (2) safe with qualifications, (3) unsafe, or (4) insufficient data. If data are considered insufficient, the panel notes what data are lacking. In practice, this conclusion of insufficient data encourages manufacturers to undertake additional studies.

NEW DRUGS

Unlike dietary supplements, premarket approval of new drugs places the burden of proof regarding safety on industry rather than on FDA. The evaluation of new drugs, new uses for approved drugs, and classification of over-the-counter drugs is an intensive interactive process

that evaluates both safety and efficacy. Manufacturers that want to develop and market a new drug must follow the FDA approval process that is modeled on a risk-benefit approach. Approval of a new drug requires extensive studies of the chemistry, manufacturing, and controls of the drug as well as toxicology and pharmacology of the compound in animals, and clinical trials of effectiveness and safety in humans. The timeframe and resources for this process are extensive (Food and Drugs, 21 CFR § 300, 2001).

A key initial step in the drug approval process is submission by the manufacturer of an Investigational New Drug (IND) application to FDA. The IND is a large collection of information that enables FDA to review the safety of the substance before clinical testing in humans is allowed to begin. The IND describes the ingredients, synthesis, manufacturing, purity, and microbiology of the drug product, as well as the stability, packaging, and labeling. Also included in the IND are data from rodent and nonrodent animal studies, such as pharmacokinetic and pharmacodynamic data from animal studies, genotoxicity studies, carcinogenicity studies, reproductive and teratogenic studies, and other toxicological data. When available, the application also includes published or unpublished human data. Because these data help FDA determine whether the human testing process will be allowed to proceed, the manufacturer also provides protocols outlining the Phase I, II, and III clinical studies it plans to conduct. After the IND is submitted, FDA has 30 days to review its content. If FDA does not contact the sponsor within that time, the proposed Phase I study may begin (Food and Drugs, 21 CFR § 312, 2001).

During Phase I studies, which focus on safety but not efficacy, human volunteers (who are usually healthy) are carefully monitored for tolerability, and pharmacokinetic data are often collected. The aim of Phase II is to evaluate the dose-response relationship and effectiveness of the drug in a few hundred subjects who have the disorder the drug is intended to treat. These studies are usually double-blind and placebo-controlled to minimize investigator and subject bias. Phase III of the investigation consists of well-controlled trials to gather evidence on both effectiveness and safety of the drug and information needed for labeling. These are large trials of several hundred to several thousand subjects.

The data collected in all of the clinical studies enable FDA to approve or disapprove a drug based on a risk-benefit analysis. Once a drug is approved and marketed, additional safety information continues to be collected through mandatory submission of adverse event information from the manufacturer to FDA via MedWatch and other reporting mechanisms. FDA may also require the manufacturer to conduct postmarketing studies.

OVER-THE-COUNTER DRUGS

The process above describes the steps required for a new drug approval (NDA). In the years after proof of effectiveness was added to the NDA requirements, FDA wrestled with how to deal with the thousands of over-the-counter (OTC) drugs that were on the market though not covered by approved NDAs. Rather than make case-by-case challenges to such products, FDA decided to review them by therapeutic class, with the assistance of expert advisory committees. The process that FDA established to accomplish this mission is known as the OTC Drug Review.

In 1972 FDA, with the help of 17 advisory panels, began its review of the more than 700 active ingredients with almost 1,500 uses in marketed OTC drug products. The aim of the review was to prepare monographs establishing the conditions under which OTC drugs would be considered generally recognized as safe and effective and not misbranded, and thus exempt from the NDA process.

The OTC Drug Review consists of several phases. In the first phase, now complete, the advisory panels made recommendations regarding the categorization of products. Category I was for those drugs that the panel deemed to be generally recognized as safe and effective and not misbranded if they satisfied specified conditions, including, among others, active ingredients and labeling indications. Category II was for products with active ingredients, labeling claims, or other conditions that resulted in them not being generally recognized as safe or effective or resulted in them being misbranded. Category III was for products with active ingredients, labeling claims, or other conditions for which the data were insufficient and for which further testing was thus required.

In the second phase of the review, FDA published the panels' recommendations as Advanced Notices of Proposed Rulemaking (ANPRs). These ANPRs included proposed monographs establishing the conditions under which OTC drugs in specific therapeutic classes would be generally recognized as safe and effective and not misbranded (Category I). In the third phase, after considering the public comments received in response to the ANPRs, the agency issued proposed rules designated Tentative Final Monographs (TFMs). In the final step of the process, the agency, after receiving further comments, publishes final monographs. As of March 1, 2001, most, but not all, of these final monographs had been published (CDER, 2001). Final monographs set forth the mandatory conditions for an OTC drug to be considered generally recognized as safe and effective and not misbranded, including active ingredients, dosages, permitted combinations of ingredients, warnings, and labeling requirements.

NEW CHEMICALS PROGRAM

Under the New Chemicals Program, the Environmental Protection Agency (EPA) is given the authority to regulate the entry and use of new chemicals into the U.S. marketplace. This program, mandated by Section 5 of the Toxic Substances Control Act (TSCA) in 1976, seeks to manage the potential risk from new chemicals both to humans and to the environment. Manufacturers or importers of new chemicals are required under TSCA to notify EPA through a premanufacturer notice (PMN) that must be submitted at least 90 days prior to manufacture or import of the new chemical. New chemicals are defined as those that are not listed on EPA's TSCA Chemical Substance Inventory of existing chemicals. The burden of proof for identifying risk rests with EPA.

