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Administration

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DIETARY SUPPLEMENTS TASK FORCE

Final Report

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

STATEMENT BY DR. DAVID KESSLER
COMMISSIONER OF FOOD AND DRUGS
ACCOMPANYING RELEASE OF
THE DIETARY SUPPLEMENTS TASK FORCE FINAL REPORT

I am pleased to release for public comment and discussion the Final Report of FDA's Dietary Supplements Task Force. I charged the Task Force in 1991 to take a new look at how FDA could possibly regulate dietary supplements and to propose for consideration a strategy that would best serve the public health. The Task Force worked hard to address comprehensively an extraordinarily complex and frequently controversial topic. I commend and thank the Task Force chairman, Mr. Gary Dykstra, and all of the FDA employees who served on the Task Force.

The issues addressed by the Task Force are even more timely and in need of attention today than they were when the Task Force began its work. Public interest in dietary supplements is on the rise; FDA is in the process of implementing the Nutrition Labeling and Education Act (NLEA), which governs disease-related claims on food labels and on dietary supplement products, as modified by the Dietary Supplement Act of 1992; and legislation has been introduced in the 103rd Congress suggesting entirely new legal paradigms for regulating dietary supplements.

As specified in the Dietary Supplement Act, FDA is conducting a comprehensive review of its policies, programs, and legislative authorities governing dietary supplements. The Task Force report is part of this overall effort to evaluate the regulation of dietary supplements.

GENERAL CONCLUSIONS

The Task Force reached several general conclusions about dietary supplements, which provided the basis for its specific recommendations. It concluded first that "safety should be the overriding concern for FDA" in regulating dietary supplements and

that "the industry should assume the burden of ensuring the safety of these products," with FDA in an audit role to verify adherence to safety standards. The Task Force also acknowledged "the strong desire of American consumers for access to dietary supplements," and concluded that "its recommendations should recognize a role for dietary supplements in ensuring a balanced diet, and with safety as an underlying principle, freedom of choice for these products should be allowed as much as possible."

The Task Force also recognized throughout its discussion and recommendations the importance of proper labeling to inform consumers in their exercise of free choice and the need to ensure that claims of nutritional benefit are properly supported and meet applicable legal requirements.

I endorse these basic precepts of the Task Force reports. They will help guide FDA's current policy review and future policy development. Safety, informative labeling, and properly supported claims are what the public needs and deserves as the basis for selecting any food product. These are goals the FDA, consumers, and the dietary supplement industry have in common, and FDA is committed to working closely with all interested parties to achieve these goals.

SPECIFIC RECOMMENDATIONS

The Task Force recommended 20 actions FDA could take in furtherance of its goals for dietary supplements. These included rulemaking activities, policy changes, enforcement strategies, intergovernmental coordination, consumer education, and even legislative change (see attached Executive Summary of the Report). Some of the recommendations would merely confirm or refine current policies and practices, while others would mark a departure from the status quo. FDA will carefully consider and

evaluate all of the Task Force recommendations, as well as any other public comments on this subject, before making any decisions to change current policy or initiate new activities.

One important consideration for FDA must be resources. Some of the Task Force recommendations, especially the ones involving promulgation of regulations, would require significant expenditure of FDA's resources. These recommendations will have to be assessed on the basis of their importance in achieving the agency's goals and their relative priority compared to other agency goals and activities.

The Task Force divided the universe of supplement products it addressed into three categories: (1) vitamins and minerals, (2) amino acid products, and (3) all other types of dietary supplement products, including nonessential chemical compounds, herbs without a documented history of traditional food use, plant extracts (including oils), and animal extracts. The Task Force did not address homeopathic products, medical foods, infant formulas, protein products, dietary fiber and certain fatty acids.

1. Vitamins and Minerals

With respect to vitamin and mineral products, the primary recommendation of the Task Force was that FDA should establish through rulemaking for each vitamin and mineral a safe daily intake level. For some vitamin and mineral supplement products, safety is not a significant concern. However, most essential nutrients are toxic when consumed in excess, and FDA-established safety levels would provide a benchmark for avoiding potential hazards in such cases.

The principle question to be resolved regarding this

recommendation is whether the significant resources and effort required to promulgate safe levels for all essential vitamins and minerals would be justified in light of other priorities and needs. FDA's Center for Food Safety and Applied Nutrition will evaluate this recommendation and discuss it with interested parties outside the agency before deciding how to proceed.

2. Amino Acids

Of all the Task Force recommendations, the one regarding amino acids has the greatest potential to alter the status quo for a particular class of dietary supplement products. Under current law, product that are claimed to have a disease-related benefit are "drugs", unless the product is a food whose claim complies with the claim provisions of NLEA. Based on such "drug" claims, FDA has in the past taken enforcement actions on a case-by-case basis against amino acids sold in capsule or tablet form that have not been approved by FDA, as the statute requires. Based on its review, the Task Force expressed concern about the potential safety hazard of high potency amino acid products and found that such products are more often than not marketed and purchased for uses that make the products drugs. The Task Force thus recommended that FDA initiate rulemaking to categorize each of the individual amino acids as drugs when sold in capsule or tablet form. The only exception would be for products in which the amino acid is present at level demonstrated to be safe and to have a recognized food (i.e., nutritional) function.

FDA will carefully evaluate this recommendation. Individual amino acid products for which the manufacturer or vender makes unapproved drug claims clearly are--and will remain--subject to enforcement action under current law. It would require development of a substantial factual record, however, to classify specific amino acids as drugs per se. FDA will consider whether

this effort is justified in light of its resources, priorities and all relevant information.

After the Task Force completed the report, FDA received an agency-commissioned report from the Federation of American Societies for Experimental Biology (FASEB) on the safety of amino acids. FASEB conducted an extensive review of the medical literature and concluded that there is insufficient evidence to establish safe upper levels of consumption for amino acid supplements. In addition, FASEB recommended that potentially vulnerable subgroups--the young, the elderly, women of childbearing age, and people with suppressed immune systems--only use amino acids under a doctor's supervision. FDA is seeking public comment on the FASEB report.

3. Other Dietary Supplement Products

With respect to the "all other" category of dietary supplement products, the Task Force recommended continued use of the food additive provisions of the statute unless drug claims are made. This recommendation appropriately reflects the fact that, absent drug claims, FDA's principle interest is to ensure that these products and their ingredients are safe. FDA has no intention, however, of taking large numbers of these products off the market using the food additive theory. FDA will work with the dietary supplement industry on the common goal of safety, including efforts to clarify the scientific basis upon which a manufacturer can determine that the ingredients in this product are "generally recognized as safe" and thus exempt from the requirement for formal FDA approval.

4. Cross-cutting Recommendations

The Task Force made several cross-cutting recommendations for all

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dietary supplement products. The most important of these involved the need to establish good manufacturing practices (GMP's), purity and identity standards, and disintegration and dissolution standards to ensure bioavailability. GMP's and purity standards are an integral part of ensuring the safety of any food product and could made a significant contribution to ensuring the safety of dietary supplements. Standards to ensure bioavailability can affect safety but also would help ensure that consumers get what they pay for. FDA will work with the dietary supplement industry and other interested parties to develop practical, effective approaches to implementing these recommendations of the Task Force.

CONCLUSION

The history of dietary supplement regulation has been marked by controversy and debate about the proper role of government regulation in achieving the widely accepted goals of safety informative labeling, and properly supported claims. FDA is conducting its current policy review to ensure that the Agency is making the best use of its current statutory authorities and to determine whether new legislation is necessary or appropriate to resolve certain issues.

Dietary supplements are used daily by an estimated 60 million Americans. It is thus incumbent on FDA and the dietary supplement industry to work toward resolving some of the controversies of the past and to establish a scientifically sound, publicly supportable basis for ensuring safety, informative labeling, and properly supported claims. This will take time and sustained effort by all parties, but FDA is fully committed to the task.

CHAIRMAN'S ACKNOWLEDGEMENT

The Chairman would like to thank Commissioner David Kessler for the opportunity to work on such a challenging subject with such a talented group of agency experts. The group worked extremely hard on a very complex issue and produced a framework for regulation of dietary supplements which should serve the agency well. The agency should be proud of this effort even though every single issue was not addressed because of the timeframe imposed.

The Chairman would, in particular, like to recognize and thank Ms. Judy Riggins for serving on the Task Force and doing such an outstanding job of assisting with meetings and with the preparation of the final report. I would also like to thank my secretary, Ms. Terri Ausfresser, for her help in managing this Task Force effort.

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EXECUTIVE SUMMARY

The Dietary Supplements Task Force was charged with examining the issues regarding dietary supplements and developing a regulatory framework for these products. The Task Force took a fresh look at dietary supplements in an attempt to strike an appropriate balance between the agency's obligations under the statute and the desires of a substantial segment of the public for dietary supplements.

The Task Force studied the universe of products in the marketplace, focusing on products sold in capsule, tablet, liquid, and powder form. To facilitate the orderly development of regulatory strategies, the Task Force divided the universe of supplements into three categories: 1) vitamin and mineral products; 2) amino acids; and 3) "all others," which include non-essential chemical compounds, herbs without a history of documented traditional food use, plant and animal extracts, and certain other substances. Homeopathic products, medical foods, infant formulas, protein products, dietary fiber, and certain fatty acids are not addressed in this report.

The Task Force considered various issues in its deliberations, including how to ensure the safety of dietary supplements; how to

limit the potential for fraud, i.e., disease claims made on labels or through other means, e.g., magazine articles, newsletters and advertisements; and what steps are necessary to ensure that the existence of dietary supplements on the market does not act as a disincentive for drug development. Balanced against these concerns is the strong desire of American consumers for access to dietary supplements. This desire was voiced at the public meeting, and it is one that FDA has tended to ignore in the past.

The Task Force has carefully examined these issues and has concluded that safety should be the overriding concern for FDA in developing a regulatory framework for this class of products. The Task Force believes that the industry should assume the burden of ensuring the safety of these products. FDA should develop programs to audit the industry's adherence to this principle.

The Task Force believes that its recommendations should recognize a role for dietary supplements in ensuring a balanced diet, and with safety as an underlying principle, freedom of choice for these products should be allowed as much as possible.

Using these conclusions as a basis, the Task Force offers the following recommendations to the Commissioner:

Vitamins and Minerals

1. Revise, by notice and comment rulemaking, the Generally Recognized as Safe (GRAS) Regulations, 21 CFR Part 184, to establish safe levels of use for vitamins and minerals as dietary supplements.

Amino Acids

2. Regulate single amino acids and mixtures of amino acids as drugs.
3. Retain the current policy in 21 CFR 172.320, 182, and 184 for regulating amino acids added as discrete ingredients to foods.

Products Other Than Vitamin, Minerals and Amino Acids

4. Regulate these substances as food additives.
5. Require a statement on the label of a substance regarding the nutritive value. If the substance does not have known nutritive value, the statement would indicate that the nutritive value has not been established. Seek legislation to strike section 403(j) from 701(e) so that formal rulemaking would not be required to effect this kind of labeling.
6. Continue to bring actions against those substances that are

represented for use as drugs.

