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Multicomponent Dietary Supplements for the *Military*

Ian D. Coulter, Sydne Newberry

Sponsored by the Samueli Institute



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Preface

The U.S. military has had a long-standing interest in the potential for dietary supplements to enhance performance and optimize health among military service personnel, functions that it refers to collectively as *metabolic defense*. In particular, the military is interested both in exploring the potential of these supplements to help service members adapt to occupational and environmental stressors and in ensuring that manufacturers of dietary supplements for military use adhere to the highest possible standards. In 2009, RAND Health assembled a panel of experts on the design, manufacture, and testing of dietary supplements and conducted an informal, one-day workshop on the manufacture and testing of multicomponent dietary supplements for the military.

The purpose of these conference proceedings is to summarize the workshop, which occurred on January 15, 2009, at the RAND Corporation office in Santa Monica, California. These proceedings should be of interest to policymakers, health care personnel who care for individuals in physically or cognitively demanding jobs, and others interested in the custom design and testing of dietary supplements.

This research was funded by the Samueli Institute and was undertaken within the RAND Center for Military Health Policy Research, a strategic initiative within RAND Health. Ian Coulter was the project leader. Comments and questions can be directed to him at Ian_Coulter@rand.org. Terri Tanielian and Sue Hosek serve as the codirectors of the Center for Military Health Policy Research. More information about RAND is available at www.rand.org.

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Richard Scalzo, herbalist, and President, Gaia Herbs

RAND Corporation Staff

Ian Coulter, PhD (moderator)

Lara Hilton, MPH

Sydne Newberry, PhD

¹ The panel was selected by an advisory committee comprising the following individuals: Ian Coulter, PhD, RAND Corporation (chair); Rebecca Costello, PhD, National Institutes of Health, Office of Dietary Supplements; Patricia Deuster, PhD, MPH, Uniformed Services University of the Health Sciences; Wayne Jonas, MD, Samueli Institute; Joan Walter, JD, Samueli Institute; Sydne Newberry, PhD, RAND Corporation; Lara Hilton, MPH, RAND Corporation; and Andy Young, PhD, Chief, Military Nutrition Research, U.S. Army Research Institute for Environmental Medicine. The panel comprised representatives from the RAND Corporation and the Samueli Institute and three members recommended by the Samueli Institute's advisory committee on the efficacy and safety of dietary supplement use by military personnel.

Invited Guests and Observers

Wayne Jonas, MD, President and Chief Executive Officer, Samueli Institute

Joan Walter, JD, Vice President, Military Programs, Samueli Institute

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Abbreviations

AIBS	American Institute of Biological Sciences
ARIEM	U.S. Army Research Institute for Environmental Medicine
ATBC	alpha tocopherol beta-carotene
CMNR	Community on Military Nutrition Research
DoD	Department of Defense
DSHEA	Dietary Supplement Health and Education Act
ERGO	Energy Rich Glucose Optimized
FDA	Food and Drug Administration
GMP	good manufacturing practice
IND	Investigational New Drug
MNP	multicomponent natural product
MRE	meal ready to eat
PSP	Peak Soldier Performance

Introduction and Background

The U.S. military has had a long-standing interest both in ensuring that service members maintain adequate nutritional status and in determining the nutrient requirements of personnel who are operating in extreme environments or under conditions that demand maximal physical or mental exertion. Research in the civilian sector over the past quarter-century has shown that particular nutrients and nutritional status in general may help to strengthen the immune system, prevent chronic disease, promote cognitive function, and enhance physical performance. The military has focused efforts of its own on identifying nutrients that might fulfill these roles. The U.S. Army Research Institute for Environmental Medicine (ARIEM) in Natick, Massachusetts, has conducted extensive work on the role of food components, such as caffeine, in performance enhancement (Doan et al., 2006; Brunyé et al., 2010). In addition, the Food and Nutrition Board's Community on Military Nutrition Research (CMNR) has conducted a series of workshops on the role of food and dietary supplements in optimizing performance under extreme environmental conditions (e.g., Marriott and Carlson, 1996; CMNR, 2001).

The term *metabolic defense* refers to physiological strategies aimed at preventing damage from environmental stimuli (such as hypoxia and changes in temperature).¹ In the U.S. military, the term *metabolic defense* refers to the issue of dietary supplements to military personnel for the purpose of health promotion, performance optimization, or stress mitigation.² The challenge for the military with respect to such use of dietary supplements is two-fold. First, it must be possible to balance any benefits against the risk of adverse events associated with the use of dietary supplements under such circumstances. Second, the military must ensure that sanctioning the use of dietary supplements under particular circumstances does not constitute blanket approval of use of all supplements, including those that might be harmful to health (many of which are aimed at weight loss, performance enhancement, or body building). No Department of Defense (DoD)-wide management or regulation of dietary supplement use currently exists, with the exception of the use of dietary supplements by individuals in specific job categories (for example, pilots) (Coulter, Newberry, and Hilton, 2011).

The Samueli Institute, in partnership with the RAND Corporation, has been jointly working with DoD on reviewing information and recommending policy on the efficacy and safety of dietary supplement use by military personnel. This effort has been led by an advisory committee comprising individuals from RAND, the National Institutes of Health Office of

¹ The term *metabolic defense* as used in this context likely originated with research by Hochachka and colleagues (Hochachka et al., 1996).

