Drug interactions with herbal products and grapefruit juice: A conference report

Shiew-Mei Huang, PhD, Stephen D. Hall, PhD, Paul Watkins, MD, Lori A. Love, MD, PhD, Cosette Serabjit-Singh, PhD, Joseph M. Betz, PhD, Freddie Ann Hoffman, MD, Peter Honig, MD, Paul M. Coates, PhD, Jonca Bull, MD, Shaw T. Chen, MD, PhD, Gregory L. Kearns, PharmD, PhD, and Michael D. Murray, PharmD, MPH

In the United States 60 million Americans use alternative ways to heal and 1 in 3 use some form of complementary or alternative medicine.1-3 Herbal supplements are used by 14% of the adult population, often concomitantly with prescribed medications.4 Herbal products are widely used by older adults,5 administered to children,6 and taken by women during pregnancy and lactation.7 Most often, solely on the basis of claims and anecdote, patients resort to these products to treat a variety of recalcitrant chronic disorders such as anxiety, depression, dementia and memory impairment, headache, weight loss, back disorders, persistent pain, prostatic hypertrophy, and cancer.8 Although it is possible that some of the components contained in botanical mixtures used to treat such disorders could have pharmacologic activity and produce favorable effects, most of the larger well-controlled trials and systematic reviews involving smaller trials have failed to reveal conclusive effects. Nonetheless, patients, proponents of alternative medicine, and, in some instances, licensed health care practitioners (nurses, pharmacists, and physicians) continue to advocate for their widespread use. In 1997 Americans spent more than $17 billion on sundry dietary supplements and $5 billion on herbal therapies.9 Despite partial reimbursement for these products in some states,10 the majority of costs are out of pocket.
Importantly, herbal products are often used concurrently with prescribed or over-the-counter medications. Patients frequently fail to tell their physicians about their use of supplements, and physicians often fail to ask. Moreover, because most herbal product purchases occur outside the pharmacy, concurrent use of herbal products and prescription drugs often evades the attention of the pharmacist and physician. As such, the use of herbal products often escapes standard mechanisms for protecting persons from harmful effects of drugs and drug interactions. The same can be said of food products that may affect the disposition of prescribed medications. Studies in the 1970s tested products such as Brussels sprouts and found that they could affect the disposition of commonly prescribed drugs. More recently, it has been demonstrated that grapefruit juice may markedly influence the pharmacokinetics of selected drugs. Compounding the problems associated with drug interactions with herbal and food products is the wide variability among many dietary supplement products and, with few exceptions, the lack of scientific data from carefully designed and conducted investigations that examine the interactions between drugs and the specific small molecules that may represent the active or inactive ingredient of botanical-derived alternative medicines. The potent effects of herbal products coupled with their risk of interactions with other commonly used drugs and the lack of governmental regulation have created a public health dilemma.

To address these issues, a symposium involving noted scientists in clinical and basic pharmacology, as well as the analytic and regulatory sciences, was held with participation of and support from the American Society for Clinical Pharmacology and Therapeutics and the US Food and Drug Administration (FDA). This report summarizes the proceedings of the educational symposium, entitled “Drug Interactions with Herbal Products & Food,” which was held July 22 and 23, 2002, in Washington, DC. The symposium objectives were as follows:

- To provide an update on clinically significant herbal drug and grapefruit juice interactions
- To understand the mechanisms by which herbal products selectively modulate cytochrome P450 (CYP)– and P-glycoprotein–mediated elimination
- To understand the clinical importance of drug–grapefruit interactions
- To discuss the regulatory standards for various food products that influence product safety and claims
- To discuss the evaluation of clinical drug-drug, drug–herbal product, and drug–grapefruit juice interactions and their impact on labeling

**RISK OF DRUG INTERACTIONS INVOLVING HERBAL AND OTHER FOOD PRODUCTS**

The use of botanical products has increased in recent years. It has been estimated that approximately 1 in 5 Americans take prescription medications concurrently with at least 1 herbal product or a high-dose vitamin, or both. The top 5 selling botanicals in the United States in 1999 included ginkgo, St John’s wort, ginseng, garlic, and echinacea, each with more than 10% market share. Concurrent use of botanicals with approved prescription drug products can result in therapeutic failures or adverse events and can produce variable outcomes of clinical trials if the concomitant use is not controlled. Recent publications have shown that coadministration of St John’s wort decreases plasma levels of concomitant indinavir, cyclosporine (INN, ciclosporin), and digoxin.