EPA receives petitions for approximately 2,000 new chemicals from manufacturers each year (Personal communication, L.Scarano, EPA, October 11, 2001). At submission, the manufacturer provides the PMN, which includes information on chemical and physical identity and properties, product uses, proposed production or importation volume, by-products, human exposure, disposal practices, environmental releases, pollution prevention efforts, and available information on health or environmental effects. A multidisciplinary team of experts is responsible for reviewing the information provided in the PMN for safety. The first step is to determine whether the substance is already on the TSCA inventory. If not already on the inventory, the team then evaluates chemical structure, how the chemical is synthesized, the intended use of the chemical, and the physical and chemical properties of the chemical. They also check for analogs in an EPA analog database. About 30 percent of the applications are not reviewed after this stage; these substances consist of polymers, which because of their molecular weight and other properties are considered unlikely to present significant hazard potential.

The next step of the process is to estimate the potential environmental and health hazards using analog analysis, quantitative structure activity relationship models, and expert judgment.

The structure activity team has identified 54 structural alert categories that may indicate a potential concern for chemicals that fall into these categories (Personal communication, L. Scarano, EPA, October 11, 2001).

The third step is to prioritize the results of the safety evaluations and to decide if further review is warranted. If further review is required, the next step is a more detailed standard review. In this step, a risk assessment is conducted, human health hazard information is evaluated, and the chemical is assigned a qualitative determination of the hazard concern level. Evidence of adverse effects in human populations and conclusive evidence of severe effects in animal studies constitute a high hazard concern level. A moderate level of concern results from suggestive animal studies and analogue data and knowledge that the chemical class has produced toxicity. The low concern level is for those chemicals for which no concern was identified. At this point, depending on the hazard concern level and considering the estimated exposures and releases, EPA will inform the manufacturer that the chemical presents potential risk issues and that more testing is needed. If EPA does not act to regulate the chemical, the manufacturer may commence production or importation.

TOLERABLE UPPER INTAKE LEVEL MODEL FOR NUTRIENTS

A risk assessment model for nutrients has been developed by the Food and Nutrition Board of the Institute of Medicine (IOM, 1998). This model is consistent with contemporary risk assessment practices and results in a characterization of the relationship between the exposure (intake) of a nutrient and the likelihood of adverse health effects in exposed individuals. The Tolerable Upper Intake Level (UL) is defined as the “highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases” (IOM, 1998).

Determination of the UL is one aspect in the process for determining nutrient-based reference values, known as Dietary Reference Intakes (DRIs), that is being undertaken by the Food and Nutrition Board. DRIs are comprised of the Recommended Dietary Allowance (RDA), the Adequate Intake, the Estimated Average Requirement, and the UL. The UL model differs from the process for determining the RDA because the RDA is a recommended intake whereas the UL is an intake level that individuals should not exceed on a chronic basis. Evaluation of data to establish a UL are completed for all nutrients that are being reviewed in the DRI process, but not all nutrients have ULs; for some nutrients insufficient data is available upon which to base a UL.

The UL model for nutrients is a four-step process. The first step is hazard identification. At this step a thorough literature review is performed for each nutrient and all information pertaining to the adverse effects of chronic intake is examined and evaluated. Data from human, animal, and in vitro studies are used to address evidence of adverse effects in humans, causality, relevance of experimental data, pharmacokinetic and metabolic data, mechanisms of toxic action, quality and completeness of the data, and identification of sensitive populations. Scientific judgment of the committee members responsible for developing ULs is key to reaching a conclusion on the nutrient's ability to cause an adverse effect in humans when consumed on a chronic basis.

The next step is a dose-response assessment to determine the relationship between nutrient intake and the adverse effect. In this step, the most critical data sets for deriving the UL are selected. Human data are preferable to animal or in vitro data for evaluating adverse effects. The route of exposure, magnitude and duration of exposure, and the critical endpoint are identified. A

no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) are determined based on these factors if data are available to do so. Next, an uncertainty factor is applied to the NOAEL or LOAEL. The uncertainty factor is based on expert judgment of the uncertainties of extrapolating from the observed data to the general population. Dividing the NOAEL or LOAEL by the uncertainty factor results in the UL.

The third step is an assessment of the range and distribution of intake or exposure of the nutrient or food component in the general population. If the adverse effect appears to be associated with intake from dietary supplements only, then the UL is for supplements only. It is clearly indicated whether the UL is for total intake, intake from supplements only, or intake from fortified foods and supplements.

The last step is a characterization of the risk. The range of reported intakes of the nutrient is compared with the UL. If a large fraction of the general population is consuming chronic intakes above the UL, this could be a potential at-risk group. The UL does not include policy decisions, but the rationale suggests risk management guidelines for determining the significance of the risk to a population consuming a nutrient at levels above the UL.

REFERENCES

Bergfeld WF, Andersen FA. 2000. The cosmetic ingredient review. In: Estrin NF, Akerson JM, eds. *Cosmetic Regulation in a Competitive Environment.* New York: Marcel Dekker. Pp. 195–216.

CDER (Center for Drug Evaluation and Research). 2001. *Milestone Status of OTC Drug Review Documents as of March 1, 2001.* Online. Food and Drug Administration. Available at http://www.fda.gov/cder/otc/milestone/pdf. Accessed March 28, 2002.

CFSAN (Center for Food Safety and Applied Nutrition). 2001. *Toxicological Principles for the Safety of Food Ingredients. Redbook 2000.* Available at http://www.cfsan.fda.gov/~redbook/red-toca.html. Accessed March 28, 2002.

Degnan FH. 2000. *FDA's Creative Application of the Law.* Washington, DC: Food, Drug, and Law Institute. Pp. 19–26.