² This definition of the term originated at the Samueli Institute.

Dietary Supplements, the Uniformed Services University of the Health Sciences, the Samueli Institute, and ARIEM. On September 16, 2008, RAND hosted an expert panel discussion on the safety issues involved in the use of dietary supplements by military personnel and on whether DoD should implement military-wide restrictions on or regulation of dietary supplements or their sale on military bases. The results of this panel meeting were summarized in a 2011 RAND publication (Coulter, Newberry, and Hilton, 2011). That earlier panel considered

- the types of policies and regulations that currently exist regarding the use of dietary supplements in civilian sector groups whose jobs demand high levels of physical or cognitive performance
- the types of policies that currently exist in the commercial domain around point-of-sale for dietary supplements
- current military policies regarding the use and purchase of dietary supplements
- the military's options with respect to regulating the use of dietary supplements.

On January 15, 2009, a second panel of experts addressed both the factors that the military would need to consider in developing and issuing multicomponent dietary supplements (which are supplements that contain some combination of active nutrients, such as vitamins, minerals, essential fatty acids, amino acids, and antioxidants) and the standards that could be imposed in the development of such supplements for specific physiological and health indications. Prior to the workshop, the panel members were provided with a brief background paper prepared by RAND on the following topics: the use of dietary supplements by military personnel; efforts by the military, the U.S. government, and other governing bodies to regulate dietary supplement use; a framework developed by the Food and Nutrition Board for testing dietary supplements for safety; and efforts by the military to test the use of particular dietary supplements designed to enhance performance.

Questions Intended to Guide the Discussion

To help facilitate the workshop discussion, RAND researchers provided the panel members with the following five questions in advance of the workshop:

1. Of the current multicomponent natural product (MNP) indication–related regulations around the world, which ones offer
 - a. the clearest and most customized path for evaluation
 - b. the best balance in providing quality, safety, efficacy, and access
 - c. the most feasible and reasonable process providing guidance on use?
2. Of the U.S. Food and Drug Administration's (FDA's) current regulations of products (including drugs, biological products, food, and medical devices), which single regulation or combination of regulations might best be used to guide MNP approaches for the military?
3. Are there alternative approaches to characterizing MNP components or effects that may be better than current chemical or drug approaches?

4. Are there special military performance or environmental requirements that justify different research and regulatory requirements for determining the use of MNPs in military settings or populations?
5. Are there ways to incentivize private industry to invest in production of MNPs for DoD and the general public?

Although the workshop discussion did not explicitly focus on answering these questions, the questions did provide the context within which much of the panel discussion occurred.

The Panel

The members of the panel were individuals identified by the project's advisory committee as having special knowledge of this content area. Thus, the panel comprised experts in the biochemistry and physiology of supplements, the manufacture of military food products, the manufacture of dietary supplements and natural products, pharmacology, and medical toxicology. The experts came from various sectors, including the private sector, universities, research institutes, the military, and other U.S. government departments. However, no member of the panel was chosen to serve as an official representative of any organization. Therefore, the views expressed in these proceedings do not necessarily represent the views of these organizations. Furthermore, the focus of the workshop was not on the regulation of supplement products, and the discussion reported here is not intended to impinge on the regulations enforced by the FDA or by any other government body.

The panel members' task was not to advise the military on which dietary supplements to use but rather to provide guidance, based on their experience, regarding the factors that the military would need to consider if it chose to develop and test multicomponent dietary supplements to address the issues of greatest military concern (i.e., performance enhancement and stress mitigation).

Issues Pertaining to the Regulation and Assessment of Efficacy and Safety and to the Special Needs of the Military

For purposes of clarity, this chapter organizes the points raised during the discussion into two categories:

- issues pertaining to the regulation and assessment of efficacy and safety
- issues pertaining to the special needs of the military.

Issues Pertaining to the Regulation and Assessment of Efficacy and Safety

One of the first issues addressed by the panel was what a multicomponent dietary supplement would comprise. Participants suggested that it could include various combinations of vitamins, minerals, and other single nutrients. One participant suggested that a botanical supplement could include multiple parts of the same plant (which could contribute different active ingredients and, possibly, some not-yet-identified active ingredients). Panelists agreed that the issues are extremely complex and that research trials would not be of help in elucidating the efficacy or safety of multicomponent dietary supplements.

The role of good manufacturing practices (GMPs). The role of GMPs in ensuring efficacious, safe, and high-quality dietary supplements was discussed. Panelists noted that GMPs are necessary but not sufficient for ensuring efficacy, safety, and quality. For example, because GMPs lack ingredient qualifications, they might ensure that every batch of a supplement has identical ingredients (i.e., that ingredients are standard across batches), but the ingredients could be of poor quality. When considering efficacy and safety, a panelist noted, the ingredients are key. In addition to standards of quality, standards of identity are needed. The panelists expressed the belief that, if implementation of, and adherence to, GMPs were required, many small manufacturers would not be able to stay in the market.