Cross-Cutting Recommendations for All Dietary Supplements

7. Establish and implement Good Manufacturing Practice (GMP) Regulations for dietary supplements.
8. Establish and implement purity and identity standards for nutrients contained in dietary supplements (see recommendation #13).
9. Establish and implement disintegration and dissolution standards for vitamins and minerals to ensure their bioavailability (see recommendation #13).
10. Establish and implement an education campaign to provide the public with accurate, scientifically objective information about the safety, proper use, benefits and risks of products.
11. Develop a compliance program for dietary supplements to provide guidance to FDA District offices regarding inspections, sample collections, sample analyses, and compliance activities.
12. Require dietary supplements to comply with all provisions of the Nutrition Labeling and Education Act (NLEA) of 1990 and regulations promulgated thereunder.
13. Establish a liaison as appropriate with nongovernment agencies, such as the United States Pharmacopeial Convention, Inc. (USP), to provide expert advice on the

- safety and standards, where necessary, and other scientific issues for the proper regulation of dietary supplements.
14. Strengthen the adverse reaction reporting system for dietary supplements.
 15. Act against misleading name claims, including brand names, on the labels of dietary supplements that imply therapeutic use, benefit, and/or treatment.
 16. Require all dietary supplements to comply with existing regulations on tamper-resistant packaging and child-proof caps.
 17. Establish a mechanism to work closely with the Federal Trade Commission (FTC) to coordinate actions regarding dietary supplements (may be included in the development of an NLEA strategy for FTC/FDA cooperation).
 18. Work with appropriate state agencies (in existing worksharing arrangements) to regulate dietary supplements.
 19. Share FDA's policies with the international community to foster good working relationships.

Recommendations that Would Require Legislative Change

20. Seek legislation to strike section 403(j) from the list of sections subject to section 701(e).

TASK FORCE REPORT

The next few sections of this report will offer a history of the agency's regulation of dietary supplements, describe the activities of the public meeting on dietary supplements, and explain in detail the issues examined by the Task Force that resulted in the above-stated recommendations. The Task Force charge can be found at Appendix 1.

HISTORY

In 1941, after the passage of the 1938 Food, Drug, and Cosmetic Act (FD&C Act), regulations were written for dietary supplements of vitamins and minerals in terms of Minimum Daily Requirements. By the early sixties however, the agency felt that these regulations were outdated. Consequently, FDA proposed a standard of identity for vitamins and minerals in June 1962. There followed a revision and stay of effective date, and hearings were held into the seventies. A lawsuit was filed, and the case was remanded to FDA. The hearing was reopened in October 1975.

In April 1976, Congress passed the Proxmire Amendment, which became effective in October 1976 (section 411 FD&C Act). This amendment precluded the agency from establishing maximum limits for the potency of vitamins and minerals based on nutritionally rational levels, except when these levels could be shown to be

unsafe. It also prohibited the agency from classifying any vitamin or mineral as a drug solely because it exceeded a potency level that FDA considered nutritionally rational or useful.

The agency rewrote the regulations to be consistent with the Proxmire Amendment, and a final rule was published the same day as the effective date of the Proxmire Amendment. Another lawsuit was filed, and in February 1978, the court remanded the case to FDA. It is now nearly 30 years since FDA proposed revising the vitamin/mineral regulations, and there are no general regulations in effect for these products, not even the old ones from the forties. See Appendix 2 for additional discussion of history.

In light of the problems that have grown out of this history, recent concerns regarding the safety of dietary supplements raised by consumers and health professionals, and an expressed interest of the industry for a consistent policy for dietary supplements, Commissioner Kessler recognized the area of dietary supplements as one in need of significant attention. As a result, Commissioner Kessler convened a Task Force in April 1991.

TASK FORCE MEMBERSHIP

The Task Force membership represents a cross-section of offices within FDA with diverse expertise in science, food and drug law, nutrition, compliance policy, consumer and industry affairs,

public health policy, legislative affairs, and drug research.

The membership is comprised of the following staff:

Gary Dykstra (Chair)
Deputy Associate Commissioner
for Regulatory Affairs (HFC-2)

John Hathcock, Ph.D
Chief, Experimental Nutrition Branch
Center for Food Safety & Applied Nutrition (HFF-268)

Alan Rulis, Ph.D
Director, Division of Food and Color Additives
Center for Food Safety & Applied Nutrition (HFF-330)

Raymond Newberry
Deputy Director, Division of Regulatory Guidance
Center for Food Safety & Applied Nutrition (HFF-310)

Richard Chastonay
Director, Division of Drug Labeling Compliance
Center for Drug Evaluation and Research (HFD-310)

Gloria Troendle, M.D.
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Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)

Phil Derfler, Esq.
Associate Chief Counsel for Foods
Office of General Counsel (GCF-1)

Amanda Pedersen, Esq.
Chief Mediator and Ombudsman
Office of the Commissioner (HF-7)

Thomas McGinnis, R.Ph.
Associate Director, Medicine Staff
Office of Health Affairs (HFY-40)

Nathaniel Geary
Office of Small Business, Scientific & Trade Affairs (HF-50)

Naomi Kulakow
Director, Public Policy Management Team
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Judy Riggins
Policy Analyst
Office of Executive Operations (HF-40)

Kay Holcombe
Deputy Associate Commissioner
for Legislative Affairs (HFW-2)

TASK FORCE'S APPROACH

The Task Force recognizes that the regulated industry believes that FDA has historically been biased against the use of dietary supplements. Although these beliefs are unfounded, the Task Force is aware that its recommendations will be closely scrutinized. The Task Force has, therefore, conducted an objective and unbiased examination of all issues regarding dietary supplements. We have taken into account the reality that people use dietary supplements for a myriad of reasons: cultural, therapeutic, ethnic, emotional, nutritional, and psychological, as well as for insurance against dietary deficiencies.

The Task Force believes that the agency needs to earn the public's confidence that its regulation of the industry will ensure the safety of dietary supplements, provide specific guidance for marketing them for the industry to meet, and provide the consumer with products that meet quality control, adequate dissolution, and proper labeling standards. In its deliberation on every issue, the Task Force has carefully considered the extent to which the agency should intervene to protect the consumer with the understanding that FDA should not seek to restrict an individual's freedom of choice, but rather work to

ensure freedom from harm and fraud.

After studying the range of products in the marketplace, the Task Force divided them into three categories. The Task Force believes that the facts involving these products suggest this three-part division. The Task Force also believes that such division will facilitate the orderly development of regulatory strategies. The categories are: 1) vitamin and mineral products; 2) amino acids; and 3) "all other substances," which includes nonessential chemical compounds, herbs without a history of documented traditional food use, and plant and animal extracts. As stated in the executive summary of this report, homeopathic products, medical foods, infant formulas, protein products, dietary fiber, and certain fatty acids are not addressed in this report.

The Task Force recognizes that many products on the market are composed of mixtures of substances that are made from more than one of these categories. However, the Task Force has concluded that the most straightforward way to present its recommendations is on a category-by-category basis. How specific supplement products are to be regulated will ultimately flow as a matter of law from how the agency regulates each category of substances that may be components of the products. For example, amino acids are regulated as drugs. A product that contains an amino acid and a substance that falls in the third category would also be

regulated as a drug product.

The Task Force considered the question of whether the agency would require additional statutory authority to implement the strategy developed for the categories of products identified. The recommendations stated elsewhere in this report reflect first, those strategies that the Task Force believes would best protect the public health without considering any statutory limitations and, second, what the Task Force believes the agency can accomplish under its present authority.

It should be noted that the Nutritional Labeling and Education Act (NLEA) of 1990 mandates that FDA promulgate regulations governing the use of health claims and descriptors on food labels, including those of dietary supplements. Therefore, the Task Force is not addressing the health claims or descriptors specified in the NLEA in this report.

Furthermore, the Task Force's considerations are limited to dietary supplements in tablet, capsule, powder, and liquid form for human use only. The Task Force is not addressing dietary supplements for animal use.

In the November 27, 1991 Federal Register, FDA proposed to define "dietary supplement" in part, as:

A food other than a conventional food, that supplies a component with nutritive value to supplement the diet by increasing the total dietary intake of that substance. A dietary supplement includes a food for special dietary use within the meaning of section 101.9(a)(2) that is in conventional food form.

The Task Force supports the definition of the term "dietary supplement" that is consistent with the definition drafted for FDA's rulemaking under the NLEA.

The Task Force has used a variety of resource documents in generating the recommendations made in this report, including the National Academy of Sciences' Report, the Surgeon General's Report, Dietary Guidelines for Americans, and written comments and verbal presentations from the August 29, 1991 public meeting. A complete bibliography of reference materials used by the Task Force is found at Appendix 6.

DESCRIPTION OF THE DIETARY SUPPLEMENT INDUSTRY

The term "dietary supplement" has been traditionally defined as an essential substance such as a non-prescription vitamin, mineral, and protein. However, in broader common usage, dietary supplements (also called "food supplements" and "nutrient supplements" by the industry) constitute an array of products,

which include nutrients, e.g., amino acids and fatty acids, as well as other substances not recognized as valid sources of nutrients, e.g., herbs, enzymes, bioflavonoids, inert glandulars, Evening Primrose Oil, RNA, DNA, PABA, and rutin.

Surveys since 1970 have shown that 35-60 percent of the population use dietary supplements daily or occasionally. Of these users, 60 million take supplements daily. In addition, 1990 survey data imply that at least 40 percent of the U.S. population has taken a vitamin or mineral supplement in the last 30 days, with usage higher among women than men.

There are, by some estimates, approximately 3,400 unique nonprescription vitamin and mineral supplements produced by some 600 manufacturers, with retail sales of approximately \$3.3 billion annually. National sales data show that nonprescription vitamin and mineral sales comprise 88 percent of these sales (\$2.9 billion) and other products, e.g., fish oil, amino acids, etc. (protein powders and herbal products excluded) represent the remainder (\$0.4 billion).

Mass market retailers (drug stores, supermarkets, and discount stores) account for about 60 percent of dietary supplement sales. Health food stores, direct selling, and mail order comprise the remaining 40 percent.

PUBLIC MEETING

On August 29, 1991, the Task Force held a public meeting at the National Institute of Health's Masur Auditorium to gather information for the development of recommendations for strategies to manage the regulation of dietary supplements.

Approximately 250 people attended, including health professionals, manufacturers, consumers, and advocacy groups. Thirty-seven (37) participants presented oral testimony, and 47 written comments were submitted to the agency which represented a broad spectrum of views about dietary supplements. The predominant themes recounted by the participants were that FDA should 1) ensure the safety of dietary supplements; 2) allow the consumer free choice to take dietary supplements; 3) require complete and accurate labeling, including full ingredient labeling and expiration dates; and 4) establish quality control and good manufacturing practice requirements to ensure the potency and proper dissolution of dietary supplements.

Most manufacturers opposed stringent regulation of dietary supplements by FDA, while most consumers demanded it. Similarly, contrasts surfaced with respect to the issue of whether dietary supplements should be regulated as foods or drugs. Manufacturers overwhelmingly said that the products should be regulated as foods with wide availability. Some advocacy groups, on the other

hand, said that the L-tryptophan experience should persuade FDA and Congress to impose the same efficacy, safety, and labeling requirements for dietary supplements as those required for drugs.

With respect to the issue of whether FDA has sufficient statutory authority to regulate dietary supplements, some believe FDA has adequate authority, while others believe that additional authority is needed.

ISSUES

The Task Force will briefly outline the issues that they have considered in the preparation of this report. Questions and considerations are presented to serve as a basis for subsequent detailed discussion elsewhere in this report.

One of the first assignments of the Task Force was to develop a definition for the term "dietary supplement." The Task Force has constructed a definition which is consistent with the proposed definition drafted for the implementation of the NLEA (refer to p. 12).

