Dietary Supplements Subcommittee[1]
of the Food Advisory Committee
Center for Food Safety and Applied Nutrition (CFSAN)
Food and Drug Administration (FDA)

SUMMARY MINUTES
March 25, 2003
Holiday Inn College Park
10000 Baltimore Boulevard
College Park, Maryland

Members Present

Johanna T. Dwyer, D.Sc., R.D., Chair
Edward Blonz, Ph.D., M.S., C.N.S., F.A.C.N. [2]
Eric P. Brass, M.D., Ph.D.[2]
Nancy M. Childs, Ph.D.
Harihara M. Mehendale, Ph.D.
Paul L. Schiff, Jr., Ph.D. [2]
Michael W. Shannon, M.D., M.P.H.

Acting Industry Representative

Annette Dickinson, Ph.D.

Guest Speaker

Edward D. Harris, Ph.D.

FDA Participants

Robert J. Moore, Ph.D.
Christine L. Taylor, Ph.D.
Susan J. Walker, M.D.
Elizabeth A. Yetley, Ph.D.

FDA Staff Present

Constance J. Hardy, M.S., R.D., Executive Secretary
Anna Belousovitch[3]
Margaret E. Cole, Ph.D.
Beatrice B. Greenberg
G. Vincent Keys
Angela F. Pope
Jenny S. Slaughter
Kathleen Smith
Linda J. Webb

Other Participants

Katherine McComas, Ph.D.[4]

[1] The entire meeting was open to the public. For the verbatim transcript of the meeting, contact FDA Dockets Management Branch (HFA-305), 12420 Parklawn Drive, Rockville, Maryland 20857.
[2] Temporary voting member.
[3] CFSAN Contractor.
[4] Department of Communications, University of Maryland, College Park, Maryland.

The Dietary Supplements Subcommittee (DSS) of the Food Advisory Committee (FAC) convened its first meeting at 8:15 a.m. on March 25, 2003, at the Holiday Inn College Park, College Park, Maryland.

Briefing Materials

The briefing packet distributed to DSS members contained the following materials: (1) tentative agenda; (2) *Federal Register* notice of the meeting; (3) roster of DSS members, temporary voting members, and guest speakers; (4) background summary with charge; (5) questions for the DSS; (6) white paper "Biochemical Facts behind the Definition and Properties of Metabolites" by Dr. Harris; and (7) reference definitions of "metabolite." In addition, DSS members received at the meeting Dr. Taylor's presentation "Dietary Supplement Food Advisory Subcommittee," Dr. Moore's presentation "Dietary Supplement Subcommittee Consideration of 'Metabolite'," and Dr. Harris's presentation "Metabolites Definitions and Properties."

FDA Presentations

Dr. Taylor welcomed everyone, reviewed the agenda for the meeting, and provided background information on FAC subcommittees and their advisory role to FDA. Dr. Taylor also provided basic information on dietary supplements and discussed evolving issues related to dietary supplements including fraudulent claims, safety standards, manufacturing standards, and definitions. She concluded by introducing DSS members to CFSAN's charge and questions for the meeting.

Dr. Moore provided a brief summary of the legal framework surrounding dietary supplements and the term "metabolite" as contained in the statutory definition of a dietary ingredient. He also provided common definitions of metabolite and presented marketplace examples. Dr. Moore concluded his presentation with a brief review of the questions CFSAN is asking the DSS to address.

Administrative Issues

The executive secretary covered procedural and ethical issues. She read the conflict of interest (COI) statement into the record and announced the appointment of temporary voting members.

Dr. McComas briefed the DSS and audience on the Joint Institute for Food Safety and Applied Nutrition-funded study she is conducting on public attitudes and opinions about COI and FDA's advisory committee meeting process and asked the audience to complete and return the questionnaire she distributed at the meeting.

DSS chair Dr. Dwyer began with introductions of DSS members and asked FDA staff to distribute, for the DSS's reference, copies of the metabolic pathways Dr. Moore had discussed during his presentation.

Dr. Dickinson reminded the DSS about legislative safeguards limiting the use of certain ingredients in dietary supplements even if these ingredients are covered by the definition.

Invited Presentation

Dr. Harris presented information on the definition and properties of metabolites. He provided definitions of metabolite and discussed factors to consider whether a substance is, or is not, a metabolite. According to Dr. Harris, six principles are critical to the definition of metabolite, i.e., a metabolite is a substance that: (1) is created in a living cell, (2) is an intermediate in a biochemical pathway, (3) is recognized and acted upon by enzymes, (4) has a limited biological time of existence, (5) does not violate principles of stereospecificity, and (6) serves some useful purpose in meeting a larger requirement of cell function.

Following Dr. Harris's presentation, the chair invited individual DSS members to ask Dr. Harris questions to clarify their understanding of his presentation. In addition, the chair asked Dr. Moore to clarify several issues about the Dietary Supplement Health and Education Act (DSHEA) of 1994 and the meaning of the terms metabolite, dietary supplement, and dietary ingredient. Before beginning the open public hearing, the chair gave DSS members another opportunity to ask additional questions of Dr. Harris, particularly in relation to the questions the DSS is charged by FDA with answering.