Standardization. According to the panelists, standardization can be imposed at different levels (e.g., the starting materials, the process, the final product). The ability to standardize a product depends on whether the active ingredients have been identified. Standardization requires a chemical marker that is easily measured. It was suggested that efforts to develop new methods of standardization be focused on new products (e.g., mangosteen) rather than on those with a well-established market (e.g., St. John's wort, valerian root).

Supplements versus foods and drugs. Panelists indicated that dietary supplements can be compared with neither foods nor drugs. Given that the FDA controls for the safety of supplements and additives but not of foods, there appears to be an assumption that the latter pose fewer safety concerns than the former. Thus, panelists suggested, standards and regulations

may differ for different components of a single product, and no “one-size-fits-all” approach will work.

Safety. One panelist noted that safety must be defined for the specific dietary supplements and uses envisioned by the military and for the specific contexts in which the supplements’ use is proposed.

Subpopulations. Several panelists emphasized that potential variations in the effects of multicomponent dietary supplements among subpopulations have been understudied, particularly in the case of groups of different ethnicity.

Issues Pertaining to the Special Needs of the Military

Panelists reported that the special needs of the military must be kept in mind when considering any formulation or testing process. Field combat situations—where sleep deprivation, extreme environments, and other stresses increase the risks considerably, and where the consequences of an unsafe product could be more severe than in an average civilian environment of lower stress—are a case in point.

Military rations. Military rations have been considered as a vehicle for enrichment (which is the addition of nutrients normally present in a food but lost during processing) or fortification (which is the addition of nutrients not normally present in a food), according to one panelist. To consider the value of fortifying ration components, several points must be understood. Standard rations, known as *meals ready to eat* (MREs), are designed to provide 3,600 calories daily (4,500 in the case of cold or high-altitude conditions; 1,600 in the case of reduced-calorie rations). The calorie content of standard MREs is thus higher than many individuals may need. The military may choose to fortify the rations, but it must consider the possibility that service members may not eat all components of the meals. For example, if the Army fortified crackers with calcium (e.g., to help women achieve the recommended calcium intake) but women tended to avoid the crackers to control calorie intake, those women would not receive the benefit of the calcium fortification. One alternative suggested by the panel is to start with the reduced-calorie rations. An additional concern is that MREs must be heat-stable and must have a long shelf life. Panelists noted that these end-product requirements may impose limits on both the types of nutrients that can be used to fortify the rations and the processes that can be applied to introduce nutrients into the food.

Market-driven development and testing. The panel agreed that the market should drive dietary supplement development. Thus, panelists argued, the military needs to determine the kinds of dietary supplements on which to focus development (or testing, if appropriate products might currently exist in the civilian sector). According to the military members of the advisory committee, the conditions on which the military currently wishes to focus are performance enhancement and stress reduction. However, it is not currently clear to the military whether the most appropriate products for its needs are multivitamins, botanicals, or other multicomponent dietary supplements.

ARIEM. According to one of the panelists from the organization, ARIEM cannot do much of the research that would be needed to test experimental compounds because of the need for Investigational New Drug (IND) approvals. Other panelists asked whether DoD could be granted waivers or could operate under separate rules for testing and use. Many panelists asked whether DoD could set its own standards.

Cases Illustrating Processes That Might Serve as Examples to Guide Military Policy on Multicomponent Dietary Supplement Development and Testing

For purposes of illustration, the panelists presented a number of examples of potential development models for various types of supplement products. The examples presented in this chapter were drawn from the panelists' own experiences in industrial, university, and military settings.

Examples from the Civilian Sector

Development of a Single-Herb Product

One of the panelists outlined the process his company used in the development of a product whose active ingredient is Echinacea.

Phase 1 consisted of the establishment of identity, safety, purity, and nonhuman efficacy and involved the following steps:

- selecting the appropriate seeds needed to grow plants that produce the desired product, plus development of the horticultural process that maximizes the yield of the desired end product (the process may depend on, e.g., time of harvest, rainfall)
- creating a model to validate the identity of the plant. Although organoleptic means are used by some companies, these processes may not be applicable in all cases. A validated reference sample, which is used to develop a chemical, microbiological, and genetic profile, is required.
- structurally determining the range of true constituents of the plant, particularly active ingredients. For this step, it is necessary to develop a biomarker for the ingredient of interest.
- developing a stability determination for the raw plant materials, active biomarkers, standard reference material, and a method to ensure the stability of the active ingredients of interest throughout the purification process
- standardizing methods for purification, isolation, structural elucidation, conducting a chemical or pharmacological profile, and using reference markers
- screening whole extracts for efficacy, purity, and safety (both in vivo and in vitro), including dose establishment for efficacy and toxicity. It is preferable to assess whole plants in addition to purified compounds in accordance with methods used for natural botanical drug development.
- developing the actual drug, including establishing optimal extraction and concentration methods, developing an optimal delivery vehicle, conducting disintegration and dissolution studies, and assessing bioavailability

- establishing GMP qualifications
- screening for drug interactions.

Phase 2 consisted of establishing the potential efficacy of the preparation and involved the following steps:

- submitting botanical IND specifications. No special IND processes exist for botanicals, but, if the product is indicated to treat a disease, an IND is needed.
- implementing Phase II preclinical trials using the herbal product.

Phase 3 consisted of determining full efficacy and involved the following steps:

- approving botanical IND status
- recruiting for and implementing Phase III clinical trials.