The Task Force believes that safety is uppermost in its assignment and the agency's mission. Consequently, it chose as its first priority, ensuring the safety of dietary supplements. In examining this issue, the Task Force has considered several

questions that would frame the parameters of FDA's responsibility to accomplish this goal. First, on whom should the burden to prove safety fall, the FDA or the manufacturer? The present food additive provisions of the FD&C Act place the burden of demonstration of safety on the manufacturer.

The Task Force believes that there is a critical need to improve the accuracy and completeness of the information provided on dietary supplement labels. This need was overwhelmingly voiced by the testimony presented and written comments submitted at the public meeting. Labeling must provide adequate directions for safe use, accurate nutrient information, complete ingredient listings, and truthful claims. For products sold as foods, FDA's traditional view has been that warning statements should be kept at a minimum but should be present when necessary. The Task Force has also considered the related problem of the misleading promotion of products in advertising.

In the past, FDA has not approved the use of disclaimers on product labels. Departing from past policy, the Task Force has considered whether the agency should require the declaration of disclaimers on the labels of dietary supplements. The Task Force has also examined avenues to address the problem of misleading product names, misleading nutrition claims, and misrepresentations on the labels of supplement products under 403(a) of the FD&C Act.

Comments from the public meeting confirm the Task Force's belief that there is a critical need to establish quality assurance and good manufacturing practice guidelines for dietary supplements. Therefore, the Task Force has explored options to ensure the purity, strength, stability, proper dissolution, bioavailability, and conformity with proper manufacturing procedure of these products.

The Task Force has also studied the concept of "intended use" as it relates to dietary supplements that are used and covertly promoted for use as drugs and has offered recommendations for the regulation of such products. A case in point is the sale of niacin at high dosage levels under the guise of a nutrient, but being used for lowering blood cholesterol.

The public generally believes that foods are inherently safer than drugs and can be consumed liberally without harm. However, adequate studies to substantiate the safety of a significant number of products currently marketed and represented as dietary supplements (foods) have not been conducted. It must be kept in mind that foods, unlike food additives and drugs, do not require premarketing clearance. On the other hand, substances used in dietary supplements must be prior-sanctioned, GRAS, or listed for this use in a food additive regulation. In contrast, an over-the-counter (OTC) drug is required to be shown as safe prior to marketing. Concern regarding this disparity in the relative risk

to the consumer from taking dietary supplements compared to taking OTC drugs has prompted the Task Force to consider a mechanism to ensure that dietary supplements are at least as safe, or safer than, OTC drugs. The Task Force has examined the related issue of an appropriate strategy for regulating the safety of products that fit into more than one category, e.g., both a food and a drug. There is also a small category of products sold as cosmetics, but the Task Force believes these products can be controlled adequately as unsafe color additives (e.g., tanning pills) or as drugs (e.g., vitamins to improve skin texture).

Lastly, the Task Force has discussed and has made recommendations for the following issues related to dietary supplements: tamper-resistant packaging, child-proof caps. Strengthening the adverse reaction reporting system, providing public education, international trade implications, and cooperative FDA/state activities.

RELATED PRODUCTS NOT SPECIFICALLY ADDRESSED BY TASK FORCE

Several products and substances, because of their nature, were purposely not addressed by the Task Force.

Homeopathic Products

A significant increase in the importation and domestic marketing of homeopathic products has resulted in a multimillion dollar industry in the U.S. Commonly represented for use as supplements, these products contain a variety of ingredients, generally in amounts so minute as to defy analyses, but often bear claims that represent them as drugs. In some cases, substances are falsely represented as dietary supplements and are labeled with homeopathic representations in an attempt to circumvent FDA's food additive approval procedure and to mislead the consumer.

FDA's policy regarding homeopathic drug products is stated in Compliance Policy Guide (CPG) 7132.15. FDA should continue to regulate products that bear homeopathic claims as drug products. The Task Force recommends that the Center for Drug Evaluation and Research (CDER) consider revising its present CPG to improve the agency's ability to deter manufacturers from employing this fraudulent practice.

Herbs

Herbal products marketed as supplements in tablet, capsule or other form, present a unique problem to the agency. These products are not taken for their taste, aroma, flavor, or nutritional value. Some have pharmacological use. The safety of a number of these herbs has not been demonstrated, and the ill-

effects, if any, are unknown. Dietary supplements containing herbs are subject to the provisions of the NLEA and to the proposed regulations currently under consideration. However, the Task Force is recommending that the Center for Food Safety and Applied Nutrition (CFSAN) and CDER work together to resolve the safety and labeling issues related to the marketing of herbs in tablet, capsule, or other forms.

Medical Foods

The Dietary Supplements Task Force is not considering foods intended to be used solely under medical supervision to meet the nutritional requirements of specific medical conditions. FDA's regulation of these products, which include enterally administered supplements of protein, vitamins, minerals, amino acids, and fatty acids, is currently being examined by a separate agency task force.

Protein Products

The Task Force has considered the agency's regulation of protein products containing added vitamins and minerals that are currently marketed and represented for a number of uses, including weight loss, weight gain, body building, and general protein and nutrient supplementation. These products will be subject to the newly proposed regulations under the NLEA. In

addition, the Task Force believes that protein products containing added vitamins, minerals, and amino acids are subject, to the extent applicable, to the recommendations made in this report. The Task Force is also recommending that CFSAN consider review of 21 CFR Part 105 to determine whether additional language to prescribe specific requirements for these products is needed.

Fatty Acids

The Task Force acknowledges that some essential fatty acids; i.e., linoleic, arachidonic, and linolenic are sold as dietary supplements. These substances will be addressed later on a case-by-case basis. Omega 3 fatty acids from fish oil are also sold as dietary supplements but are labeled with claims for lowering blood cholesterol and for preventing heart disease. Omega 3 fatty acids have recently been the subject of regulatory letters issued by CDER. In addition, CFSAN has reviewed the available data on the relationship of Omega 3 fatty acids to heart disease as a part of the implementation of the NLEA. The safety of these fatty acids for use as dietary supplements has not been demonstrated. The agency may obtain more definitive scientific data through the rulemaking process currently underway for the NLEA. The Task Force recommends that CFSAN move to determine the GRAS or food additive status of other fatty acids presently sold for supplementation.

Carnitine

Carnitine may be described as a conditionally essential nutrient. It is not required in the diet of normal human adults, but it is metabolically essential and is not synthesized by newborn infants at rates that are sufficient to maintain normal blood levels. The Task Force focused numerous discussions on concerns related to carnitine because of its unique nutritional status and because it has been represented by purveyors for various unapproved therapeutic uses. A further discussion of the Task Force's considerations regarding carnitine is found in Appendix 5.

VITAMINS/ESSENTIAL MINERALS

Introduction

The Task Force identified vitamins and essential minerals as the first category of materials used in dietary supplements for specific attention. This category includes materials that have a long history of such use. It is not the purpose of this report to recommend for or against the use of vitamin/mineral dietary supplements, but instead it is to provide the agency with a practical approach to regulating these products. These substances may present certain health risks at higher levels of intake. However, there are no documented reports that daily

multiple vitamin and mineral supplements equaling the Recommended Daily Allowance (RDA) are harmful for the general population. The recommended intake levels¹ for these substances, and higher levels where there is high presumptive risk, span a range of intakes that varies from "useful" to "useless," and from "safe" to "unsafe."

Support for separating vitamins and minerals into a distinct category of dietary supplements was voiced at the public meeting. Concerns regarding the safety of excessive intakes of vitamins and minerals, and the agency's inadequate regulation of high intakes of vitamins and minerals, were also expressed. A discussion of specific comments submitted on these issues is found in Appendix 3.

Background

The Dietary Supplements Task Force reviewed the history of the agency's approaches to regulating vitamins and minerals. Highlights of this history are summarized in Appendix 4.

Vitamins and essential minerals occur naturally in food. It has long been a tenet of many in the nutrition and health communities that a well-balanced or varied diet supplies adequate intakes of

¹Diet and Health, NRC, 1989. Surgeon General's Report, 1988. RDA's, 10th Ed., NRC, 1989. Dietary Guidelines for Americans, USDA, DHHS, 3rd Ed., 1990.

all of the individual vitamins and minerals and supplementation is generally not required. Some exceptions as a consequence of certain health conditions are recognized, however.

Dr. Robert E. Olsen of the State University of New York at Stonybrook addressed this question at the public meeting and stated opposition to the need for dietary supplementation.

He said:

Healthy adult men and nonpregnant, nonlactating women consuming a varied diet do not need vitamin supplements, and I think the studies that have been cited today with respect to surveys of large numbers of people in this country support that view. The fact that there is a percentage that do not meet the RDA does not mean they are nutritionally deficient because the RDA is a high number. It is placed at two standard deviations beyond the mean in human studies.

Dr. Olsen's comments are representative of the predominant view of the nutrition research and health practitioner communities, that the currently available clinical and biochemical evidence of nutritional well-being indicates little or no nutritional inadequacies of vitamins and minerals in the U.S. population.

However, the opposing view offered by the food and dietary supplement industry and some health practitioners is that diets

may not always be "well-balanced," and there are plausible arguments to justify dietary supplementation. This viewpoint cites several uncertainties that the consumer may feel in relation to the need for dietary supplementation: 1) How does one judge whether the diet is "well balanced?" 2) How much deviation from such a diet would be needed to cause deficiency of one or more essential nutrients? 3) How can the consumer know which nutrient or nutrients are most likely to be consumed in inadequate quantities? 4) Can health professionals be certain that all nutritional requirements are now recognized, and if not, what should be the consumer's nutrient intake objectives in the meantime? 5) Are there any benefits from consumption of nutrients in amounts greater than the RDAs, possibly through reducing the risk of chronic disease rather than prevention of classic nutritional deficiencies? This set of uncertainties appears to form the basis for the rationale of many individuals who are regular consumers of vitamin and mineral dietary supplements.

Certain nutrients for certain population groups are more likely than others to be needed in increased intakes, e.g., iron for pregnant women, and calcium for adolescent and postmenopausal women. Additionally, consumers may choose to use dietary supplements as "insurance" against perceived risks of nutritional deficiencies or on advice of physicians; and safe supplement products should be available to them under these

circumstances.

Dietary supplements, however, is not an effective replacement for eating a varied diet and is not likely to be effective in achieving adequate nutrient intake in all population groups. Sound public health policy dictates that when a nutrient deficit has been shown to affect a significant segment of the population, the use of fortification principles provides the most effective means of reaching the greatest number in need.

Section 411 of the FD&C Act specifically prohibits regulation of potency to levels that the Secretary determines to be nutritionally rational. Although the agency may not use nutritional efficacy to regulate potency of vitamin and mineral dietary supplements under current law, safety (assuming label instructions are followed) should be a prerequisite before products are made available to consumers.

Vitamin/Mineral Regulatory Schemes

This section will first present definitions and then a possible regulatory scheme that would be workable in the context of existing statutory authority.

Definitions

For the purpose of the following discussion of regulatory schemes for vitamins and minerals, the Task Force believes that vitamins and minerals should be defined as follows:

Vitamin: An organic substance that is essential for health but cannot be synthesized by humans, and therefore, must be provided by the diet. This definition excludes essential fatty acids and essential amino acids as vitamins. These substances are discussed in other sections of this report.

Some substances that can be synthesized by humans have been classified by nutrition authorities as vitamins. For example, nicotinic acid is synthesized in humans, but not in amounts sufficient to meet the niacin requirement. Also, it might be desirable to allow a conditional class of nutrients: those that are essential in the diet only under certain circumstances. A detailed discussion of carnitine is found at Appendix 5.