Hallagan JB, Hall RL. 1995. FEMA GRAS—A GRAS assessment program for flavor ingredients. Flavor and Extract Manufacturers Association. *Regul Toxicol Pharmacol* 21:422–430.

IOM (Institute of Medicine). 1998. *Dietary Reference Intakes. A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients.* Washington, DC: National Academy Press.

Woods LA, Doull J. 1991. GRAS evaluation of flavoring substances by the Expert Panel of FEMA. *Regul Toxicol Pharmacol* 14:48–58.

Appendix C

Possible Combinations of Scores

There are 625 possible combinations of scores that fall under Priority Groups I through V. These are all listed below, in the priority order that would be indicated by the proposed framework. As described in Chapter 5, high prevalence of use would shift supplements to the highest priority within each Priority Group. NAD=no appropriate data.

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
I	3	3	3	3
	3	3	3	2
	3	3	3	NAD
	3	3	3	1
	3	3	3	0
	3	3	2	3
	3	3	NAD	3
	3	3	1	3
	3	3	0	3
	3	3	2	2
	3	3	2	NAD
	3	3	2	1
	3	3	2	0
	3	3	NAD	2
	3	3	NAD	NAD
	3	3	NAD	1
	3	3	NAD	0
	3	3	1	2
	3	3	1	NAD
	3	3	1	1
	3	3	1	0
	3	3	0	2
	3	3	0	NAD
	3	3	0	1
	3	3	0	0

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
II	3	2	3	3
	3	NAD	3	3
	3	1	3	3
	3	0	3	3
	3	2	3	2
	3	2	3	NAD
	3	2	3	1
	3	2	3	0
	3	2	2	3
	3	2	NAD	3
	3	2	1	3
	3	2	0	3
	3	NAD	3	2
	3	NAD	3	NAD
	3	NAD	3	1
	3	NAD	3	0
	3	NAD	2	3
	3	NAD	NAD	3
	3	NAD	1	3
	3	NAD	0	3
	3	1	3	2
	3	1	3	NAD
	3	1	3	1
	3	1	3	0
	3	1	2	3
	3	1	NAD	3
	3	1	1	3
	3	1	0	3
	3	0	3	2
	3	0	3	NAD
	3	0	3	1
	3	0	3	0
	3	0	2	3
	3	0	NAD	3
	3	0	1	3
	3	0	0	3
	3	2	2	2
	3	2	2	NAD
	3	2	2	1
	3	2	2	0
	3	2	NAD	2
	3	2	NAD	NAD
	3	2	NAD	1
	3	2	NAD	0
	3	2	1	2
	3	2	1	NAD
	3	2	1	1
	3	2	1	0

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
II	3	2	0	2
	3	2	0	NAD
	3	2	0	1
	3	2	0	0
	3	NAD	2	2
	3	NAD	2	NAD
	3	NAD	2	1
	3	NAD	2	0
	3	NAD	NAD	2
	3	NAD	NAD	NAD
	3	NAD	NAD	1
	3	NAD	NAD	0
	3	NAD	1	2
	3	NAD	1	NAD
	3	NAD	1	1
	3	NAD	1	0
	3	NAD	0	2
	3	NAD	0	NAD
	3	NAD	0	1
	3	NAD	0	0
	3	1	2	2
	3	1	2	NAD
	3	1	2	1
	3	1	2	0
	3	1	NAD	2
	3	1	NAD	NAD
	3	1	NAD	1
	3	1	NAD	0
	3	1	1	2
	3	1	1	NAD
	3	1	1	1
	3	1	1	0
	3	1	0	2
	3	1	0	NAD
	3	1	0	1
	3	1	0	0
	3	0	2	2
	3	0	2	NAD
	3	0	2	1
	3	0	2	0
	3	0	NAD	2
	3	0	NAD	NAD
	3	0	NAD	1
	3	0	NAD	0
	3	0	1	2
	3	0	1	NAD
	3	0	1	1
	3	0	1	0

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
II	3	0	0	2
	3	0	0	NAD
	3	0	0	1
	3	0	0	0
III	NAD	3	3	3
	2	3	3	3
	1	3	3	3
	0	3	3	3
	NAD	3	3	2
	NAD	3	3	NAD
	NAD	3	3	1
	NAD	3	3	0
	NAD	3	2	3
	NAD	3	NAD	3
	NAD	3	1	3
	NAD	3	0	3
	2	3	3	2
	2	3	3	NAD
	2	3	3	1
	2	3	3	0
	2	3	2	3
	2	3	NAD	3
	2	3	1	3
	2	3	0	3
	1	3	3	2
	1	3	3	NAD
	1	3	3	1
	1	3	3	0
	1	3	2	3
	1	3	NAD	3
	1	3	1	3
	1	3	0	3
	0	3	3	2
	0	3	3	NAD
	0	3	3	1
	0	3	3	0
	0	3	2	3
	0	3	NAD	3
	0	3	1	3
	0	3	0	3
	NAD	3	2	2
	NAD	3	2	NAD
	NAD	3	2	1
	NAD	3	2	0
	NAD	3	NAD	2
	NAD	3	NAD	NAD
	NAD	3	NAD	1
	NAD	3	NAD	0