Public Comment

The chair began the open public hearing. The following members of the public made oral presentations: Phillip Harvey, Ph.D., National Nutritional Foods Association (NNFA), and Steven Dentali, Ph.D., American Herbal Products Association. The chair permitted DSS members to ask clarifying questions of the speakers at the conclusion of each presentation. The DSS also received written comments from the following members of the public: John L. Zenk, M.D., Humanetics Corporation, and I. Scott Bass and Emily Marden, Sidley Austin Brown & Wood on behalf of NNFA.

Discussion of Charge and Questions

Following the open public hearing, the chair led the discussion of the individual questions CFSAN had asked the DSS to address and gave each member adequate opportunity to express their individual opinions on each question. As needed, the chair asked for clarification of certain issues from FDA participants.

Question 1: Is it possible to identify particular scientific criteria, principles, or conventions that enable a determination to be made about when a substance is or is not a metabolite of another dietary ingredient?[1]

The DSS discussion began with the proposal of a definition of the term metabolite:

> *X is a metabolite of Y if ingestion of Y by humans results in net production of/ increased flux of X, incorporating structural elements of Y.*

[1] For present purposes, "another dietary ingredient" means a vitamin, mineral, herb or other botanical, amino acid, or dietary substance for use by man to supplement the diet by increasing the total dietary intake.

DSS members asked questions to clarify their understanding of the proposed definition. DSS members also used diagrams as aids to enhance their discussion of what encompasses dietary ingredients and metabolites.

The DSS agreed that the proposed definition covered the issues raised in Question 1 well. Points of disagreement with acceptance of the definition as proposed centered on the following issues:

(1) The definition should be specific to DSHEA, e.g., include reference to "a vitamin, mineral, herb or other botanical, amino acid, or dietary substance for use by man to supplement the diet by increasing the total dietary intake" as well as constituents of these substances.
(2) The definition should be independent of exogenous effectors, e.g., alcohol.
(3) The definition should consider population differences, e.g., age, gender, disease status, smoking habits.
(4) The definition should include a safety factor.
(5) The definition should clarify the meaning of human ingestion.

One committee member recommended including as a component of the definition the condition that "For the purposes of herb or other botanical, a metabolite is understood to be a metabolite of an individual constituent."

Dr. Moore clarified that the definition of metabolite need not include a safety provision because safety is a separate issue addressed elsewhere by DSHEA. He also clarified that constituents of an herb or botanical are dietary supplements if they are the reason for its use.

Dr. Walker clarified that the definition of metabolite need not address population differences.

DSS members discussed human ingestion and agreed it included changes in substances by microflora in the human gut.

Question 2: Consider and discuss the scientific strengths and weaknesses of the following concepts with respect to their usefulness in identifying whether a substance is or is not a metabolite of another dietary ingredient:

a) Direct or indirect participation in catabolic and/or anabolic sequences or pathways;
b) Proximity (i.e., in terms of number of enzymatic steps away) to another dietary ingredient;
c) Semblance to another dietary ingredient preceding it in a pathway or preceding reaction with respect to:
  i) Function
  ii) Structure
  iii) Combination of both
d) Possessing qualities or similarities to another dietary ingredient relative to:
  i) Speed/time (i.e. clock-time conversion, enzymatic reaction rates, retention rates or impact on equilibrium concentrations/homeostasis)
  ii) Compartmentalization (e.g., intracellular vs. extracellular activity; intracellular compartmentalization)
  iii) Fate (i.e. final conversion, excretion or end-product retention by the body)

DSS members generally agreed that the items listed in Question 2 were either adequately addressed by the proposed definition or irrelevant to the definition. DSS members disagreed whether most sequences or pathways involving metabolites of dietary ingredients are catabolic (but not anabolic). One member noted precursors (Question 2c) and analogous substances (Question 2d) are not metabolites.

Question 3: Discuss the scientific validity and likely usefulness of the concepts above for identifying when a substance is or is not a "metabolite" of another dietary ingredient. If so, what characteristic(s) associated with the criterion make(s) it valid or useful?

The DSS agreed that the proposed definition is scientifically valid and useful because it emphasizes: (1) the product-precursor relationship, (2) metabolite formation as a result of human ingestion, and (3) net production of product from precursor. Additionally, the definition is useful because it incorporates structural elements. In addition to its usefulness, other comments about the definition mentioned its functionality, flexibility and conciseness and noted the definition has scientific rigor and establishes boundaries. The chair also led the members in a discussion of the applicability of the definition to the marketplace examples Dr. Moore presented earlier.

Several DSS members repeated their reservations about the lack of a safety component in the definition. One DSS member expressed specific concerns that the proposed definition does not consider: (1) "biofunctionality," i.e., a product in the marketplace starts out as benign but becomes the precursor of a dangerous substance or (2) "critical control points," i.e., the metabolite passes a critical control point that leads to a negative influence. Two DSS members remarked the proposed definition places the burden on FDA to protect the public by increasing surveillance of the marketplace.

The chair adjourned the meeting at 2:25 p.m.

I certify I attended the March 25, 2003, meeting of the Dietary Supplement Subcommittee of the Food Advisory Committee, and these summary minutes accurately reflect what transpired.

/S/
Constance J. Hardy, M.S., R.D. Date
Executive Secretary

/S/
Johanna Dwyer, D.Sc., R.D. Date
Chair