Postmarketing reports from the FDA database up to July 2002 suggested interactions of St John’s wort with oral contraceptives (with reports of breakthrough bleeding and pregnancies), selective serotonin reuptake inhibitors (hypertension, serotonin syndrome), cyclosporine (organ rejection, reduced plasma levels), and sildenafil (loss of efficacy). The FDA issued a Public Health Advisory in February 2000 indicating that “...concomitant use of St John’s wort with protease inhibitors or non-nucleoside reverse transcriptase inhibitors is not recommended” and contracted studies to further evaluate the mechanistic basis of interactions. Initial findings with the use of specific CYP enzyme and P-glycoprotein probes indicated that long-term administration (>14 days) of St John’s wort appeared to induce the intestinal CYP3A and P-glycoprotein, consistent with earlier case reports and specific clinical studies. Another recent survey of postmarketing adverse event reports yielded reports that implicate grapefruit juice as being capable of producing clinically significant interaction with drugs. Grapefruit juice appears to have contributed to the exaggerated pharmacologic effects of several calcium channel blockers (hypotension, dizziness, syncope), statins (eg, myalgia, rhabdomyolysis), and others. Data from the medical literature suggest that components in grapefruit juice can inhibit the activity of intestinal CYP3A and other enzymes, in addition to the P-glycoprotein transporter. It is also possible that grapefruit juice and other fruit juices may be affecting other intestinal
transporters, such as organic anion transporting polypeptides.  

**EFFECT OF HERBAL PRODUCTS ON CYP ENZYMES AND P-GLYCOPROTEIN**

St John’s wort has been implicated in numerous interactions with prescription drugs that appear to lack a unifying mechanism but have demonstrated profound clinical consequences (Table I). The critical examination of interactions between dietary supplements, foods, and drugs requires the ability to accurately determine not only the presence of altered metabolism and transport but also the ability to quantitate the extent of the interaction. Wang et al developed and validated the use of a “pharmacologic cocktail” of CYP probe substrates to efficiently quantify the potential for interactions between dietary supplements and drugs. In these studies neither short-term administration (900-mg single dose) nor long-term administration (300 mg 3 times daily) of St John’s wort had any effect on the activity of CYP1A2 (assessed by the apparent oral clearance of caffeine), CYP2C9 (assessed by the apparent oral clearance of tolbutamide), or CYP2D6 (assessed by quantitating the molar ratio of dextromethorphan and its metabolites). However, long-term St John’s wort administration caused a significant ($P < .05$) increase in oral clearance of midazolam from 121.8 ± 70.7 to 254.5 ± 127.8 and a corresponding significant decline in oral bioavailability from 0.28 ± 0.15 to 0.17 ± 0.06. In contrast to the more than 50% decrease in the area under the plasma concentration versus time curve (AUC) when midazolam was administered orally, long-term St John’s wort administration caused only a 20% decrease in AUC when midazolam was given intravenously. Thus induction was most pronounced in the wall of the small intestine, where availability declined by 25% consequent to induction of CYP3A enzymes residing in the enterocyte.

The efflux transporter P-glycoprotein can also function to reduce intestinal drug absorption of specific drug substrates. Therefore the effect of St John’s wort on the apparent oral clearance of the P-glycoprotein probe fexofenadine was also determined. Short-term administration (900-mg single dose) of St John’s wort significantly ($P < .05$) increased the maximum plasma drug concentration of fexofenadine by 45% and significantly