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
III	NAD	3	1	2
	NAD	3	1	NAD
	NAD	3	1	1
	NAD	3	1	0
	NAD	3	0	2
	NAD	3	0	NAD
	NAD	3	0	1
	NAD	3	0	0
	2	3	2	2
	2	3	2	NAD
	2	3	2	1
	2	3	2	0
	2	3	NAD	2
	2	3	NAD	NAD
	2	3	NAD	1
	2	3	NAD	0
	2	3	1	2
	2	3	1	NAD
	2	3	1	1
	2	3	1	0
	2	3	0	2
	2	3	0	NAD
	2	3	0	1
	2	3	0	0
	1	3	2	2
	1	3	2	NAD
	1	3	2	1
	1	3	2	0
	1	3	NAD	2
	1	3	NAD	NAD
	1	3	NAD	1
	1	3	NAD	0
	1	3	1	2
	1	3	1	NAD
	1	3	1	1
	1	3	1	0
	1	3	0	2
	1	3	0	NAD
	1	3	0	1
	1	3	0	0
	0	3	2	2
	0	3	2	NAD
	0	3	2	1
	0	3	2	0
	0	3	NAD	2
	0	3	NAD	NAD
	0	3	NAD	1
	0	3	NAD	0

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
III	0	3	1	2
	0	3	1	NAD
	0	3	1	1
	0	3	1	0
	0	3	0	2
	0	3	0	NAD
	0	3	0	1
	0	3	0	0
IV	NAD	2	3	3
	NAD	NAD	3	3
	NAD	1	3	3
	NAD	0	3	3
	2	2	3	3
	2	NAD	3	3
	2	1	3	3
	2	0	3	3
	1	2	3	3
	1	NAD	3	3
	1	1	3	3
	1	0	3	3
	0	2	3	3
	0	NAD	3	3
	0	1	3	3
	0	0	3	3
	NAD	2	3	2
	NAD	2	3	NAD
	NAD	2	3	1
	NAD	2	3	0
	NAD	NAD	3	2
	NAD	NAD	3	NAD
	NAD	NAD	3	1
	NAD	NAD	3	0
	NAD	1	3	2
	NAD	1	3	NAD
	NAD	1	3	1
	NAD	1	3	0
	NAD	0	3	2
	NAD	0	3	NAD
	NAD	0	3	1
	NAD	0	3	0
	2	2	3	2
	2	2	3	NAD
	2	2	3	1
	2	2	3	0
	2	2	2	3
	2	2	NAD	3
	2	2	1	3
	2	2	0	3

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
IV	2	NAD	3	2
	2	NAD	3	NAD
	2	NAD	3	1
	2	NAD	3	0
	2	NAD	2	3
	2	NAD	NAD	3
	2	NAD	1	3
	2	NAD	0	3
	2	1	3	2
	2	1	3	NAD
	2	1	3	1
	2	1	3	0
	2	1	2	3
	2	1	NAD	3
	2	1	1	3
	2	1	0	3
	2	0	3	2
	2	0	3	NAD
	2	0	3	1
	2	0	3	0
	2	0	2	3
	2	0	NAD	3
	2	0	1	3
	2	0	0	3
	NAD	2	2	3
	NAD	2	NAD	3
	NAD	2	1	3
	NAD	2	0	3
	NAD	NAD	2	3
	NAD	NAD	NAD	3
	NAD	NAD	1	3
	NAD	NAD	0	3
	NAD	1	2	3
	NAD	1	NAD	3
	NAD	1	1	3
	NAD	1	0	3
	NAD	0	2	3
	NAD	0	NAD	3
	NAD	0	1	3
	NAD	0	0	3
	1	2	3	2
	1	2	3	NAD
	1	2	3	1
	1	2	3	0
	1	2	2	3
	1	2	NAD	3
	1	2	1	3
	1	2	0	3

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
IV	1	NAD	3	2
	1	NAD	3	NAD
	1	NAD	3	1
	1	NAD	3	0
	1	NAD	2	3
	1	NAD	NAD	3
	1	NAD	1	3
	1	NAD	0	3
	1	1	3	2
	1	1	3	NAD
	1	1	3	1
	1	1	3	0
	1	1	2	3
	1	1	NAD	3
	1	1	1	3
	1	1	0	3
	1	0	3	2
	1	0	3	NAD
	1	0	3	1
	1	0	3	0
	1	0	2	3
	1	0	NAD	3
	1	0	1	3
	1	0	0	3
	0	2	3	2
	0	2	3	NAD
	0	2	3	1
	0	2	3	0
	0	2	2	3
	0	2	NAD	3
	0	2	1	3
	0	2	0	3
	0	NAD	3	2
	0	NAD	3	NAD
	0	NAD	3	1
	0	NAD	3	0
	0	NAD	2	3
	0	NAD	NAD	3
	0	NAD	1	3
	0	NAD	0	3
	0	1	3	2
	0	1	3	NAD
	0	1	3	1
	0	1	3	0
	0	1	2	3
	0	1	NAD	3
	0	1	1	3
	0	1	0	3

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
IV	0	0	3	2
	0	0	3	NAD
	0	0	3	1
	0	0	3	0
	0	0	2	3
	0	0	NAD	3
	0	0	1	3
	0	0	0	3
V	2	2	2	2
	2	2	2	NAD
	2	2	2	1
	2	2	2	0
	2	2	NAD	2
	2	2	NAD	NAD
	2	2	NAD	1
	2	2	NAD	0
	2	2	1	2
	2	2	1	NAD
	2	2	1	1
	2	2	1	0
	2	2	0	2
	2	2	0	NAD
	2	2	0	1
	2	2	0	0
	2	NAD	2	2
	2	NAD	2	NAD
	2	NAD	2	1
	2	NAD	2	0
	2	NAD	NAD	2
	2	NAD	NAD	NAD
	2	NAD	NAD	1
	2	NAD	NAD	0
	2	NAD	1	2
	2	NAD	1	NAD
	2	NAD	1	1
	2	NAD	1	0
	2	NAD	0	2
	2	NAD	0	NAD
	2	NAD	0	1
	2	NAD	0	0
	2	1	2	2
	2	1	2	NAD
	2	1	2	1
	2	1	2	0
	2	1	NAD	2
	2	1	NAD	NAD
	2	1	NAD	1
	2	1	NAD	0