Essential Mineral: A mineral element that is required by the human body and is, therefore, essential in the diet. However, cobalt is not considered to be an essential element, even though it is required as a component of vitamin B₁₂ (cobalamin).

There are several corollaries to the above definitions as follows:

For Vitamins:

- o If a substance is not essential in the diet, it is not a vitamin.
- o A substance may be semi-essential; i.e., it may be synthesized in the body, but not at a rate that is sufficient to meet physiological needs, and therefore, part of the amount needed must be provided by the diet. New evidence suggests that choline may fall into this category, although it heretofore has not been considered to be essential, and therefore, not a vitamin.
- o A substance may be a vitamin for special subpopulations but not for most persons, e.g., carnitine may be essential for neonates, and if so, could be described as a nutrient for infants (see Appendix 5).
- o A substance may be a vitamin for some species, but not for humans (and vice versa), e.g., Vitamin C is a vitamin for humans, but not for most other animal species.

For Minerals:

- o Many minerals are nonessential.
- o Any mineral in the environment may get into the food chain and be found in foods consumed by humans. If minerals occur in foods, some will be absorbed and incorporated into human tissues. Their mere presence there does not signify that they have any nutritional function.
- o The presence of an essential mineral in a food or a supplement does not automatically mean that it is bioavailable and useful.

The corollaries, as well as the definitions, should be taken into account in any regulatory scheme for vitamins and minerals.

Recommended Regulatory Scheme in Context of Current Statute

The Dietary Supplements Task Force recommends consideration of the following options under existing statute:

REGULATORY SCHEME

The Task Force believes that there are two basic components needed in any approach to regulation of dietary supplements: 1)

regulation of the label, including claims, and 2) regulation of characteristics of the products themselves, including safety, potency, purity, and bioavailability.

Depending on the claims made for them, dietary supplements may be divided into three categories.

1. Regulation of the Label Including Claims

- a. Those with therapeutic/drug claims that are not NLEA-approved health claims.**

Those products bearing therapeutic/drug claims will be handled primarily by CDER with appropriate drug charges. In the event that the firm is willing to delete all such claims, one of the other sections of this scheme may be applicable.

- b. Those with NLEA-approved health claims.**

Those products with NLEA-approved health claims will be governed by the final regulations concerning such claims.

- c. Those with no therapeutic or with NLEA health claims.**

Those products with no therapeutic/drug claims or with NLEA approved health claims will be classified in one or more of the

following and handled as indicated:

i) If the products contain nutrients that have specific set levels (U.S. RDAs/RDIs), their potencies will be listed on the label. If the product contains one or more nutrients that have no officially set levels, they will be listed in terms of potency but not in percentages.

ii) If the products contain mixtures of essential nutrients and nonessential substances, action can be taken under the Proxmire Amendment if any of the non-essential substances are featured anywhere on the label except as part of a complete ingredient statement. Action can be taken if a potency is listed for the nonessential substances.

iii) Products that are indicated on the label as containing insignificant amounts of nutrients will be subject to action. In FDA's pending proposals under the NLEA, the agency has defined "source" and "high." If the nutrient is present in a smaller amount than that which is defined as a "source," action can be taken.

iv) Products with unsafe levels of nutrients or other

components will be subject to action. Those against which FDA has taken action in the past are high levels of Vitamins A, D, and B₆. Since the agency has no specific levels at which it would charge that such products are poisonous or deleterious, these will be handled on a case-by-case basis depending on the level (dosage) and the target population.

v) Those products containing substances that are not GRAS involve one of the most important and controversial categories. The point at which the agency has been willing to take action on a food additive charge has generally been based on a determination that the agency could show some degree of toxicity or potential toxicity. For years, FDA has been reluctant to set safe levels for nutrients in dietary supplements under the food additive regulations because the industry has shown in the past that setting such levels provides it with a cut-off point just below which FDA will not take action even though such levels are high. Such levels then become the industry marketing norm. Nevertheless, the Task Force believes that setting such levels is appropriate.

2. Regulation of Vitamin/Mineral Product Characteristics

While vitamins and minerals may be regulated on the basis of potency, purity, and bioavailability, the Task Force places major emphasis on the issue of safety.

- a. To ensure the safety of vitamin and mineral products, the Task Force recommends that the agency adopt a "Dietary Supplement Limit" (DSL), which would be the maximum daily intake for a given vitamin or mineral that the agency deems to be safe.

The DSL for any vitamin or mineral might range from near the current RDA to higher values, depending on available evidence.

- b) To ensure the purity of vitamin and mineral supplements, the Task Force recommends that the agency
 - 1) establish Good Manufacturing Practice Standards; and
 - 2) establish and implement purity identity and bioavailability standards.

FDA should develop standards incorporating the best ideas from standards developed by the USP. USP is currently considering standards for vitamins, minerals, and nutritional supplements. Issues identified include analytical methodology, disintegration, dissolution, composition uniformity, weight variation, chemical interactions of components, and content microbial limits. FDA

should establish and implement standards for chemical identity. The standards should include specification of acceptable analytical methods for determining identity and quantity for each of the vitamins and minerals.

- c. To ensure that vitamin and mineral products are presented to the body in forms conducive for absorption and utilization, the Task Force recommends that the agency 1) establish and implement disintegration standards; 2) establish dissolution standards; and 3) consider evidence other than disintegration and dissolution when such data are needed.

The Task Force notes that GRAS regulations (21 CFR Parts 182 & 184) and food additive regulations (21 CFR Part 172) exist for certain vitamins and minerals. In most cases, the agency has interpreted these regulations as permitting nutrient supplementation of processed foods and has interpreted 21 CFR 170.3(o) in that way. In the September 5, 1980 Federal Register, the agency made a distinction between the use of vitamins and minerals for nutrient supplementation (addition to foods) and the use of these substances in dietary supplements. The agency has not, however, included use in dietary supplements as a technical effect under section 170.3(o).

The Task Force believes that the agency has a number of regulatory options available to it in the context of the above recommendations on vitamin and mineral products. Specifically, the agency could, and the Task Force believes that it should, propose in the Federal Register to define a new technical effect in 21 CFR 170.3 (o) for "dietary supplement." In addition, the agency should initiate rulemaking to establish safe levels of use for vitamins and minerals in dietary supplements. Alternatively, the agency could call for the submission of food additive or GRAS affirmation petitions on the use of essential vitamins or minerals in "dietary supplements." One approach would be for the agency to propose to affirm as GRAS (with certain specific exceptions) the highest RDA levels listed by the National Academy of Sciences. The burden would then shift to the commenters to submit evidence that would justify a higher DSL. Such an approach would facilitate the publication of a proposal (or proposals) and focus the work of agency scientists in preparing the final rule or rules.

The Task Force recommends such actions because they believe that it is appropriate for the agency to distinguish between those dietary supplements whose use is safe and have a reasonable rationale from those whose use creates public health concern. The Task Force believes that drawing such a distinction will advance the agency in its pursuit of its regulatory goals by focusing the agency on those products of real concern and by

limiting the opposition to the agency's actions in the dietary supplement area. Finally, these actions will address the obvious public interest expressed at the meeting, in safe vitamin and mineral products.

Recommendations

1. The agency should propose in the Federal Register to define a new technical effect for food ingredient in 21 CFR 170.3(o) of "dietary supplements."

2. The agency should then institute a process involving a proposal or proposals issued on the agency's own initiative or the submission of either food additive or GRAS affirmation petitions to establish safe levels for the use of certain essential vitamins or minerals in dietary supplements. It should also establish purity and bioavailability standards.

3. The agency should take regulatory action against those supplements that exceed the above quantitative guidelines as "unsafe food additives" under section 402(a)(2)(C) of the FD&C Act.

AMINO ACIDS

Introduction

Current regulations treat amino acids as food additives under 21 CFR § 172.320 and as GRAS substances for certain technological uses under § 182 and § 184. The safety of amino acids when used according to the conditions set forth in these regulations has been established. In addition, FDA recognizes them as drugs under 201(g)(1)(B) of the Act when represented for therapeutic use or to prevent disease.

There is a lack of consensus, however, about how FDA should regulate discrete amino acids, sold to users in capsule, tablet, liquid, powder, or any other form. Presently, under 21 CFR 172.320, they are unapproved food additives. Some critics, however, point to the fact that such products containing amino acids are widely sold, and they contend that the current regulatory scheme does not control these products. The manufacturers of these products, on the other hand, contend that they have made their own determination that this use of amino acids is GRAS.

In response to the eosinophilia-myalgia syndrome (EMS) epidemic, FDA has taken action to remove all supplements that contain L-

Tryptophan from the market. Manufacturers, retailers, and users of amino acids are questioning FDA's action, however, particularly its implications for other amino acid supplements. Many object to FDA not treating all these products the same way. They note that amino acids, other than L-Tryptophan, are being marketed, and they fault the agency for an inconsistent policy. Because of regulatory action stimulated by EMS, L-Tryptophan can no longer be sold. On the basis of studies in the animal model performed to date, it would appear that a contaminant may have a role in EMS. However, these studies also indicate that L-Tryptophan itself may have a role in EMS. Additional studies are planned. The L-Tryptophan problem has heightened public interest in the agency's enforcement policy for all amino acids.

Discussion of the Problem

The Task Force considered the suitability of the agency's regulatory scheme for amino acids and tried to identify any gaps that needed to be addressed. It carefully considered the testimony and comments presented at or received in response to the public meeting, along with other materials that were presented in testimony before the Human Resources and Intergovernmental Relations Subcommittee of the House Committee on Government Operations on L-Tryptophan on July 18, 1991. Additional information on this issue may be forthcoming from an FDA contract with the Federated Associated Societies of

Experimental Biology (FASEB) to evaluate whether there are any particular safety concerns about amino acids. However, the FASEB information will not be available until some time in 1992, and thus, was not available to the Task Force in preparation of these recommendations.

Summary of the Public Meeting

At the public meeting on August 29, 1991, manufacturers and some users of dietary supplements contended that amino acids are foods and, therefore, should be regulated as conventional foods. The presenters who felt amino acids should only be regulated as foods justified their position by stating that "dietary food supplements" should be broadly defined as any food extract, food concentrate, or food substance; the only exception being a substance that is clearly toxic.

In contrast, those contending that amino acids should be regulated as drugs argued that:

Any products which are believed by competent scientists to carry the risk of significant harm if taken in isolation or in excessive dosages--such as the amino acids--should be made available only as prescription drugs so as to permit medical determination of patient need for these substances, medical supervision of their ingestion, and medical research

into claims of their safety and beneficial effects. This solution would also offer physicians and consumers the protection of package inserts, which would provide information as to contraindications, side effects, dosages, etc. (Norma J. Hart, Psy.D., an EMS victim and former L-Tryptophan user). (See also comments of Abbey Meyers, Executive Director of the National Organization for Rare Diseases, p. 147.)

Some testimony evidences that the use of amino acid products has been directed primarily toward the treatment, cure, mitigation or prevention of disease. Dr. Hart stated:

... I took Tryptophan because I have been a rather hyper person all my life and always had trouble sleeping, always wanted to avoid becoming dependent on habit-forming prescription drugs. I was told in nutrition columns in the New York Times and by physicians and people in health food stores that L-Tryptophan was a natural substance occurring in milk and turkey. With two master's degrees and a doctorate, I thought they boiled down milk and turkey and made pills."