Phase 4 consisted of commercialization. It involved adopting the botanical medicine for military use.

Development of a Multicomponent Supplement by Private Industry

Another panelist outlined a set of steps that would be necessary to develop a standard process for compounding multicomponent herbal formulations that is based on a naturopathic model for compounding (i.e., mixing a drug or botanical in such a way as to maximize its bioavailability for a particular patient—a process for which many models have been developed). The model was based on the assumption that the final preparation would contain multiple botanicals, not one herb with multiple active ingredients. The panelist recommended establishing therapeutic categories for which multicomponents would be created (which would define the required testing process). He also recommended limiting the number of ingredients to no more than three or four, thereby limiting the potential number of interactions among bioactive constituents, maintaining better control over bioavailability, and minimizing the potential for toxicity during the testing process. Traditional Chinese medicine and ayurvedic products were cited as examples of products with a model to follow because of the large number of herbs in these mixtures (although ayurvedics may depend on synergy among the components for their effects).

The example of creating adaptogens from botanicals was discussed. Adaptogens are products designed to assist with recovery from or adaptation to stress, which is a new field of research. The use of botanicals for this purpose was suggested as an appropriate focus for the military because of the propensity for polypharmacy—the use of many pharmacologically active agents at the same time—among military personnel. *Rhodeola rosea* is a botanical with adaptogen properties that one panelist suggested could be considered. Adaptogens might be helpful in another related area of interest to the military: resilience induction. Resilience is often considered only in relation to psychological stressors, but it might refer to physical stressors as well.

Panelists identified several issues of concern regarding the development, testing, and use of botanicals and other dietary supplements, including education and insurance. Physicians lack education about botanicals and their use, and access to high-quality scientific information is limited. Further, health insurance in general and TRICARE in particular do not cover

the use of naturopathic doctors or herbal remedies, which prevents military personnel and allopathic physicians from gaining more information about herbal and other multicomponent dietary supplements.

A Commercial Approach to Dietary Supplement Development That Relies on Existing Randomized- and Controlled-Trial Literature

One of the concerns about developing and testing any new product is the length of time and the huge cost involved in conducting the necessary trials. A panelist presented a model for an abbreviated testing process that would take advantage of the FDA's relaxed standards for demonstrating efficacy. These standards are based on the FDA's willingness to accept single, well-designed studies involving the target populations.

According to the panelist, the first step involves determining the key indication and working backwards. The second step involves reviewing the evidence base to select a promising candidate agent based on a minimal set of criteria. The third step is to identify and implement an inexpensive in vitro system to test for toxicity and possible drug interactions; this information should be sufficient to formulate a product based on data and efficacy dosage. The fourth step is to enlist research and development professionals and to define ingredients and required dosages.

In this model, claims about the product would be based only on the literature and on one good, rigorous, pivotal trial, preferably on a target population similar to the population of interest. With such a model, the panelist indicated, development to market launch could potentially occur in just 18 months, which includes the time needed to find suppliers and to solve quality control issues.

One panelist mentioned that his group had tried to do rigorous controlled trials on multicomponent supplements and that they were difficult to conduct. He noted that absorption studies alone can cost \$3 million for 300 subjects.

It was pointed out that, to conduct this type of trial, the product must, by law, be sold as a supplement, not for treating a condition.

Examples from the Military

DoD and the individual service branches have already engaged in research studies on the efficacy and safety of dietary supplements for various purposes. Several of these studies were discussed by panel members.

Adding Carbohydrate Supplements to Rations

The panelists reflected on the Army Natick Laboratory's development of the Army's own version of the PowerBar[®] in the 1990s. The Energy Rich Glucose Optimized (ERGO) bar, initially called the "Hooah Bar," incorporates a mixture of simple and complex carbohydrates. It was first tested with timed bouts of running, followed by multifactorial recovery testing of the constituent carbohydrates against a placebo. Consumption of the bar was associated with increases in physical and cognitive performance as well as changes in psychological affect. These changes were thought to constitute stronger evidence than biomarkers.

The bar was released for use in 1996. It was subsequently renamed the "First Strike" bar and included in First Strike rations as part of the "Point of the Spear" initiative aimed at ser-

vice members with the most-intense performance requirements. The bar is increasingly being added to more MREs.

The “Peak Soldier Performance” Model

The Peak Soldier Performance (PSP) example discussed by panelists involves a potential dietary supplement component whose effectiveness was evaluated by a scientific panel created for that purpose. According to one panelist involved in the project, the Defense Advanced Research Projects Agency began the PSP research program in 2007 to identify interventions that could increase endurance in combat. One substance that appeared promising in studies of laboratory animals was quercetin, a flavonoid with antioxidant properties that is found in some fruits and vegetables. Small studies in humans found that ingestion of 1,000 mg of quercetin daily (approximately 20–40 times the normal daily intake obtained from food) improved physical and mental performance. Based on these results, DoD contracted with a small manufacturer in Massachusetts to produce a chewable quercetin-containing candy. A large trial funded by the company reported positive effects.