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
V	2	1	1	2
	2	1	1	NAD
	2	1	1	1
	2	1	1	0
	2	1	0	2
	2	1	0	NAD
	2	1	0	1
	2	1	0	0
	2	0	2	2
	2	0	2	NAD
	2	0	2	1
	2	0	2	0
	2	0	NAD	2
	2	0	NAD	NAD
	2	0	NAD	1
	2	0	NAD	0
	2	0	1	2
	2	0	1	NAD
	2	0	1	1
	2	0	1	0
	2	0	0	2
	2	0	0	NAD
	2	0	0	1
	NAD	2	2	2
	NAD	2	2	NAD
	NAD	2	2	1
	NAD	2	2	0
	NAD	2	NAD	2
	NAD	2	NAD	NAD
	NAD	2	NAD	1
	NAD	2	NAD	0
	NAD	2	1	2
	NAD	2	1	NAD
	NAD	2	1	1
	NAD	2	1	0
	NAD	2	0	2
	NAD	2	0	NAD
	NAD	2	0	1
	NAD	2	0	0
	NAD	NAD	2	2
	NAD	NAD	2	NAD
	NAD	NAD	2	1
	NAD	NAD	2	0
	NAD	NAD	NAD	2
	NAD	NAD	NAD	NAD
	NAD	NAD	NAD	1
	NAD	NAD	NAD	0
	NAD	NAD	1	2

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
V	NAD	NAD	1	NAD
	NAD	NAD	1	1
	NAD	NAD	1	0
	NAD	NAD	0	2
	NAD	NAD	0	NAD
	NAD	NAD	0	1
	NAD	NAD	0	0
	NAD	1	2	2
	NAD	1	2	NAD
	NAD	1	2	1
	NAD	1	2	0
	NAD	1	NAD	2
	NAD	1	NAD	NAD
	NAD	1	NAD	1
	NAD	1	NAD	0
	NAD	1	1	2
	NAD	1	1	NAD
	NAD	1	1	1
	NAD	1	1	0
	NAD	1	0	2
	NAD	1	0	NAD
	NAD	1	0	1
	NAD	1	0	0
	NAD	0	2	2
	NAD	0	2	NAD
	NAD	0	2	1
	NAD	0	2	0
	NAD	0	NAD	2
	NAD	0	NAD	NAD
	NAD	0	NAD	1
	NAD	0	NAD	0
	NAD	0	1	2
	NAD	0	1	NAD
	NAD	0	1	1
	NAD	0	1	0
	NAD	0	0	2
	NAD	0	0	NAD
	NAD	0	0	1
	NAD	0	0	0
	1	2	2	2
	1	2	2	NAD
	1	2	2	1
	1	2	2	0
	1	2	NAD	2
	1	2	NAD	NAD
	1	2	NAD	1
	1	2	NAD	0
	1	2	1	2

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
V	1	2	1	NAD
	1	2	1	1
	1	2	1	0
	1	2	0	2
	1	2	0	NAD
	1	2	0	1
	1	2	0	0
	1	NAD	2	2
	1	NAD	2	NAD
	1	NAD	2	1
	1	NAD	2	0
	1	NAD	NAD	2
	1	NAD	NAD	NAD
	1	NAD	NAD	1
	1	NAD	NAD	0
	1	NAD	1	2
	1	NAD	1	NAD
	1	NAD	1	1
	1	NAD	1	0
	1	NAD	0	2
	1	NAD	0	NAD
	1	NAD	0	1
	1	NAD	0	0
	1	1	2	2
	1	1	2	NAD
	1	1	2	1
	1	1	2	0
	1	1	NAD	2
	1	1	NAD	NAD
	1	1	NAD	1
	1	1	NAD	0
	1	1	1	2
	1	1	1	NAD
	1	1	1	1
	1	1	1	0
	1	1	0	2
	1	1	0	NAD
	1	1	0	1
	1	1	0	0
	1	0	2	2
	1	0	2	NAD
	1	0	2	1
	1	0	2	0
	1	0	NAD	2
	1	0	NAD	NAD
	1	0	NAD	1
	1	0	NAD	0
	1	0	1	2

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
V	1	0	1	NAD
	1	0	1	1
	1	0	1	0
	1	0	0	2
	1	0	0	NAD
	1	0	0	1
	1	0	0	0
	1	0	0	0
	0	2	2	2
	0	2	2	NAD
	0	2	2	1
	0	2	2	0
	0	2	NAD	2
	0	2	NAD	NAD
	0	2	NAD	1
	0	2	NAD	0
	0	2	1	2
	0	2	1	NAD
	0	2	1	1
	0	2	1	0
	0	2	0	2
	0	2	0	NAD
	0	2	0	1
	0	2	0	0
	0	NAD	2	2
	0	NAD	2	NAD
	0	NAD	2	1
	0	NAD	2	0
	0	NAD	NAD	2
	0	NAD	NAD	NAD
	0	NAD	NAD	1
	0	NAD	NAD	0
	0	NAD	1	2
	0	NAD	1	NAD
	0	NAD	1	1
	0	NAD	1	0
	0	NAD	0	2
	0	NAD	0	NAD
	0	NAD	0	1
	0	NAD	0	0
	0	1	2	2
	0	1	2	NAD
	0	1	2	1
	0	1	2	0
	0	1	NAD	2
	0	1	NAD	NAD
	0	1	NAD	1
	0	1	NAD	0

