



**National Center for
Complementary and
Alternative Medicine**

**Dietary Supplement-Drug Interaction
Expert Panel Meeting**

April 1, 2013

Neuroscience Center
Conference Room B1-B2
6001 Executive Boulevard
Rockville, MD 20852

EXECUTIVE SUMMARY

Background and Purpose

National surveys have shown that millions of Americans consume dietary supplements, many of whom also take prescription drugs concurrently. In the late 1990s, reports began to emerge of negative interactions between dietary supplements (or other foods or beverages) and pharmaceuticals—e.g., between St. John’s wort and numerous drugs such as cyclosporin.

The scientific evidence on supplement-drug interactions has been very limited, extremely variable, and largely in the form of preclinical models, case studies, and hypothetical arguments. This has led to questions of clinical relevance. Concerns among the public, health care providers, and researchers exist not only about interactions that can be serious or even life-threatening, but about less severe interactions, which can impact medical treatments and quality of life. Adding further to this picture, research has identified some potentially beneficial supplement-drug interactions in certain contexts. In short, the landscape on supplement-drug interactions has often been confusing.

To address this public health problem, the National Center for Complementary and Alternative Medicine (NCCAM), the Office of Dietary Supplements, and the National Cancer Institute cosponsored a roundtable meeting of subject experts on dietary supplement-drug interactions in March 2012. Based on recommendations from that meeting, NCCAM developed a Concept Proposal, “Systematic Evaluation of Dietary Supplement/Drug Interactions.” NCCAM’s advisory council approved the proposal in June 2012.

As a result, NCCAM has begun implementing a three-phase initiative for systematic *in vitro* and *in vivo* characterization of potential supplement-drug interactions. The overall goal is to produce a repository of carefully controlled experiments and their ensuing results. Those resources are expected to enhance assessment of the risks and/or benefits of selected supplement-drug combinations and understanding of metabolic pathways for a large number of supplements.

In Phase I of the initiative, NCCAM has assembled a Dietary Supplement-Drug Interaction Expert Panel to identify and discuss criteria to be used in prioritizing *in vitro* and *in vivo* research and help guide the Center’s future investments in this area. These criteria will then be used to generate a matrix for testing potential supplement-drug interactions. Potential candidates for supplements, pharmaceuticals, supplement/drug/disease groupings, and assays are being identified to create a testing matrix for evaluation using moderate- to high-throughput screening. Moving directly to human subjects research may be appropriate for some combinations, based on the literature.

Organization

The meeting was divided into five sessions:

Session I. Literature Review

Craig Hopp, Ph.D., NCCAM, Moderator

The journal *Planta Medica* published a special issue in September 2012 on herb-drug interactions, co-edited by Veronika Butterweck, Ph.D., of the University of Applied Sciences and Arts Northwestern Switzerland. In this session, Dr. Butterweck provided an overview via teleconference of the strengths and weaknesses of the evidence base of these interactions. Shiew-Mei Huang, Ph.D., U.S. Food and Drug Administration (FDA), then presented the agency's draft guidance for industry on drug-interaction testing, updated in 2012, including a simplified decision tree for evaluating enzyme inhibition/induction, and recent additions on transporter-based interactions.

Session II. Criteria for Inclusion of *In Vitro* Assays in Testing Matrix

John Markowitz, Pharm.D., University of Florida, Moderator

In vitro testing allows quick screening of a large number of possible interactions in multiple assays. These assay systems must be chosen carefully to minimize false positives and negatives while also providing meaningful signals about potential interactions with clinical significance. The panel discussed the following possible criteria: (1) focusing initially on pathways most commonly associated with significant drug interactions (e.g., CYP and Pgp) and (2) using assays that both allow for detection of inhibition and induction mechanisms and are amenable to high-throughput screening.

Session III. Criteria for Inclusion of Supplements in Testing Matrix

David Greenblatt, M.D., Tufts University School of Medicine, Moderator

The panel discussed possible criteria to rationally prioritize supplements for inclusion into the testing matrix. Possible criteria included prevalence of use, abundance in the food supply, structural classes, isolated compounds, and metabolites.

Session IV. Criteria for Inclusion of Drugs in Testing Matrix

Reginald Frye, Pharm.D., Ph.D., FCCP, University of Florida, Moderator

This session addressed criteria that should be used when making decisions about including pharmaceuticals in the testing matrix. Possible criteria included drugs with a narrow therapeutic index, most-commonly-prescribed drugs, and known probe drugs.

Session IV. Criteria for Advancing to Clinical Study

Bill Gurley, Ph.D., University of Arkansas, Moderator

Clinical studies represent the definitive way to assess the statistical and clinical significance of any interaction, but their costs and risks pose numerous challenges. Possible criteria discussed included: (1) following the FDA guidance for industry on drug-interaction studies to determine which *in vitro* data requires clinical testing; (2) using existing literature, where available and sufficient to prioritize immediate clinical studies; and (3) if no literature exists regarding human exposure, conducting pharmacokinetic profiling on high-priority supplements in parallel with *in vitro* assays in order to gain a better understanding of possible mechanisms of interaction, plasma concentrations, and potential active metabolites.