In September 2008, ARIEM commissioned a review of the effectiveness of quercetin. The independent, two-day scientific panel was conducted by the American Institute of Biological Sciences (AIBS) and involved panelists selected by the chair, E. Wayne Askew, PhD (former Director, Nutrition Division, USARIEM) and by AIBS. The AIBS panel considered two sets of questions about the benefits of quercetin: whether it affects performance (the more difficult effect to demonstrate) and whether it promotes health (the realm in which benefits usually occur). Specifically, the AIBS panel considered the following questions (AIBS, 2008):

1. Currently, are there published data, in humans, that justify the incorporation of Quercetin into or as part of the military ration for either a performance or health benefit?
 - a) If so, specify the benefit and amount of expected improvement.
 - b) If so, specify the dose and regimen of Quercetin required.
 - c) If so, indicate whether Quercetin should be provided to the entire force or applied to specific operational conditions, personnel or situations. For example, might Quercetin have a unique advantage for Soldiers consuming the First Strike Ration?
2. Identify any current on-going human studies that are evaluating a performance and/or health benefit of Quercetin. Indicate what new information these studies will provide and the anticipated dates of completion.
3. Are there any safety or medical issues/concerns with the use of Quercetin by Soldiers in the military operational setting?
 - a) Are there beneficial or deleterious interactions with Quercetin and other nutrients and/or pharmacological agents?
 - b) Are there any documented/anticipated adverse events with Warfighters consuming recommended levels of Quercetin who are sleep deprived, dehydrated and/or in a negative caloric balance?

- c) Is there documented scientific evidence concerning the effects of excessive consumption of Quercetin?
4. With respect to the studies on Quercetin that have been completed or are currently underway or planned, identify significant “gap” areas, questions, or issues that will need to be addressed before Quercetin could or should be incorporated into a military ration.
5. Is enough information known on the physiological mechanism(s) of action of Quercetin to predict the response of Quercetin over and [sic] extended period of time?

The AIBS panel deliberations were intended to result in a recommendation about whether to move forward with development of a quercetin product for the military. The panel process led to a report that was distributed within the Army, where the potential for a quercetin product had raised significant interest. The report authors concluded that the completed research to date was too heterogeneous in its methodology and too preliminary in its findings to allow firm conclusions to be drawn (AIBS, 2008). The report identified ongoing studies on the effects of quercetin on performance, health, bioavailability, and pharmacokinetics. The authors concluded that further research is needed on the basic mechanisms of action of quercetin and on the safety of large doses before moving ahead with the development of a product designed for the military (AIBS, 2008).

Mark Davis’s Animal and Human Models of Performance Enhancement

J. Mark Davis, PhD, a faculty member and researcher at the University of South Carolina, has developed an animal model, based on the central fatigue hypothesis, to assess the effects of various substances on central fatigue and performance (Davis, Murphy, and Carmichael, 2009). His laboratory has studied the effects of changing brain serotonin levels on the physical performance of rats, finding that the changes in brain serotonin are effected by altering the carbohydrate and branched chain amino acid content of the diet. In addition, the laboratory is assessing the effects of other potential adaptogens, including quercetin, turmeric, and muscidine. If one or more of these substances shows beneficial effects in the animal model, the researchers, who are working with ARIEM, will test their effects on soldiers by adding the substances to a ration, such as the First Strike ration. The first human field studies are being conducted in Northern California (for further information, see Davis, Murphy, and Carmichael, 2009).

Long-Term Development

Another member of the panel, drawing on his company’s experience, outlined a model sequence of events and a timetable for long-term development of a product designed for the military. The particular example was a type of ration that would ensure that service members obtain the nutrients they require, regardless of whether they consume all their rations or only portions of them. The entire process from inception to testing involved five to seven years of research. During this time, using the basic science as their starting point, the researchers developed a product, conducted preclinical trials of the reformulated ration, conducted controlled clinical trials, and, at the time of the workshop, were in the process of conducting field tests.

Examples from Established Research Methods

During the discussion, panel members drew on their varied experience to present a number of possible approaches for developing multicomponent dietary supplements. Many of these approaches are outlined earlier in this chapter. In this section, we organize suggestions provided by panel members according to issues of concern to the military.

Using Historical Exposure for Safety in Trials of Efficacy

The group acknowledged that military commanders are not willing to accept any risk to their personnel if the efficacy of a product has not been proven. Therefore, the first goal for product development should be to generate valid, accepted evidence for efficacy. Having established a product's efficacy, the overall safety issue might be approached through use of historical data, at least initially.

One potentially relevant model presented by a panelist involves target- or indication-based drug development or product development and promotion. This model could be considered a hybrid of what is known about over-the-counter drugs and of current marketing approaches. In this model, the developers look at the key indication and work backwards to develop a product and to identify potential efficacy and safety issues. Thus, products that are already on the market would be the leading candidates for assessment and potential modification. Validation of efficacy and safety and of a model for the development of an effective agent would be less onerous than if the product were based on entirely untested ingredients.

According to the panelist, how to assess safety would depend on the type of product. In the case of combination products for which similar products are already on the market, safety data from exposures have already been collected by manufacturers and the FDA. For new combination products that present heretofore unknown interactions, it might be possible to incorporate relatively inexpensive *in vitro* assay systems for drug-drug interactions to develop some degree of confidence in the safety of these multicomponent products that is based on their predicted individual *in vivo* effects. To some extent, the panelist said, this process is analogous to the current drug development process.