Priority Group	Human Data	Animal Data	Structure Data	In Vitro Data
V	0	1	1	2
	0	1	1	NAD
	0	1	1	1
	0	1	1	0
	0	1	0	2
	0	1	0	NAD
	0	1	0	1
	0	1	0	0
	0	0	2	2
	0	0	2	NAD
	0	0	2	1
	0	0	2	0
	0	0	NAD	2
	0	0	NAD	NAD
	0	0	NAD	1
	0	0	NAD	0
	0	0	1	2
	0	0	1	NAD
	0	0	1	1
	0	0	1	0
	0	0	0	2
	0	0	0	NAD
	0	0	0	1
	0	0	0	0

Appendix D

Table of Food and Drug Administration Actions on Dietary Supplements

This table provides an abbreviated list of some of the Food and Drug Administration (FDA) actions that have been described on the FDA Medwatch website: http//www.fda.gov/medwatch/safety.htm.

TABLE D-1 Abbreviated List of FDA Actions on Dietary Supplements

Year	Dietary Supplement	FDA Action
2002	PC SPES	FDA warned consumers to stop use
2001	Aristolochic Acid	FDA issued a Consumer Advisory advising consumers to immediately discontinue use
		FDA sent updated letters to industry and health care professionals (HCPs) about the safety concerns of these products
		FDA requested voluntary recall by manufacturers and distributors; several issued a recall
2001	Comfrey	FDA recommended that manufacturers remove product from the market and alert customers to immediately stop use
2001	Kava	FDA requested HCPs to review liver toxicity cases and to report possible kava-related cases to MedWatch
2001	Lipokinetix	FDA warned consumers to stop use immediately
		FDA alerted HCPs that Lipokinetix may be a serious health risk and asked HCPs to review and report cases of possible Lipokinetix-related hepatitis
		FDA recommended to distributor that it remove product from market and alert customers
2001	Neo Concept Aller Relief	FDA informed manufacturer of possible contamination of the product and manufacturer issued recall
2000	St. John's Wort	FDA notified HCP of the risk of drug interactions
2000	Tiratricol	FDA warned consumers to stop use immediately

Year	Dietary Supplement	FDA Action
1999	Asian Remedy for Menstrual Cramps—Koo Sar	Centers for Diseaase Control and Prevention report attributed lead poisoning case to product (posted on FDA website)
1999	Gamma Butyrolactone (GBL)	FDA warned consumers not to consume FDA requested manufacturers to voluntarily recall products (at least one manufacturer agreed to recall)
1999	GBL, Gamma Hydroxybutyric Acid (GHB) and 1,4 Gutanediol (BD)	FDA notified HCPs and continues to warn public that these substances are unapproved new drugs that may cause harm FDA conducted seizures of product
1999	GBL-Related Products	FDA warned the public that these are unapproved new drugs that may cause harm FDA conducted seizures of product
1998	"Sleeping Buddha"	FDA warned consumers not to use product because it contains an unlabeled prescription drug ingredient
1998	5-hydroxy-L-tryptophan	FDA noted the presence of impurities in some products
1998	Cholestin	FDA determined product was an unapproved drug (later upheld by court ruling[a])
1997	Chomper	FDA warned consumers not to consume product
1997	Ephedrine Dietary Supplements	FDA proposed limits to epedrine alkaloids allowed in products. Proposes adding warnings and information in labeling and marketing
1997	Gamma Hydroxybutyric Acid (GHB)	FDA reissued warning against use of substance because it is an unapproved and potentially dangerous new drug FDA and Department of Justice took enforcement actions (restrict importation, embargoes, etc.)
1997	"Herbal Fen-Phen"	FDA warned consumers that product is an unapproved and potentially dangerous new drug FDA took action to remove product from the market
1997	Infant Formula (homemade)	FDA informed pediatricians about safety concerns with use
1997	"Plantain" Containing Dietary Supplements	FDA warned consumers not to consume dietary supplement products containing plantain because of possible digitalis contamination FDA worked with manufacturers to identify and recall possibly contaminated products
1996	Street Drugs Containing Botanical Ephedrine	FDA warned consumers not to consume products
1992	Chaparral	FDA warned consumers to stop use immediately

[a] The most recent court ruling held that cholestin was a drug and would be subject to regulation by FDA; however, the case is being appealed (Pharmanex v. Shalala, No. 2:97CV262k, 2001 WL 741419 [D. Utah March 30, 2001], *appeal docketed,* No. 01–4108 [10th Cir. May 31, 2001]).

Appendix E

Presenters at the Open Sessions of the Project on the Framework for Evaluating the Safety of Dietary Supplements

F.Alan Andersen, Cosmetic Ingredient Review, Washington, D.C.
Dennis V.C.Awang, Mediplant, British Columbia
Joseph M.Betz, Office of Dietary Supplements, National Institutes of Health, Bethesda, MD
Paul Coates, Office of Dietary Supplements, National Institutes of Health, Bethesda, MD
Annette Dickinson, Council for Responsible Nutrition, Washington, D.C.
David J.Graham, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD
Richard L.Hall, Flavor and Extract Manufacturers Association, Towson, MD
Claire L.Kruger, ENVIRON International Corporation, Arlington, VA
Gilbert A.Leveille, McNeill Consumer Healthcare, Fort Washington, PA
Christine Lewis Taylor, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, MD
Hulon McCain, Whitehall-Robins Healthcare, Madison, NJ
Sanford Miller, Bethesda, MD
Joseph V.Rodricks, ENVIRON International Corporation, Arlington, VA
Alan Rulis, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, MD
Louis Scarano, Environmental Protection Agency, Washington, D.C.
David Schardt, Center for Science in the Public Interest, Washington, D.C.
Bruce Silverglade, Center for Science in the Public Interest, Washington, D.C.
R.William Soller, Consumer Healthcare Products Association, Washington, D.C.
Susan Trimbo, Nutricia, Boca Raton, FL
Sidney M.Wolfe, Public Citizen's Health Research Group, Washington, D.C.