Congressional Testimony

The agency notes that the Health Protection Branch (HPB) of

Health and Welfare Canada, FDA's Canadian counterpart for the regulation of food and drug products, has determined, in an information letter to the industry in May 1985, that products containing single amino acids are drugs. Simon N. Young, Ph.D., Professor, Department of Psychiatry and Professor, School of Dietetics and Human Nutrition, McGill University, in testimony before the Human Resources and Intergovernmental Relations Subcommittee of the U.S. House of Representatives, said that according to HPB "products containing single amino acids or mixtures of amino acids which have demonstrated pharmacological effects or for which drug claims are made or implied are considered to be drugs as defined in the Food and Drugs Act." Canada classified the following amino acids, in all isomeric forms, as drugs: arginine, lysine, methionine, ornithine, phenylalanine, tryptophan, and tyrosine. With some exceptions for methionine, all were deemed to be new drugs requiring "evidence of the safety and effectiveness of the product when used as directed..."

The following amino acids, according to Richard J. Wurtman, M.D., Professor of Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology (Weiss Hearing 7/18/91) have physiological and medical effects and are consumed for that purpose, not for correcting "spurious nutritional deficiency": L-Threonine, L-Tryptophan, L-Tyrosine, and L-Carnitine (another substance with physiologic effect which the Task Force addresses

in the vitamin-mineral section of this report).

Task Force Deliberations

The Task Force directed its attention to all aspects of the issue of how to regulate amino acids. First, the Task Force concluded that current regulatory controls of amino acids for uses listed under 21 CFR § 172.320, § 182, and § 184 of the Act are adequate, if enforced, for providing assurances to the consumer that the covered uses will be safe.

Next, the Task Force examined the agency's regulation of single amino acids and mixtures of amino acids sold in tablet, capsule, liquid, powder or any other form. Although the marketing of these products is in violation of section 172.320, the Task Force wished to consider them separately. It discerned that some members of Congress considered them to be under-regulated by FDA whereas, others, e.g., the Council for Responsible Nutrition (CRN), considered them to be GRAS substances. Thus, the Task Force recognized the need to address the following KEY ISSUE:

How should single amino acids or mixtures of amino acids be regulated by the FDA when sold to the user in capsule, tablet, liquid, powder or other forms?

History shows that during almost 30 years of marketing, these

products have been used for drug, not food, purposes. Research efforts over this same period indicate that there were attempts to develop these products as drugs. This impression was reinforced in the popular literature, which has been substantially oriented toward drug, not nutritional, usage. Moreover, the testimony at the public meeting also evidences that these products are recommended by physicians, discussed in the popular media (print and broadcast), and consumed by the public for their medical, not nutritional, benefits.

The Task Force noted that ingestion of amino acids, if not properly balanced, may result in adverse effects in three ways:

1. Excessive intake of individual amino acids may result in toxicity which is alleviated only by decreasing the excessive intake of the amino acid. For example, methionine or tryptophan might result in toxicity, but there is little or no similarity of effect from one amino acid to another.

2. Excessive intake of one or more individual amino acids may result in an imbalance that can be alleviated by supplementing with the amino acids that have been rendered relatively deficient. For example, threonine may produce a tryptophan deficiency unless there is adequate tryptophan or niacin to compensate.

3. An excess of one amino acid might inhibit absorption, transport or t-RNA activation of another, and the effects could be alleviated by decreasing the excessive amino acid or by increasing the one it is inhibiting. For example, either lysine or arginine could inhibit functions of the other if present in excess.

The Task Force recognizes that such adverse effects would be expected to be dose-dependent and that a sufficiently low level of intake may be identified at which the adverse effects would not be expected to occur. Given the potential of adverse effects, however, ensuring the safety of the use of amino acids needs to be a key element of any regulatory scheme that is developed.

Options

The Task Force considered the following options:

Option 1: Regulate single amino acids and mixtures of amino acids as drugs.

Given the history of how single and multiple amino acid products have been marketed, the Task Force believes that one option would be to institute rulemaking to classify the amino acids as drugs when sold for any use other than those uses that are listed as

safe in FDA's food additive regulations or as generally recognized as safe in 21 CFR 182 or 184. The advantage of such a rulemaking is that it would establish that these products are drugs as a matter of law, thereby rendering the case-by-case approach that the agency has taken to these products unnecessary. It would also respond to criticisms that these products are being sold as drugs, regardless of what label claims are actually being made and, therefore, that the agency is remiss in not regulating them as such. This criticism was voiced at the Weiss hearing.

A disadvantage of such a rulemaking is that, although there are no known nutritional uses for these amino acids, there is always the potential that some might be developed. The suggested rulemaking may make it difficult for the agency to accommodate such uses. Moreover, an additional difficulty with this course of action is the question of whether it can be done consistently with the Act. The agency's last attempt to classify ingredients of dietary supplements (high levels of vitamins A and D) ended with the rules being invalidated because they were arbitrary and capricious. However, even in throwing out the agency's rules, the court held out the possibility that in appropriate circumstances, such a rulemaking could be upheld.

The Task Force believes that the facts surrounding the use of amino acids are distinguishable from those in the vitamin A and D rulemaking; they justify renewed efforts in this regard, and they

make a different outcome possible. It is important to emphasize, however, that putting a regulation in place that classifies amino acids as drugs will undoubtedly be contentious and will occur only after a difficult legal fight.

The Task Force believes that FDA can find that amino acids are drugs under section 201(g)(1)(B) of the Act. This section provided the main basis for the agency's action with respect to Vitamins A and D. Under section 201(g)(1)(B), an article is a drug if it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in man or other animals. In National Nutritional Foods Association v. Weinberger, 512 F.2d 688, 703 (2d Cir. 1975), the court held that a showing that vitamins A and D, at the regulated purposes, were used almost exclusively for therapeutic purposes, coupled with a lack of recognized nutrition use at those levels would be sufficient to justify a finding that these substances were intended for use in the treatment of disease and thus were drugs.

In that case, however, the agency did not make an adequate showing. In National Nutritional Foods Association v. Matthews, 557 F.2d 325 (2d Cir. 1971), the agency's main concern regarding the safety of the levels of vitamins A and D was at issue, not their drug use; the evidence of use of these vitamins to prevent or treat disease was drawn from promotion of such uses by persons not associated with the manufacturers or vendors of such

products; and the court was unable to find, given the agency's concern with the toxicity of the products, that there was not nutritional value at the levels at issue. Id.

The Task Force believes that a completely different factual situation applies with respect to amino acids. The available evidence, including the testimony and other information discussed above, makes clear that most, if not all, of the amino acids have been promoted by their manufacturers or vendors for therapeutic purposes. The evidence also shows that these claims have been widespread and not limited to one or two manufacturers. Finally, the evidence also shows that while it is true that not all manufacturers have made such claims in their labels or labeling, there are no known nutritional uses of amino acids other than to improve the protein quality of foods that are natural sources of protein (see 21 CFR 172.320) or as ingredients of nutritional products, such as exempt infant formulas or medical foods, designed for people who are unable to tolerate protein. The single or multiple amino acid dietary supplements have no nutritive value.

FDA's review of numerous amino acid package labels has revealed a pervasive use of drug claims by manufacturers and promoters of these products. Specific examples of label claims are:

"Nature's Tranquilizer" L-TRYPTOPHAN TABLETS - This

important amino acid is probably the most widely researched of them all. The body converts L-Tryptophan into Serotonin, a chemical messenger of the brain that acts as a natural tranquilizer.

L-Citrulline...stimulates the immune system; therefore, beneficial in the presence of any illness, disease, traumatic injury or wound.

L-Cysteine... Acts as a detoxifier; aids healing. Essential for proper formation of the skin...hair growth...preventing not only hangovers but brain and liver damage from alcohol...helps prevent damages from the ill effects of cigarette smoke...rheumatoid arthritis.

L-Glutamic Acid...increases the blood sugar level; used in the treatment of hypoglycemia.

L-Glutamine...reduce cravings for alcohol and sweets...decrease mental fatigue...used in the treatment of alcoholism...used in the treatment of schizophrenia and senility.

In addition, FDA's review of articles published in popular periodicals indicates that numerous claims are made for the effectiveness of amino acids in treating numerous conditions,

including insomnia, migraines, weight control/obesity, heart attacks and heart disease, immunity, and phenylketonuria (PKU). Specific examples are as follows:

L-Tryptophan - "The Nutritional Approach to Sleeping Disorders" by Philip W. Zimmerman, Ph.D. as published in Health World (Sept/Oct 1989) (pp. 23-26).

Health Foods Business (August 1988) (p. 13)...stimulates the release of growth hormone which burns body fat and acts as an aid in weight control.

"Amino Acids, The Building Blocks of Life", by Keith Stepro, Let's Live, (July 1986) (p. 14) "Reduces heart attack risk."

Lysine, Tryptophan, and Other Amino Acids, by Robert Garrison, published by Keats Publishing Company.

"Alive and Well! Amino Acids: New Benefits and Protection", Health News & Review, (July/August 1987), Keats Publishing Inc.

FDA has taken regulatory actions against single and combination amino acid products falsely represented for drug use. In 1991, FDA filed 9 seizure actions against approximately 14 amino acid products. Five of these seizures have been completed.

Violations included unapproved new drugs, section 505(a), inadequate directions for use, section 502 (f)(1), and false and misleading labeling, section 502(a). The products contained a number of amino acids including L-glycine, L-tryptophan, L-carnitine, L-glutamine, l-phenylalanine, L-alanine, L-histidine, L-taurine, L-asparagine, L-arginine, isoleucine, L-tyrosine, L-valine, L-cysteine, L-ornithine, L-aspartic acid, l-methionine, L-serine, L-threonine, and L-citrulline.

Thus the evidence with respect to the amino acids supports that the products are not being consumed for nutritional purposes, but that a significant percentage, if not all, are being consumed for drug purposes. Given these facts, the agency would propose to find that the therapeutic use of these products, which is in large measure attributable to the vendors and manufacturers, so far outweighs their use as dietary supplements that the intent attributable to any manufacturer of such products is to market them as drugs.

Option 2: Regulate amino acids solely as food additives or GRAS substances, unless drug claims are made for the particular product.

Under such an approach, the agency would set a DSL for each amino acid. Products containing a single amino acid or mixture of amino acids would be permitted if the following conditions are

met:

- a. The product does not exceed the DSL set in a manner analogous to that for vitamins and minerals.
- b. The amount of an amino acid permitted by the DSL is not trivial compared with its requirement (identified by the National Research Council).

In consideration of the possible nutritional usefulness, the Task Force examined the option of extending the "dietary supplement" category proposed for vitamins and minerals to include amino acids. The Task Force believes that such an expansion would be possible.

Recommendations

1. Regulate single amino acids and mixtures of amino acids as drugs.
2. Retain current policy in 21 CFR 172.320, 182, and 184 for regulating amino acids added as discrete ingredients to foods.

The Task Force recommends this approach because it better reflects the requirements of the Act and the current factual situation. The Act states that articles intended for use in the treatment or prevention of disease are drugs, 21 USC 321(g)(1)(B). The evidence cited above demonstrates that single

and multiple amino acids sold in tablet and capsule form are widely represented for drug use. Therefore, the Task Force recommends that these products be clearly and effectively regulated under the drug provisions of the Act. Exemptions to such regulation should only be created where evidence that clearly establishes that a particular use of amino acid is safe, and that the amino acid will have its intended food effect, is presented to the Agency.