The costs of clinical trials may be prohibitively high, but panelists reported that it may be possible to perform relatively inexpensive dose-ranging studies, as well as one pivotal trial, to establish efficacy. If safety issues are revealed through subgroup analysis or follow-ups, they can be analyzed. According to the panelist who proposed this scheme, these trials should cost less than \$3 million and are important to establish risks and benefits.

Another possible solution to the need to demonstrate safety is to establish a scientific (empirical) basis for efficacy and then to demonstrate safety through postmarket analysis. This approach builds on history in the target population and on current scientific methods. Incentives for implementing the kind of model just described could be provided through a combination of government funds and private funds, and the model would aim to prove efficacy in a particular population (e.g., a particular occupational specialty, such as special forces). According to the panelist who presented this idea, the cost of this testing would be incorporated into the business model for product development.

Yet another model of assuring some degree of product safety prior to efficacy testing was provided by another panelist, who described the effort to seek a botanical with anti-inflammatory effects analogous to those provided by nonsteroidal anti-inflammatory drugs. The idea of trying to identify such a substance, another panelist said, raises several questions.

For example, what is the target (condition), and what is the study model? The panelist proposed that an animal model should be considered, keeping in mind that many substances act differently in laboratory animals than in humans. Taking a substance through Phases Ib and IIa would provide data on safety and dosing for efficacy.¹ Before moving to efficacy testing in Phase IIb, a high-quality product would be needed. Panelists indicated that such a study would be costly for a large company but not prohibitively so. The early studies permit conceptualization all the way up to the product. Panelists indicated that this approach falls within the bounds of FDA trials.

Developing a Product to Deliver Multiple Micronutrients

According to one panelist, the first consideration in developing a multiple nutrient product is to conceptualize the issue or condition to be addressed. The second consideration involves what types of biochemical markers are common to diverse agents and could be used in the study. Relevant markers for micronutrient status might include oxidative stress and chronic inflammation. Therefore, according to this panelist, a beneficial multicomponent agent might be one that targets oxidative stress, chronic inflammation, and immune system problems.

According to a military member of the advisory committee, of currently available supplements, dietary antioxidant combinations are closest to the type of supplement DoD is considering for development. Other factors to consider in designing the necessary multistep evaluation process include the fact that antioxidants are processed differently by different organs and cells. The design of the study would need to consider the literature on safe dosages for the individual antioxidants (whether dietary or endogenous). Multivitamin products can be designed based on this process and vetted by a third party for analysis. Another consideration is that certain combinations of micronutrients—such as iron/copper/magnesium—should be avoided because they may increase iron stores in the body.

The panelist explained that, once the optimal product is developed, it becomes necessary to demonstrate the efficacy of the multiple components. A pilot study must be conducted, with or without a placebo, and this study will serve as the basis for a larger study. The design of the study must consider the issues of compliance and withdrawal. Because military personnel deploy or change duty stations relatively frequently, studies need to be short term. The use of animal studies should be limited, even for establishing a basic model, given their general lack of applicability.

If efficacy data are convincing, the panelist continued, the product can then be used on a broad population. However, it might be important to tailor use and dose for each target population (e.g., younger men) and for those with a particular health-related condition or disorder.

¹ The clinical testing of prospective drug products (which follows preclinical testing and the granting of IND status) is conducted in phases. Phase Ia tests bioavailability, and Phase Ib tests pharmacokinetics in small laboratory studies. Phase IIa tests dosing requirements, and Phase IIb tests efficacy and safety in small trials. Phase III tests the effectiveness of the drug in large-scale trials under “real-life” conditions. The results of the trials then undergo regulatory review. If the drug receives New Drug approval, it enters Phase IV, which is postmarket surveillance.

The Panel's Consideration of the Examples

The panel discussed the benefits and drawbacks of the various examples from the standpoint of identifying issues that would be expected to affect the design of a multicomponent dietary supplement. These issues are summarized in this section.

Historical Use Demonstrates Safety and Efficacy

Many substances now defined as dietary supplements—particularly botanicals and other substances from natural sources—have been safely used for a long time (sometimes hundreds or thousands of years) by various cultures. These supplements contain multiple compounds that are digested into other compounds with no ill effects or unsafe interactions. According to one panelist, the use of these substances throughout history provides evidence of safety and dose-dependent effectiveness.

Attempts to Isolate Active Ingredients May Negate the Activity

Researchers and manufacturers engage in lengthy, complex processes to identify substances that produce desired effects and to purify the active ingredients in an attempt to concentrate their potency. However, in doing so, they may risk losing all activity and rendering useless all that has been learned over the course of the history of use of the whole plant or substance (Ribnicky et al., 2008).

Trials May Not Replicate the Findings of Epidemiological Studies

Attempts to replicate the effects of whole foods observed in cohort studies by administering the putative active components in trials have in some cases demonstrated lack of efficacy and even resulted in harm. (The most well-known example may be the alpha tocopherol beta-carotene [ATBC] study on the effects of antioxidant supplements on Finnish male smokers [Virtamo et al., 2003]). Therefore, in designing a study to evaluate the effectiveness of a supplement, it is important to consider the appropriate outcome variables. For the military population, panelists questioned whether it was possible to identify relevant biomarkers (e.g., oxidative stress).