Appendix F

Biographical Sketches of Committee Members

Barbara O.Schneeman, Ph.D. *(chair)* served formerly as dean, College of Agricultural and Environmental Sciences, and currently serves as a professor of nutrition in the Department of Nutrition and in the Division of Clinical Nutrition and Metabolism, University of California at Davis. Her professional activities include membership on the U.S. Department of Agriculture (USDA)/Department of Health and Human Services 1990 and 1995 Dietary Guidelines for Americans Advisory Committees, the Board of Trustees of the International Life Sciences Institute, and the editorial boards of *Proceedings of the Society of Experimental Biology and Medicine, Food and Nutrition Series* of Academic Press, *Nutrition Reviews, Journal of Nutrition,* and *California Agriculture.* Professional honors include the Institute of Food Technologists' Samuel Gate Prescott Award for research, the Commissioner's Special Citation, and the Harvey W.Wiley Medal from the Food and Drug Administration (FDA) in recognition of her contributions toward the advancement of scientific research. Dr. Schneeman has also been active in developing state and national nutrition policy as an appointed member of the California State Board of Food and Agriculture and the USD A Public Advisory Board. She is currently president of the Dannon Institute, a nonprofit foundation funded by Dannon, Inc. She has served as chair of the Institute of Medicine (IOM) Committee on Body Composition, Nutrition, and Health of Military Women and recently served as Deputy Administrator for Human Nutrition of the USDA Agricultural Research Service (on leave from U.C. Davis). Dr. Schneeman's research areas include fat absorption, complex carbohydrates, dietary fiber, and gastrointestinal function.

Daniel L.Azarnoff, M.D. is president of D.L.Azarnoff Associates, through which he does consulting with the pharmaceutical industry. He also serves as Senior Vice President of Clinical/Regulatory Affairs at Cellegy Pharmaceuticals, Inc. The companies he is involved with do not market dietary supplements. Dr. Azarnoff s expertise includes pharmaceutical industry administration, pharmacology, clinical pharmacology, and general internal medicine. His research interests include the drug approval process, including preclinical (pharmacology, toxicology, pharmaceutics) and clinical (therapeutic, bioequivalence trials); drugs to treat hyperlipoproteinemia; and transdermal drug delivery. Dr. Azarnoff earned his M.D. from the University of Kansas where he became KUMC Distinguished Professor of Medicine and Pharmacology and previously served as President of Research and Development for the Searle Pharmaceutical Company. He has been an IOM member since 1978 with membership on

numerous IOM committees including the Committee on Halcion, the Committee on Understanding the Biology of Sex and Gender Differences, and the Committee to Assess the System for the Protection of Human Research Subjects.

Cindy L.Christiansen, Ph.D. is chief of the Statistics Section, Center for Health Quality, Outcomes, and Economic Research at Bedford Veterans Affairs and an associate professor of health services at Boston University. Dr. Christiansen serves as chair of the American Statistical Association Section on Health Policy Statistics. She is one of the country's leading experts on hierarchical and predictive models and their use in health services research. Her research interests include the development and implementation of multi-level and prediction models for health service and medical applications, and her methodological work has focused on Poisson models and on models for grouped ordinal data.

Alice M.Clark, Ph.D. holds her Ph.D. in pharmacognosy from the University of Mississippi and serves as Vice Chancellor for Research and Sponsored Programs, Frederick A.P.Barnard Distinguished Professor of Pharmacognosy and research professor of the Research Institute of Pharmaceutical Sciences at the University of Mississippi. Prior to assuming her current position in July 2001, Dr. Clark was director of the National Center for Natural Products Research, which operates as a drug discovery and development program that works on acquisition, preparation, and in vitro evaluation of extracts of higher plants for beneficial activity. It combines drug discovery, in vitro, and in vivo evaluations of efficacy and toxicity, working in collaboration with USDA's Agriculture Research Service and industry to develop therapeutics from plants. Faculty at the Center conduct research on dietary supplements and potential therapeutics. The Center is well known for its efforts in enhancing the safety and efficacy of botanical dietary supplements. Dr. dark's research interests are in evaluation of natural compounds for antibiotic and antifungal activity, as well as in the utilization of microorganisms as predictive models for drug metabolism and as synthetic adjuncts. She is part of an NCNPR group working on a Centers for Disease Control and Prevention-funded project to evaluate the potential for botanical dietary supplements to interact with pharmaceuticals, to review the scientific literature on specific botanicals, and to review consumer use of botanical dietary supplements. Dr. Clark also serves as associate editor for the *Journal of Natural Products.*