REGULATORY SCHEME FOR PRODUCTS OTHER THAN
VITAMIN/MINERALS AND AMINO ACIDS

This category contains a broad array of substances that are offered for sale as components of dietary supplements, but do not meet the criteria for inclusion in category one (vitamins and minerals) or two (amino acids). Although the manufacturers and vendors of many of these substances probably would be unable to show that the substances meet the definition of a common sense food set out in Nutrilab, Inc. v. Schweiker, 713 F.2d 335 (7th Cir. 1983) (i.e., food is a substance consumed for its taste, aroma or nutritive value), the agency has been content to acquiesce in the marketing of such substances as food ingredients, except when clear therapeutic or disease prevention claims are made on the label or in the labeling of the products that contain these substances. As food ingredients, these substances are subject to regulation under the food additive provisions of the Act (sections 201(s) and 409). However, the Act does not explicitly restrict marketing to substances whose safety has been determined by FDA. Therefore, many of these substances are marketed without any safety review by the agency. Because of resource requirements of an enforcement action based on a food additive charge, FDA has limited its enforcement actions to those instances in which it believes there is a particular reason to be concerned about the safety of the substance (e.g., oil of evening primrose).

Many of the substances in this category are promoted by nonlabel or labeling means for health-related uses. As a result, they have developed particularly strong constituencies supporting "freedom of choice" in food and medicine and also are defended by those who argue that too much of the medical profession is prescribing "pills" when "healthy lifestyles" could prevent or ameliorate many illnesses. However, as stated above, many of the "natural" substances or "dietary substitutes" have not been studied sufficiently to know whether they pose any safety problems. Moreover, Congress' judgment that substances intended for use in the cure, treatment, prevention or mitigation of disease should be shown to be effective for their intended use (21 U.S.C. 355) is the law of the land.

FDA's traditional approach of regulating these substances on a case-by-case basis is controversial. While this approach is strongly defended by the supplement industry, as well as by some in Congress, who argue that this industry should be "left alone," it is an approach that is criticized by others in Congress and in the public as an example of FDA waiting until the "bodies are lying in the doorway." A number of public health organizations have advocated regulation of these substances prospectively because many of them are potentially unsafe.

Much of the testimony received for the Task Force's public

meeting stressed the importance of assuring the safety of products containing these substances. However, there was little sentiment expressed in this testimony, nor has such inclination been indicated by the Congress, for regulation of these products as drugs or for creating a regulatory scheme that would result in all such products being removed from the market.

The ultimate goals of the Task Force with respect to these products can be defined as follows: (1) to ensure the safe use of category three substances (this may mean reviewing the safety of these ingredients before they are allowed on the market or engaging in active surveillance of those that are on the market, and ensuring that those substances, not proven safe or effective as drugs, are not substituted for effective drugs); (2) to ensure a "level playing field" (materials intended to be used as drugs should be regulated as drugs); and (3) to ensure, to the extent possible, freedom of choice for consumers by making a wide variety of products available.

There are several critical problems, however, with establishing a regulatory scheme to achieve these goals fully. The following discussion lays out regulatory options and describes the difficulties associated with implementing the proposals.

Option 1: Continued Regulation as Food Additives

It has been FDA's practice to regulate ingredients of dietary supplements as food additives. If the ingredient's use in the dietary supplement has not been listed by FDA, the supplement is adulterated under section 402(a)(2)(C) of the Act. (An unapproved ingredient is also subject to regulation as an added substance under section 402(a)(1) of the Act). This practice has been challenged in several pending enforcement actions. If the agency prevails in these court cases, and given some recent successes, there is every reason to believe that it will, it may establish the appropriateness of this approach (although given the resources of the dietary supplement industry and its willingness to litigate, it is difficult to be optimistic).

However, in the event that FDA's approach is rejected by the courts, the Task Force would recommend that the agency seek legislative change. Such court action would have the effect of, for example, defining the blackcurrant oil in blackcurrant oil capsules, and not the finished supplement capsule, as the food. As a result, this ingredient would likely be considered to not be an added substance in the food. Under section 402(a)(1) of the Act, a component that is not added renders a food adulterated only if it is "ordinarily injurious" to health. Thus, action against such an ingredient of a supplement would be feasible only if FDA could substantiate an "ordinarily injurious" charge.

The case of L-tryptophan illustrates the difficulty that this

kind of court decision would create. If L-tryptophan had been determined not to be added to the dietary supplements that caused the EMS outbreak in 1989, FDA might have been powerless to act. Because not everyone who took L-Tryptophan supplements became ill (although more than 30 died and 1500 did become ill), FDA would have had great difficulty in proving that the product was ordinarily injurious. Such a situation would clearly be unacceptable and would require that strong consideration be given to seeking a legislative change.

Option 2: Requirement of Safety Determination

To ensure the safety of the ingredients in these substances, FDA could seek to require that manufacturers supply safety data. Currently, as stated above, manufacturers can market these substances based on their own GRAS determinations. Thus, a requirement for agency premarket review of safety would require a change in the Act, which may be difficult to justify. Although there have been some safety problems (e.g., L-tryptophan), there have not been widespread problems sufficient to motivate Congress to act. In addition, a change in the Act also would affect conventional foods. It is not clear that FDA has the resources or capacity to review every new use of a food ingredient.²

²There has been a growing and potentially significant trend to file a GRAS affirmation petition and then begin marketing the product without waiting for FDA's decision. While this trend could create increased risk to consumers, the Task Force is not aware of any evidence to date of specific harm having been caused.

Option 3: Special Labeling Requirements

The Task Force also considered special labeling requirements for these products. Such an approach, however, raises concerns about the applicability of such requirements.

A. The Task Force considered recommending that the agency undertake rulemaking under section 201(n) and 403(a) requiring that any dietary supplement that contained ingredients whose safety had not been determined by FDA bear a statement to that effect prominently on its label. The Task Force was drawn to this approach because of testimony that it heard at the public meeting, that most consumers assume that FDA has determined the safety of the ingredients of dietary supplements. However, it is difficult to justify why the lack of safety determination by FDA would be a material fact on dietary supplements but not, for example, on a breakfast cereal that contains psyllium seed husk.

The proposed statement would likely need to appear on a large number of foods. The Task Force believed that widespread use of such a statement would create concern, largely unwarranted, about the safety of the food supply. As a result, the Task Force believed that it could not recommend such an action.

B. The Task Force believes that the public is entitled to,

and should be given, more information about the components of dietary supplements. One action to provide the information would be to require a statement on the label of dietary supplements that the need in human nutrition has not been determined for any substance for which neither an RDA nor an Estimated Safe and Adequate Daily Dietary Intake has not been established.

The Task Force's interest in providing information to consumers also led it to review the role of section 403(j) of the Act, which relates to foods for special dietary use. Many dietary supplements are represented as such foods. Under section 403(j), a food for special dietary use is misbranded "...unless its label bears such information concerning its vitamin, mineral, and other dietary properties as the Secretary determines to be, and by regulations prescribes as, necessary in order fully to inform purchasers as to its value for such uses." Thus, section 403(j) could provide a useful means by which FDA could ensure that the purchasers of dietary supplements, many of which are foods for special dietary use, have necessary information about the products.

However, FDA's use of section 403(j) has been limited because regulations adopted under the authority of this section are subject to formal rulemaking procedures under section 701(e). Formal rulemaking can be extremely resource intensive and time consuming. After notice and opportunity for comment, the

agency's final rule is subject to objection and, if the objections present issues of fact, a formal evidentiary hearing can be scheduled. While the hearing proceeds, the effect of the final rule is stayed. Rulemakings under this procedure have taken as long as a decade.

One comment after the August public hearing, while acknowledging that the agency has had problems with formal rulemaking, particularly in the vitamin and mineral rulemaking, asserted that FDA could still propose and adopt sensible regulations under section 403(j). The Task Force does not agree. Rulemaking under section 701(e) has proven to be a problem in many areas, not only with respect to dietary supplements. The requirements of this section have inhibited FDA from instituting actions to update the agency's regulations with respect to food standards and tolerances for added poisonous and deleterious substances as well as dietary supplements.

If the agency is to use section 403(j) to require that appropriate information be given to consumers, it must be able to do so in a prompt and responsive manner. Section 701(e) rulemaking prevents FDA from doing so.

Therefore, the Task Force recommends that FDA seek legislation striking section 403(j) from the list of sections subject to section 701(e). Congress struck section 401 from the coverage of

section 701(e) as part of the NLEA, and the effects of this change have been beneficial (e.g., the proposal on generic food standards).

One anomaly that these suggestions would create, however, is that while the labels of dietary supplements would be more informative, they would omit the most significant fact--that the safety of some or all of the ingredients has not been established.

Option 4: Drug Regulation

A. The Task Force also considered whether the agency could declare that a substance (even an herb or other food such as garlic) sold in the form of a pill, tablet or capsule, is, by its marketing form, intended either as a bona fide dietary supplement or intended for a drug use. However, in that form the product would not have either the taste or aroma associated with a food use. Furthermore, if the substance does not have recognized nutritive value, it would not qualify as a food, and therefore, its addition to a capsule would not provide a technical effect. The product, in this form, would thus necessarily either be classified as a drug or as an adulterated food under section 402(b). This approach, however, would make virtually every product in this category illegal. It is questionable whether this approach could withstand challenge, and it seems contrary to

what the public appears to desire.

B. There is no question that FDA should continue to bring actions against category three substances that are represented for use as drugs. In appropriate circumstances, rulemaking along the lines outlined in the section on amino acids could be undertaken to declare substances to be drugs. Moreover, the agency should continue to bring food additive actions against category three substances about which it has particular safety concerns.

Option 5: Consumer Education

The major role that FDA can and should play is to educate consumers about these products. One thrust of any such education effort should be to ensure that consumers are aware that these products have not been evaluated by FDA for safety, nutritive value, or effectiveness for any health/drug purpose. Other essential features of consumer education are described in another section of this report. Further, education programs associated with the NLEA, designed to educate consumers about health claims on food labels, should include reference to these kinds of supplements as appropriate, so that consumers will recognize that insufficient evidence exists to substantiate any drug use for these products. Health and nutrient content claims for category three supplements will be regulated under the regulations

promulgated to implement the NLEA.

Option 6: Compliance Program

Another step that the agency could take would be to initiate a compliance program targeted to survey the dietary supplement industry. Under such a program, FDA would, 1) initiate inspection of a significant number of manufacturers of category three substances, and 2) obtain samples of products for analysis. Such a program would allow the agency to accomplish two things. First, the inspections would provide increased knowledge about the extent to which food Good Manufacturing Practices are being observed by category three manufacturers. Second, sampling and analysis of products would allow, to the extent analysis is chemically feasible, a determination of whether the products contain what they purport to contain and whether they contain contaminants. The information achieved through such a compliance program would permit the agency to determine more clearly whether there are particular problems in this segment of the industry and, if so, what these problems are, what risks they pose to consumers, and how they might be corrected. Such information would be invaluable as part of the overall consumer education recommended by the Task Force. The potential difficulties with such a program are, 1) the resources needed to obtain a reasonable and workable level of knowledge, and 2) potential major difficulties with chemical analysis of substances for which

analytical techniques are not currently available. Resources permitting, the Task Force recommends such a compliance program.

In conclusion, the Task Force recommends that FDA pursue options 2, 3b, 4b, 5, and 6.

- 2: Regulate category three substances as food additives.
- 3b: Require a statement on the label of a category three substance regarding the nutritive value. If the substance does not have known nutritive value, the statement would indicate that the nutritive value has not been established. Seek legislation to strike section 403(j) from 701(e) so that formal rulemaking would not be required to effect this kind of labeling.
- 4b: Continue to bring actions against category three substances that are represented for use as drugs.
- 5: Emphasize consumer education.
- 6: Maintain a regular inspection program to ensure that GMPs are being observed and to gain additional information about category three substances, including ingredients and nature and extent of contaminants.