Summary and Recommendations

The major recommendations for NCCAM to consider in supplement-drug interaction studies are:

- To use good, fundamental science that is relevant to human medicine
- To use the right designs, full safety precautions, and maximally sensitive testing mechanisms so that it will be possible to definitively state to the public, health care providers, and others whether interaction potential exists in studied substances
- To design experiments so that multiple data points can be collected simultaneously.

The variability in supplements and in their constituents (whether as single forms or complex mixtures) is a major challenge, with much work remaining to be done to understand their pharmacologic properties. Substances must be well characterized prior to initiating any research.

Regarding the FDA's 2012 guidance, investigators should: (1) consider *in vitro* evaluation to understand potential mechanisms of interactions with drugs; (2) include, for *in vivo* clinical studies, measures of product content (marker constituents) and of systemic exposure of marker constituents of these modulators; (3) use the safest, most sensitive probes; and (4) use modeling where appropriate.

Examples of "low-hanging fruit" that represent good *in vitro* screening options for potential interactions include major cytochrome P450 (CYP) enzymes (3A4, 2C9, 2D6, etc.); selected transporters present in the intestine (Pgp, BCRP, OATP1A2, etc.); and a small panel of nuclear receptors (PXR, AHR, CAR). The CYP assays could be conducted using microsomes. However, the transporter assays would have to use a different platform. The FDA guidance suggests using Caco-2 cells or MDR1 overexpressing polarized epithelial cells. The nuclear receptors can indicate potential induction of multiple pathways, but the FDA guidance requires that hits in

these assays be followed up in a lower throughput hepatocyte assay to confirm and quantify the induction interaction mechanism.

Recommended criteria for selecting substances to study include:

- Popularity, as ascertained using a range of data beyond dollar values of sales
- Significant level of public exposure
- Data available at least on chemistry and bioavailability, if not on interactions
- Existence of a biological signal of interaction and/or reports of clinically significant interactions
- Data obtained through existing reports in the literature, adverse-event reports, case reports (especially if pertinent to a pharmacokinetic interaction), IND submissions, or clinicaltrials.gov
- Safety for study
- Data from survey results (e.g., from Federal national health surveys, or surveys in vulnerable subpopulations such as people who are elderly or have diabetes).

Additional discussions revolved around how to choose among the multiple available sources, constituents, and formulations for a specific plant. Here it was suggested that emphasis be placed on availability in a form that reaches the intestinal mucosa, especially as whole extracts and/or pure chemicals. In light of the extreme variability in commercial product composition, a custom preparation may be needed. Original plant materials, although variable, are generally less so than products in the marketplace. The consensus of the panel was that products should be chosen that are consistent with the chemistry of the source plant while also being representative of products that the public commonly consumes. A limited number of major constituents in the extract should be included if they are commercially available.

Criteria for advancing to clinical studies centered on the recommendations laid out in the FDA guidance. However, it was recognized that this document is intended as industry guidance to assist in the development of pharmaceuticals, and, therefore, does not directly apply to dietary supplements and botanicals, for which different criteria may be needed. In general, it was recommended that, for transporters, the products with the largest I/K_i values be prioritized for clinical investigation, as they represent the most significant risk. It may not be possible to set a strict cut-off value for what *in vitro* screening data warrants before moving to clinical study. The practical recommendation was to evaluate the *in vitro* data generated and choose for clinical interaction studies those products having the strongest interaction/induction potentials. Furthermore, it was recommended that clinical studies initially be conducted using the safest, most selective probe drugs in healthy volunteers. If a significant interaction was observed in this population, additional studies could be considered using elderly or sick patients and narrow therapeutic index drugs.

Overall, the panel recommended examining where studies can be done together—e.g., measuring the pharmacokinetics for a plant product and a drug simultaneously, or designing a clinical study to test both inhibition and induction mechanisms. Cost-effectiveness is important. Other ways to achieve it include analyzing banked samples from previous studies and leveraging existing NIH resources or Federal facilities that might be available to NCCAM—for example, through collaboration with the National Center for Advancing Translational Sciences and/or the U.S. Department of Agriculture.

In summation, a clear framework was established for carrying out the necessary research. However, more work needs to be done before a list of specific substances to be tested can be finalized. NCCAM would like to develop as soon as possible a short list of products that could then be refined further.

Chair

Craig Hopp, Ph.D., NCCAM

Participants

Veronika Butterweck, Ph.D., University of Applied Sciences and Arts Northwestern Switzerland

Reginald Frye, Pharm. D., Ph.D., FCCP, University of Florida

David Greenblatt, M.D., Tufts University School of Medicine

Bill Gurley, Ph.D., University of Arkansas

John Markowitz, Pharm.D., University of Florida

Shiew-Mei Huang, Ph.D., U.S. Food and Drug Administration