Related to this issue is the fact that human performance, whether physical or cognitive, is extremely complex and unlikely to involve single metabolic pathways or genes. Therefore, single products—and even multicomponent products—may not yield optimal improvement in performance, or at least not without unwanted side effects.

Regulatory Issues Abound

Some discussion was devoted to the difference between, on the one hand, substances for which manufacturers are making a disease claim (i.e., drugs) and, on the other, foods, which provide nutrients (i.e., substances required for health). Where do dietary supplements fall on this spectrum? Panelists noted that, if the military is proposing the development of a product to meet specific physiological needs (that is, to treat a disease or condition), then, by definition, this product would be making a health claim. Several panel members noted that manufacturers avoid such products because they fall under the purview of drug regulation and cannot be considered supplements. Thus, the military might be prevented by federal regulations from doing what it wants to do if it ties the use of dietary supplements to a specific health need.

One panelist suggested establishing a process of evidence review to investigate the effectiveness of dietary supplements under various physiological conditions; in this model, claims

of effectiveness in treating a condition would not be explicitly tested. However, panelists indicated that the available evidence is insufficient to conduct such investigations. Furthermore, they indicated that the military may be looking for dietary supplements with two different, possibly opposing types of benefits: (1) short-term performance enhancement in the field and (2) long-term optimization of health. The considerations involved in choosing and testing products for each of these goals are very different.

With the mapping of the human genome and the development of the field of nutrigenomics, panelists remarked, the idea of individualized nutrition is becoming increasingly attractive. It may be of particular interest to the military if it desires to optimize performance under extreme, unusual conditions. Panelists noted that the ability to identify an individual's unique nutritional needs may be on the horizon.

One of the panelists suggested that one way to regulate the development and testing of the kinds of dietary supplements the military desires might be to create a regulatory system that lies somewhere between the FDA approval process for pharmaceuticals and those used for supplements, which are mandated under the Dietary Supplement Health and Education Act (DSHEA). The military may want to implement its own IND approval process for botanicals of interest. Whether the FDA treats a substance as a drug, a biological, a food, or a supplement depends on the indication provided.

Also discussed was the concern that different varieties of the same species of plant can have completely different biological activities. People of various ethnic cultures who have developed botanicals for medicinal uses are familiar with these differences in effects, but others may not be.

Prioritizing the Desired Outcomes

During the session, an additional question was posed for the panel's discussion: If the military decides to move forward with the development of multicomponent dietary supplements, what process should be used to decide what model it will adopt in determining the desired health and performance outcomes and the evaluative mechanisms to be used?

According to one panelist, a major deciding factor in the model adopted for evaluating new products is whether a product includes components that are entirely new or instead consists solely of components that have been tested and marketed in the past. If a product includes a brand new component, then the manufacturer is obliged to conduct a pilot and, if the product shows strong potential, trials. However, if a product consists only of components with established use, efficacy, and safety, then development can occur rapidly.

The DoD cross-service Nutrition Committee has a new charter that establishes a Subcommittee on Dietary Supplements (see DoD, 2011). According to a military member of the advisory committee, the proposed role of this subcommittee is to serve as a clearinghouse. But the implementation of the charter has been in progress for two years, and, as of the conclusion of the workshop, what would happen to it, given the then-upcoming change of administration, remained to be seen. The recommendations of this or a similar panel could influence the direction of the Nutrition Committee. One possibility is for the committee to establish different metrics for different populations (e.g., deployed elite forces versus desk-bound senior officers approaching retirement) and different functions (e.g., alertness versus immune support). What are needed, according to this panelist, are new models that DoD can use to address current and future needs.

Addressing the Questions

During the workshop, the panel did not directly address the key questions they were asked to consider prior to the meeting (see the numbered list in Chapter One). Nevertheless, their discussion highlighted issues that were relevant to these questions, and this chapter summarizes the discussion points relevant to each question.

As the military members of the advisory committee established at the outset of the workshop, it is critical to approach the issue of dietary supplement design from the perspective of the service member, who faces potential benefits and risks that differ from those faced by the average person on the street. There are higher stakes for warfighters who take a product of unknown efficacy and safety. Although it would be helpful to employ the thousands of years of history of natural product use to predict the likely benefits and risks of new products, the evidence on multicomponent dietary supplements—at least those that combine ingredients from multiple sources—is inadequate to guide our determination of the appropriate indications for use.

Question 1

1. Of the current MNP indication–related regulations around the world, which ones offer
 - a. the clearest and most customized path for evaluation
 - b. the best balance in providing quality, safety, efficacy, and access
 - c. the most feasible and reasonable process providing guidance on use?

Several panelists pointed out that the FDA guidelines do not currently address multicomponent dietary supplements. Many of the kinds of supplements under consideration lie in a gray zone. Decision trees would help in designing evaluation processes. For example, if a substance will be added to rations, it will be considered a food. We also need to ask what nutrients service members need in larger amounts that could easily be supplied through the consumption of reasonable quantities of fresh fruits and vegetables. There is growing receptivity among military personnel for “smart combinations” of food-based items.