The Task Force does not believe that FDA's current legal authority provides a reasonable and defensible mechanism for increased regulation of products in this category. Further, although the safety of many of these products has not been established, there is no clear-cut evidence that category three products present a serious risk to consumers. Thus, the Task Force is not recommending that FDA seek additional regulatory authority. Rather, the Task Force believes a conscientious commitment to consumer education should permit consumers to make more informed choices, and thereby reduce potential risk.

PUBLIC EDUCATION

In its effort to craft an all-inclusive strategy for dietary supplements, the FDA Task Force also considered ways the agency could serve the public health that do not require regulation. The most widely supported recommendation was that FDA carry out a long-term, comprehensive education campaign, targeting the general public, specific populations at risk, as well as current and potential users of these products.

Justification

The need for such a public education campaign was highlighted throughout the public meeting by proponents of dietary supplements as well as national consumer health advocacy groups. As one consumer advocate pointed out, "Roughly half the population takes some kind of dietary supplement, but because the FDA and most health authorities largely ignore supplements, consumers approach supplement counters uninformed..." (Bonnie Liebman, CSPI, p. 94). Other speakers reminded the Task Force of FDA's mission to "get the proper scientific nutrition information to the public." (Patricia Heydlauff, Executive Director, National Nutritional Foods Association, p. 105) It was frequently noted that the public wants access to accurate and reliable nutritional information in order to make intelligent decisions in the marketplace. When consumers have difficulty distinguishing these

products from pharmaceuticals sold in tablet, capsule, powder, or liquid form, this need becomes even more compelling. The lack of adequate information can lead to other types of harm as well.

Dr. John Renner, family physician, president of Consumer Health Information Research Institute, and board member of the National Council Against Health Fraud, spoke of other ways consumers could be harmed:

Now, one thing...I think we have got to think about (is) more than just death as a type of harm, because we do have tremendous economic harm happening with some patients, especially some of our elderly. I have talked with elderly [persons who] are spending \$400 to \$600 a month on products they do not need to take. I think many times these products are substituted for appropriate medical services, and the harm is done not in taking the product but in substituting for worthwhile activity (pp. 188-9).

Dr. Renner also spoke of frequent problems interpreting lab tests accurately when patients take dietary supplements and fail to inform their physicians accordingly.

Providing consumers and health professionals with nutrition information that helps people maintain healthy dietary practices is not just a legal requirement (NLEA), but also a public health responsibility. Increasingly, consumers are seeking broader

access to reliable information which has been reinforced by government and scientific confirmation of the relationship between maintaining a good diet and sustaining good health. Yet consumers cannot make informed decisions in an information vacuum or in an environment where contradictory information prevails. Given that 60 million Americans take supplements daily, it is essential that people be as informed as possible of the appropriate and safe use of these products. Currently, consumers have no way of distinguishing truthful statements from half truths or total falsehoods.

Recommendations

It is, therefore, the Task Force's judgment that beyond label disclosure, FDA should take affirmative steps to educate the public, providing accurate, scientifically objective information about the safety, proper use, benefits and risks of these products. Recognizing that many questions remain unanswered, the agency will need to reveal when it has incomplete information or when warnings are needed. While FDA will be tightening its regulatory control over supplement product labels and claims under the NLEA, consumers will need as much help as possible interpreting this information to avoid unnecessary exposure to risks and to maximize their ability to make wise health choices in the marketplace. The Task Force also recognizes that the need to educate reaches beyond educating consumers alone--that public

education should also include health professionals, manufacturers, retailers, and other relevant groups and that the communication mechanisms and educational tools will undoubtedly differ according to the audience being targeted.

To implement an education campaign, the Task Force recommends that the agency establish an internal working group, composed of representatives from CFSAN, CDER, the Offices of Consumer, Health, Public, and Regulatory Affairs, and other appropriate agency components. This working group should be charged with the responsibility for:

- Identifying Target Populations
- Establishing and/or Coordinating Coalitions
- Designing Visual and Written Materials
- Determining Message Content and Accuracy
- Identifying Communication Mechanisms for Target Audiences
- Coordinating Conferences, Workshops, or Other Meetings

It is the Task Force's considered opinion that an education campaign should customize information, taking into account literacy levels, print size, complexity of messages, and language, cultural and religious differences. In addition to the various ways FDA generally communicates health information to consumers, the Task Force believes that, to reach certain users of dietary supplements, special avenues of communication will be needed to relay information in less traditional ways, for example, at health food stores, in newsletters, and on health-oriented television programs. Finally, it is recommended that the agency institutionalize the education process so that consumers, especially those at risk, will receive important messages on a continuous basis or when new information emerges.

Research and Resources

The Task Force believes that to effectively carry out the recommendations in this report, the agency must devote adequate resources to and place priority on regulations development implementation, enforcement, and compliance activities. Additionally, the agency must devote resources to obtain information on what types of dietary supplements are marketed, what populations use dietary supplements, why dietary supplements are used, as well as contaminants and safety data on supplements. In addition, research is needed to acquire the tools to competently communicate this information once it is obtained.

CONCLUSIONS

The Task Force considered various issues in its deliberations, including how to ensure the safety of dietary supplements; how to limit the potential for fraud; i.e., disease claims made on labels or through other means, e.g., magazine articles and advertisements; and what steps are necessary to ensure that the existence of dietary supplements on the market does not act as a disincentive for drug development. Balanced against these concerns is the strong desire of American consumers for access to dietary supplements. This desire was voiced at the public meeting. Some consumers claim that FDA has tended to ignore this desire in the past.

The Task Force has carefully examined these issues and has concluded that safety should be the overriding concern for FDA in developing a regulatory framework for this class of products. The Task Force believes that the industry should assume the burden of ensuring the safety of these products. FDA should develop programs to monitor the industry's adherence to this principle.

The Task Force believes that its recommendations should recognize a role for dietary supplements in ensuring a balanced diet and, with safety as an underlying principle, freedom of choice for these products should be allowed as much as possible.

RECOMMENDATIONS

The Task Force offers the following recommendations:

Vitamins and Minerals

1. Revise, by notice and comment rulemaking, the Generally Recognized as Safe (GRAS) Regulations, 21 CFR Part 184, to establish safe levels of use for vitamins and minerals as dietary supplements.

Amino Acids

2. Regulate single amino acids and mixtures of amino acids as drugs.
3. Retain the current policy in 21 CFR 172.320, 182, and 184 for regulating amino acids added as discrete ingredients to foods.

Products Other Than Vitamins, Minerals and Amino Acids

4. Regulate these substances as food additives.
5. Require a statement on the label of a substance regarding the nutritive value. If the substance does not have known nutritive value, the statement would indicate that the nutritive value has not been established. Seek legislation

to strike section 403(j) from 701(e) so that formal rulemaking would not be required to effect this kind of labeling.

6. Continue to bring actions against those substances that are represented for use as drugs.

Cross-Cutting Recommendations for All Dietary Supplements

7. Establish and implement Good Manufacturing Practice (GMP) Regulations for dietary supplements.
8. Establish and implement purity and identity standards for nutrients contained in dietary supplements (see recommendation #13).
9. Establish and implement disintegration and dissolution standards for vitamins and minerals to ensure their bioavailability (see recommendation #13).
10. Establish and implement an education campaign to provide the public with accurate, scientifically objective information about the safety, proper use, benefits and risks of products.
11. Develop a compliance program for dietary supplements to provide guidance to FDA District offices regarding inspections, sample collections, sample analyses, and compliance activities.
12. Require dietary supplements to comply with all provisions of the Nutrition Labeling and Education Act (NLEA) of 1990 and

regulations promulgated thereunder.

13. Establish a liaison as appropriate with nongovernment agencies, such as the United States Pharmacopeial Convention, Inc. (USP), to provide expert advice on the safety and standards, where necessary, and other scientific issues for the proper regulation of dietary supplements.
14. Strengthen the adverse reaction reporting system for dietary supplements.
15. Act against misleading name claims, including brand names, on the labels of dietary supplements that imply therapeutic use, benefit, and/or treatment.
16. Require all dietary supplements to comply with existing regulations on tamper-resistant packaging and child-proof caps.
17. Establish a mechanism to work closely with the Federal Trade Commission (FTC) to coordinate actions regarding dietary supplements (may be included in the development of an NLEA strategy for FTC/FDA cooperation).
18. Work with appropriate state agencies (in existing worksharing arrangements) to regulate dietary supplements.
19. Share FDA's policies with the international community to foster good working relationships.

Recommendations that Would Require Legislative Change

20. Seek legislation to strike section 403(j) from the list of sections subject to 701(e).

APPENDIX 1 - CHARGE TO THE TASK FORCE

Commissioner Kessler asked the Task Force to review FDA's historical regulation of dietary supplements and to take a completely new look at how the agency should regulate dietary supplements. He also directed the task force to: 1) consider, without regard to any limits on FDA's ability to regulate these products, what approach would best serve the public health; 2) consider the benefits and advantages offered by dietary supplements, as well as the risks and problems that they create; 3) to craft a strategy to regulate dietary supplements; and 4) consider whether FDA would be able to implement this approach under its current statutory authority or whether new legislation would be needed to effect the approach.

APPENDIX 2 - ADDITIONAL DISCUSSION OF HISTORY

Prior to the enactment of the Proxmire Amendment, FDA had employed an approach to regulate dietary supplements which included three components: 1) to charge under sections 403(a) and 201(n) of the FD&C Act that the label was misleading because it failed to reveal the material fact that the excess amounts of water soluble vitamins could not be utilized by the body, were unnecessary, and were eliminated from the body as waste; 2) to set standards for vitamins and minerals (FDA subsequently published a Federal Register reproposal in 1976 after the Proxmire Amendment was enacted to implement labeling and standards for vitamins and minerals which was successfully challenged by industry and ultimately remanded by the court back to FDA); and 3) to declare vitamins A and D at levels higher than those considered to be safe for nutritional purposes to be drugs. This approach by the agency was unsuccessful in the courts and in the Congress.

The passage of the Proxmire Amendment dramatically changed the way that FDA approached the regulation of dietary supplements. The agency found that the limitations imposed by section 411 made it more difficult to maintain a consistent policy and to protect the public against health fraud.

FDA correctly considered dietary supplements to be foods, and the

substances contained in dietary supplements to be food additives or GRAS substances. This approach was consistent with the law and remains the only approach that makes sense. Without this approach, FDA would not have been able to take action in cases where there was a hazard to public health, e.g., L-tryptophan.

FDA attempted to ensure the safety of dietary supplements through the food additive provisions of the FD&C Act. However, this approach was frequently challenged and, therefore, resource intensive. Thus, although the agency believed that it had the authority to set standards and ensure the safety of dietary supplements, the legal setbacks coupled with decreasing resources, diminished the agency's incentive to take regulatory actions.

The history of FDA's regulation of amino acids dates back to 1958 after the passage of the Food Additive Amendments. FDA listed amino acids as GRAS. At that time, amino acids were not being commonly marketed as single entities or in combination in capsule or tablet form as dietary supplements. In 1973, the agency removed amino acids from the GRAS list and established a food additive regulation, 21 CFR 172.320, after evidence raised concerns about the risk of adverse effects when free amino acids were used at levels that produced an amino acid imbalanced diet. Since 1973, the only legal nutritive use has been to improve the biological quality of proteins; i.e., to improve the balance of

amino acids by adding those present in disproportionately low amounts. The only exceptions have been in infant formulas and in foods for special dietary use intended to be used solely under medical supervision to meet nutritional requirements in specific medical conditions (medical foods).