Norman R.Farnsworth, Ph.D. is a distinguished university professor, research professor of pharmacognosy, director of the Pharmacognosy Graduate Program, and the director of the Program for Collaborative Research in the Pharmaceutical Sciences at the University of Illinois at Chicago (UIC). Dr. Farnsworth also serves as director of the UIC/National Institutes of Health (NIH) Dietary Supplements Research Center. He is credited with designing a worldwide computer database called NAPRALERT that compiles scientific literature on the safety and efficacy of herbal medicines, plants, marine organisms, and fungi. As director of the World Health Organization (WHO) Collaborating Center for Traditional Medicine, Dr. Farnsworth has used this database to lead the WHO'S publication of numerous monographs reviewing traditional medicinals. He is a member of Health Canada's Expert Advisory Committee on Natural Health Products and served on the Commission on Dietary Supplement Labels authorized by the Dietary Supplement Health and Education Act of 1994. Dr. Farnsworth serves on the Scientific Advisory Board of the Herb Research Foundation, the Board of Trustees of the American Botanical Council, and the editorial advisory board of several peer-reviewed journals and *Herbalgram.* He

also consults with various companies on pharmacognosy questions (currently these include Pharmavite, Shaklee, and Tom's of Maine). He has authored a number of publications about botanicals, including *Botanical Dietary Supplements: Quality, Safety, and Efficacy*. His research interests include analysis of chemical and biological data on natural products and isolation, identification, and structure elucidation of biologically active plant constituents.

Ted Gansler, M.D., M.B.A. is Director of Medical Information Strategy at the American Cancer Society (ACS) and editor of the ACS publication, *CA: A Cancer Journal for Clinicians.* At ACS, Dr. Gansler is responsible for assuring the accuracy of printed and electronic information products for patients, the general public, and health professionals. He is a graduate of Duke University, University of Pittsburgh School of Medicine, and Georgia State University School of Business Administration, and completed a pathology residency and cytopathology fellowship at the University of Pennsylvania. Dr. Gansler is also an adjunct associate professor of pathology at Emory University.

Philip S.Guzelian, M.D. serves as the Director of Medical Toxicology and co-director of the Hepatobiliary Research Center at the University of Colorado Health Sciences Center. Dr. Guzelian earned his M.D. at the University of Wisconsin-Madison. His research interests, largely supported by grants from NIH, include liver disease, hepatic drug metabolism and toxicity, medical toxicology, and cytochrome P450. His research objective is to understand how cells recognize the presence of foreign chemicals and activate host defenses. Dr. Guzelian has been a member of the NIH National Advisory Environmental Health Sciences Council, chairman of the Toxicology Advisory Committee of the Burroughs Wellcome Fund, and a member of the Drug Safety Scientific Advisory Committee for Rhone-Poulenc Rorer Pharmaceuticals, the Board of Scientific Directors of the International Life Sciences Institute, and the Board of Scientific and Policy Advisors of the American Council of Science and Health. He is also an ad hoc member of the Environmental Protection Agency's (EPA) Office of Science Coordination and Policy Scientific Advisory Panel and has served on EPA's Science Review Board for the Food Quality Protection Act.

Elizabeth Jeffery, Ph.D. serves as a professor of nutritional toxicology for the Department of Food Science and Human Nutrition, the Division of Nutritional Sciences and the Department of Pharmacology at the University of Illinois, Urbana-Champaign. She has a Ph.D. in biochemistry from the University of London (United Kingdom) and teaches and conducts research in the area of safety and efficacy of functional foods and dietary supplements. Dr. Jeffery investigates the potential for soy to affect bone health and for broccoli and other crucifers with major support from NIH and USDA, and a gift from Standard Process, Inc. Dr. Jeffery is past editor of the American Society for Pharmacology and Experimental Therapeutics *Drug Metabolism Newsletter* and past associate editor of *Toxicology and Applied Pharmacology.* She is presently chair of the Bioactive Components Research Interest Section of American Society for Nutritional Sciences, chair of the Toxicology Division of American Society for Pharmacology and Experimental Therapeutics, and secretary/treasurer of the Food Safety Specialty Section of the Society of Toxicology.

Joseph Lau, M.D. is a professor of medicine at the Tufts University School of Medicine and professor of clinical research at the Sackler School of Graduate Biomedical Sciences at Tufts

University. He is also co-director of the New England Cochrane Center and director of one of the twelve Agency for Healthcare Research and Quality Evidence-based Practice Centers located at the New England Medical Center in Boston. Dr. Lau is interested in methodological issues in meta-analysis and the translation of evidence into practice. He developed the method of cumulative meta-analysis and has published extensively on the methodologies and clinical applications of meta-analysis. Dr. Lau is a member of the editorial board of *Clinical Evidence* and has served on study sections for the Agency for Healthcare Research and Quality Initial Review Group. Dr. Lau received his M.D. from Tufts University School of Medicine.

Susan S.Percival, **Ph.D.** is a professor in the Food Science and Human Nutrition Department at the University of Florida. She is a recipient of the Future Leaders Award from the International Life Sciences Institute Nutrition Foundation. Her research interests include nutrition and immunity; effects of botanicals, phytochemicals, and trace elements on immune function; antioxidant bioavailability and impact on immunity; efficacy of dietary supplements in humans; and mechanistic studies in animal and cell culture models. While much of her research has focused on the metabolism of copper and other trace elements, Dr. Percival's research currently focuses on health effects of different fruit phytochemicals, echinacea and components of green tea, with support from industry.

Cheryl L.Rock, Ph.D., R.D. is a professor in the Department of Family and Preventive Medicine and the Cancer Prevention and Control Program at the University of California, San Diego School of Medicine. She received her Ph.D. in nutritional sciences from the University of California, Los Angeles School of Public Health. Dr. Rock's primary NTH-funded research efforts are focused on the role of nutritional and dietary factors in the development and progression of cancer in women, particularly breast and cervical cancer, and her research efforts also address eating pathology and weight concerns in women. She is presently involved in randomized trials that are testing whether modifications in diet and level of physical activity can alter biological processes and progression of cancer. She currently serves on editorial boards for several peer-reviewed journals and has been an invited participant in several NIH review committees, workshops, and meetings.