At least one panelist emphasized that our guidelines need to be consistent with European Economic Union regulations and guidelines. This panelist expressed the belief that the United States could achieve such unity by creating a hybrid of European Economic Union and U.S. regulations.

Question 2

2. Of the FDA's current regulations of products (including drugs, biological products, food, and medical devices), which single regulation or combination of regulations might best be used to guide MNP approaches for the military?

The panel suggested that a collaborative conversation among DoD, FDA, and the Institute of Medicine would help to determine what DoD is trying to accomplish with different populations (as distinct from the general population) and thereby facilitate the development of a regulatory process tailored to the kinds of products that the military is considering.

In terms of regulation, the pharmaceutical industry's GMPs include excellent record-keeping. But assay methods are needed early in the purification process, and standards of identity (i.e., for a product to call itself "X," it must contain a minimum of Y percent of Z) are needed further along in the process. Some products may provide real-world lessons. For example, quinine (cinchona bark) is a natural substance that has shown evidence of protective properties and has both historical and traditional uses. If DoD were to modify its indications from the traditional uses, a different set of standards would then need to be applied.

A multitiered system of regulations might provide the needed flexibility. The first tier would consider historical and traditional use. If the proposed use represented a departure from traditional use, then efficacy testing would need to be appropriately modified. There is a gap between recent scientific progress and the empirical discoveries made many years ago. Extant records of these older efforts might contain valuable information.

Question 3

3. Are there alternative approaches to characterizing MNP components or effects that may be better than current chemical or drug approaches?

The consensus of the panelists was that ultimately what is needed is a mechanism that ties clinical outcomes back to safety at a range of doses and durations. Also, they emphasized that it is critical to consider the possibility of synergistic effects among the components.

In addition, regarding botanicals and their use for the physiological conditions of interest to the military, the panel expressed the belief that it is important to consider the sources of the botanicals and the possibility that they could contain toxic substances. It may be advantageous to obtain particular substances in the form of a whole-plant product, but there may also be dangerous disadvantages in some cases.

With botanicals, it is critical to consider synergy among the components. For example, one panelist related that, in Germany in the 1990s, insurance companies reimbursed patients for a botanical used in the successful treatment of irritable bowel syndrome. Then, the government decided that, for these kinds of multicomponent mixtures, each individual component had to be tested. It was discovered that, on its own, one component of a particular herb was hepatotoxic but that the whole herb was safe and effective as a treatment. This example suggests the need to identify the appropriate approach for testing efficacy and safety. There is now a burden of proof to show that every component contributes to effectiveness and is safe. The totality of the evidence needs to drive the decisionmaking processes.

Question 4

4. Are there special military performance or environmental requirements that justify different research and regulatory requirements for determining the use of MNPs in military settings or populations?

In designing products for the military, the essential need is to understand the etiology of the dysfunctions of concern. For example, what are the triggers and stressors affecting these special populations, and which ones are quantifiable? Using a biomarkers approach, what performance indicators best reflect the effects of these stressors?

A military member of the advisory committee emphasized that needing to optimize performance for an entire population is a different mandate than needing to enable special populations to achieve peak performance in particular situations. To help the military “be all it can be,” panelists suggested that scientists could focus on just those situations. The military may also wish to consider potential racial, ethnic, and gender differences in responses to particular products. Finally, the military attendees agreed that, in keeping with the frequently changing needs of service members, development of these targeted products must occur within a short time frame.

Throughout the discussion, several panelists noted that it is important to emphasize that health promotion is different from disease treatment. The criteria for fundamental health define global health measures that can be used to assess relative risk and the changes that occur with aging. These markers may be ideal for demonstrating evidence of efficacy (e.g., what is the effect of using a product rather than not doing anything at all?).

Finally, based on our panelists’ experience with antioxidant supplements, it appears that military commanders will promote the use of supplements only if they have seen evidence of efficacy under field conditions. Recommendations are also needed regarding how to educate military personnel about the use of these products.

Question 5

5. Are there ways to incentivize private industry to invest in production of MNPs for DoD and the general public?

Some encouragement may be needed to facilitate responsible government-industry collaboration. Methods to incentivize industry must be created. Panelists emphasized that industry needs a guarantee of protection of intellectual property in order to be willing to invest in and collaborate on designing and manufacturing new products. Several panel members also emphasized the need to allow manufacturers to control the supply chain.

Panelist described several approaches for evaluating the efficacy and safety of multicomponent dietary supplements. They also emphasized the importance of not underestimating the influence of the supply chain and of the need to control the entire process from the outset rather than focusing solely on product development. Safety and regulatory issues do not pose impossible barriers.

The panelists also suggested that manufacturers should be encouraged to develop an approach based on a certain category of products so that the development of one product will

naturally lead to the development of the next product. The direction of the path (i.e., what gets added to or modified in the original supplement product) will be driven by the needs of the consumer.

Closing Comments

The military has been conducting research on food intake and dietary supplement use and has been attempting to determine optimal nutrient intake for physical and cognitive performance. Participants in the workshop identified key issues that must be considered in the design of dietary supplements and presented some alternative models that could be used to begin to conceptualize, develop, and test the efficacy and safety of such products.

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