Attempts in the late 1970s to bring action in the courts charging that amino acid supplements were unapproved food additives were unsuccessful and led FDA to employ the policy of "regulatory discretion." Despite the fact that FDA considered these products to be illegal, it did not challenge the continued marketing of amino acids as supplements, provided there was no evidence of harm and no explicit drug claims on the labels.

In 1989 and 1990, an outbreak of eosinophilia-myalgia syndrome (EMS) occurred which was linked to the consumption of the amino acid L-Tryptophan, offered primarily as a dietary supplement (in one case as an "exempt" infant formula), but consumed largely for drug-type indications. To protect the public health, FDA halted the importation of L-Tryptophan and conducted a nationwide recall of all products to which manufactured L-Tryptophan was added in violation of food additive regulations. The outbreak peaked and reported cases dropped dramatically after the recall. FDA is still working to identify why supplements containing added L-Tryptophan caused the EMS illness.

APPENDIX 3 - COMMENTS FROM THE PUBLIC MEETING

Presenters at the public meeting expressed the view that vitamins and minerals should be separated as a distinct category of dietary supplements as follows:

Dr. John H. Renner, a family physician representing the National Council Against Health Fraud and the Consumer Health Information Research Institute at the FDA Open Hearing stated:

Dietary supplements, category one, should be strictly classified as only those supplements proved to be necessary in the diet by the human body. This should exclude supplements of free amino acids which are neither necessary nor normally found in the diet, which is why there is an RDA for protein but not for amino acids. This category should not include or refer to any other herbals or food supplements. Specifically, this category should refer to the dietary supplements of vitamins, minerals, and trace elements.... There are 13 vitamins essential for humans: A, D, E, K, C, and the eight B vitamins, B₁, B₂, B₆, B₁₂, niacin, pantothenic acid, biotin, and folic acid.... There are 6 major minerals -- sodium, potassium, calcium, phosphorous, magnesium, and chloride -- and 10 trace elements -- iron, iodine, fluorine or fluoride, zinc, copper, cobalt, chromium, selenium, manganese, and molybdenum.... (These)

should be regulated by the FDA and should follow standards such as those of the USP governing product integrity, label contents, bioavailability, adequate directions for use, and dissolution.

Dr. Irwin Rosenberg's testimony at the public meeting provides perspectives on the 1979 rulemakings of the agency regarding dietary supplements. Dr. Rosenberg stated that he was chair of the FDA Vitamin and Mineral OTC Panel which made its report in 1979 addressing many of the issues before the current FDA panel. That panel deliberated for more than 3 years and published its final report in the Federal Register of March 16, 1979.

In his oral testimony, Dr. Rosenberg stated:

FDA should have authority to establish a category [of] dietary supplements sold over-the-counter and without prescription which are neither drugs nor foods. Issues of safety and effectiveness remove this category of products from the category of foods. They are not apples or oranges or bullion cubes. People die from inappropriate use of vitamins and minerals. So a special category is needed, perhaps similar to that of medical foods--I am not sure. These products should be safe and bioavailable.

A number of presenters made statements that are relevant to the

safety, efficacy, and regulation of vitamins and minerals. Dr. R. William Soller of the Nonprescription Drug Manufacturers Association stated:

First, the FD&C Act has, since its inception, authorized FDA to regulate vitamin-mineral dietary supplements. FDA has uniformly characterized these products as foods for special dietary use subject not only to the general provisions of the Act, but also the special FDA regulations issued under 403(j) of the Act....

Mr. Anthony Iannarone of Hoffman-LaRoche, Inc., stated the following:

...while safety is always an important consideration, the issue of vitamin safety has been greatly exaggerated. Frequent generalities that vitamins can be toxic are not helpful and are actually misleading in the absence of specifics. Safety of vitamins and minerals basically involves the purity of the materials and levels of the constituent ingredients.

The Task Force believes that this view represents only part of the legitimate concern about safety. In addition to the concern about the purity of products, there are documented cases of human toxicity resulting from excessive intakes of the vitamins and

minerals themselves. These effects are also legitimate concerns.

Presenter Dr. Joe Valentino, Associate Executive Director of the United States Pharmacopeial Convention, described the nature of the USP and noted that:

...at the March 1991 meeting of the USP Convention, a resolution was passed encouraging USP to expand its programs to develop public standards and information for practitioners and consumers for vitamins and minerals used as dietary supplements...

Dr. Robert E. Olson, physician and professor of medicine at the State University of New York at Stonybrook addressed toxicity of vitamins A and D: "It is fatuous to state...that supplements can never be toxic. He also recommended repeal of the Proxmire Amendment, and restriction of potency to 50% to 100% of the RDA.

Dr. Bernard Rimland objected strongly to the "FDA's continuing attempts to place restrictions on our constitutional rights as free Americans to purchase whichever nutritional supplements we choose in whatever quantities we choose." He stated, "There have only been two deaths in recorded human history from overdoses of vitamin A..." The Task Force notes that Dr. Rimland did not address the numbers of persons who have had their health adversely affected by excessive vitamin A. One recent

publication cites forty-odd cases of cirrhosis and related diseases of the liver caused by prolonged intakes of moderate excesses of vitamin A. (ref)

APPENDIX 4 - HISTORY OF FDA'S APPROACH TO THE
REGULATION OF VITAMIN AND MINERAL SUPPLEMENTS

- o Hearing in October 1940 on "Foods for Special Dietary Use."
- o FR publication of November 1941 on "Foods for Special Dietary Use."
- o FR of November 22, 1941: Vitamin/Mineral Labeling Regulations Established; "Minimum Daily Requirements" (MDRs) first established (Finding of Fact Number 24).
- o The first edition of Recommended Dietary Allowances (RDA's) published in 1943.
- o Updated regulations between 1962 and 1968, using the 1958 RDA's as a basic guide. June 20, 1962: Original FR proposal for standard of identity for vitamins and minerals.
- o FR of June 18, 1966: Revised Regulation.
- o FR of December 14, 1966: Stay of effective date of the June 18, 1966 order.

- o Public Hearings were held between June 20, 1968, and May 14, 1970.
- o January 25, 1971: Hearing Examiner's Report.
- o Final order published in the FR of August 2, 1972, on "Special Dietary Use."
- o The August 1972 FR also included the final order for the standard for dietary supplements of vitamins and minerals.
- o Following the 1972 publications, various Federal Courts of Appeals were petitioned to review them.
- o FR of January 19, 1973: FDA issuance of proposed findings of fact, conclusions, and a tentative order following the hearings on "Foods for Special Dietary Use." New Proposed Vitamin/Mineral Regulations.
- o August of 1973, a suit was filed seeking declaration and injunctive relief against these regulations.
- o FR of August 2, 1973: Publication of findings of fact and final order.

- o Regulation went into effect on October 1, 1973, which restricted to prescription sale any excess of vitamin A over 10,000 I.U. and any excess of vitamin D over 400 I.U.
- o FR of October 15, 1973 (38 FR 28581), Request for data on all active ingredients used in OTC Vitamin and Mineral and hematinic drug products.
- o August 15, 1974: Vitamin/Mineral labeling regulations remanded (National Nutritional Foods Association v. FDA, 504 F.2nd 761, 786).
- o February 24, 1975: Supreme Court denied certiorari for review of appeals court decision.
- o May 28, 1975: Additional Formulations Applications; Notice of Hearing.
- o October, 1975: Hearing reopened.
- o February 20, 1976: Administrative Law Judge rendered report and Findings of Fact.
- o April 19, 1976: FDA denied petitions re: proposal for a formal hearing.

- o April 22, 1976: Section 411 of the FD&C Act (the Proxmire Amendment) passed by Congress; effective October 1976.
- o July 2, 1976: District Court sustains FDA's regulations Section 250.109/110 re: drug status of vitamins A and D (National Nutritional Foods Association and Solgar Co., Inc. v. F. David Mathews, Secretary of HEW, U.S. District Court for the Southern District of New York, No. 73 Civ. 3348, July 2, 1976, 418 F. Supp. 394).
- o October 19, 1976: Final rule for Vitamin/Mineral labeling regulations published in the FR.
- o June 7, 1977: Appeals Court overturns decision on vitamins A and D (National Nutritional Foods Association v. F. David Mathews, Secretary of HEW, U.S. Court of Appeals for the Second Circuit, No. 76-6135, June 7, 1977).
- o February 16, 1978: Vitamin/Mineral labeling regulations remanded (National Nutritional Foods Association v. Kennedy, 572 F.2d 377).
- o March 14, 1978: Regulations on Vitamins A and D

revoked.

- o March 16, 1979: Regulations on Vitamin/Mineral labeling revoked.
- o March 16, 1979: Monograph for OTC (drugs) vitamins proposed.
- o November 27, 1981: Monograph for OTC (drugs) vitamins revoked.

APPENDIX 5 - DISCUSSION OF CARNITINE

Carnitine may be described as a conditionally essential nutrient. It is not required in the diet of normal adults, but it is metabolically essential and is not synthesized by newborn infants at rates which are sufficient to maintain normal blood levels.

Carnitine is required metabolically for the transport of long-chain fatty acids into the mitochondria, the site of oxidation. It, therefore, plays a critical role in energy metabolism and in the metabolism and clearance of long-chain fatty acids.

Carnitine is synthesized in the liver and kidney of adults from the amino acids lysine and methionine. Although most adults can synthesize adequate amounts of carnitine, newborn infants have smaller stores of carnitine and reduced capacity for producing it. Human milk contains adequate amounts of carnitine. Infants fed nonmilk formulas or maintained on total parenteral nutrition receive no carnitine, unless it is added to their formulas, and such infants have lower plasma levels of carnitine than those fed human milk. A crucial question is whether the infants with lower plasma carnitine have functional deficits.

Carnitine can have beneficial effects under several different conditions:

1. For newborn infants, especially those who are

premature, carnitine appears to be an essential nutrient.

2. Genetic carnitine deficiency results in a deficiency syndrome, unless the person is given adequate amounts of carnitine.
3. Exposure to certain carboxylic acid drugs or xenobiotics depletes carnitine and induces deficiency, unless the intake is adequate to prevent this effect.
4. Long-term total parenteral nutrition (TPN) causes carnitine deficiency, unless the TPN formula contains adequate carnitine.
5. Renal dialysis may cause carnitine deficiency by depleting blood levels, an effect that is prevented by adequate intake.
6. Acetyl carnitine is used in treatment the dementia of Alzheimer's disease.
7. Propionyl carnitine is used to minimize the cardiac muscle damage in certain heart disease patients.

Of these uses for carnitine, numbers 1 and 5 may be appropriate for infant formula or medical food uses. Uses numbers 2, 3, 4, 6, and 7 should be described as drug uses.

Appropriate infant formulas should be made available to meet the needs under use number 1 above. Appropriate medical foods should be made available to meet the needs under number 2 above. Products intended for the other uses described should be available only as prescription drugs. Carnitine should not be available OTC as a dietary supplement because all conditions in which it is useful as a single substance require medical supervision.

Carnitine should not be generally classified as a vitamin because it is required only by special target populations and not by the ordinary consumer, and, consequently, there seems to be no prospect that a recommended dietary allowance will be set. Carnitine is temporarily required by the newborn infant and by other persons under special conditions, conditions which require medical supervision.

APPENDIX 6 - REFERENCES

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