<p>| Table I. Effects of St John’s wort on drug pharmacokinetics and response |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>St John’s wort treatment</th>
<th>Response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (n = 12)</td>
<td>900 mg qd 14 d, nortryptiline C &lt;sub&gt;ss&lt;/sub&gt; ↓ 40%</td>
<td>Amitriptyline C &lt;sub&gt;ss&lt;/sub&gt; ↓ 22%</td>
<td>Johne et al&lt;sup&gt;49&lt;/sup&gt; (2002)</td>
</tr>
<tr>
<td>Cyclosporine (n = 2)</td>
<td>300 mg tid</td>
<td>C &lt;sub&gt;ss&lt;/sub&gt; ↓ 52%, Acute heart rejection</td>
<td>Ruschitzka et al&lt;sup&gt;19&lt;/sup&gt; (2000)</td>
</tr>
<tr>
<td>Cyclosporine (n = 11)</td>
<td>600 mg qd 14 d</td>
<td>AUC ↓ 46%</td>
<td>Bauer et al&lt;sup&gt;50&lt;/sup&gt; (2003)</td>
</tr>
<tr>
<td>Digoxin (n = 13, 12)</td>
<td>900 mg single dose, 300 mg tid 10 d</td>
<td>C &lt;sub&gt;ss&lt;/sub&gt; ↓ 25%</td>
<td>Johne et al&lt;sup&gt;20&lt;/sup&gt; (1999)</td>
</tr>
<tr>
<td>6-β-Hydroxycortisol (n = 13)</td>
<td>300 mg tid 14 d</td>
<td>6-β-Hydroxycortisol/cortisol urine ratio ↑ 114%</td>
<td>Roby et al&lt;sup&gt;51&lt;/sup&gt; (2000)</td>
</tr>
<tr>
<td>Indinavir (n = 8)</td>
<td>300 mg tid 14 d</td>
<td>AUC ↓ 57%</td>
<td>Piscitelli et al&lt;sup&gt;18&lt;/sup&gt; (2000)</td>
</tr>
<tr>
<td>Methadone (n = 4)</td>
<td>900 mg qd ≥14 d</td>
<td>AUC ↓ 19%-60%, withdrawal symptoms</td>
<td>Eich-Hochli et al&lt;sup&gt;52&lt;/sup&gt; (2003)</td>
</tr>
<tr>
<td>Simvastatin (n = 8)</td>
<td>300 mg tid 14 d</td>
<td>AUC ↓ 50%</td>
<td>Sugimoto et al&lt;sup&gt;53&lt;/sup&gt; (2001)</td>
</tr>
<tr>
<td>Pravastatin (n = 8)</td>
<td>300 mg tid 14 d</td>
<td>AUC no change</td>
<td>Sugimoto et al&lt;sup&gt;53&lt;/sup&gt; (2001)</td>
</tr>
<tr>
<td>Tacrolimus (n = 1)</td>
<td>600 mg qd 1 mo</td>
<td>C &lt;sub&gt;ss&lt;/sub&gt; ↓ 80%</td>
<td>Bolley et al&lt;sup&gt;54&lt;/sup&gt; (2002)</td>
</tr>
<tr>
<td>Theophylline (n = 1)</td>
<td>300 mg qd</td>
<td>Maintenance dose ↑ 50%</td>
<td>Nebel et al&lt;sup&gt;55&lt;/sup&gt; (1999)</td>
</tr>
<tr>
<td>Ethinyl estradiol–desogestrel</td>
<td>Breakthrough bleeding</td>
<td>Yue et al&lt;sup&gt;56&lt;/sup&gt; (2000)</td>
<td></td>
</tr>
<tr>
<td>Warfarin-phenprocoumon</td>
<td>INR ↓ 50%</td>
<td>Yue et al&lt;sup&gt;56&lt;/sup&gt; (2000)</td>
<td></td>
</tr>
</tbody>
</table>

qd, Daily; C<sub>ss</sub>, steady-state concentration; tid, 3 times daily; AUC, area under plasma concentration versus time curve; INR, international normalized ratio for prothrombin time.
(P < .05) decreased the oral clearance by 20% with no change in half-life or renal clearance. Long-term St John’s wort administration (300 mg 3 times daily) did not cause a significant change in fexofenadine disposition relative to the untreated phase. When compared with the immediate treatment phase, long-term St John’s wort administration caused a significant 35% decrease (P < .05) in the maximum plasma drug concentration and a significant 47% increase (P < .05) in fexofenadine oral clearance. Thus the bioavailability of fexofenadine appeared to be increased by short-term St John wort dosing and reduced during long-term dosing. This pattern mirrors that of the digoxin–St John’s wort interaction, and the effects were consistent with an increase in immunodetectable CYP3A4 and P-glycoprotein in intestinal biopsy specimens observed after 14 days’ treatment with St John’s wort. The mechanism behind the coordinated induction of CYP3A4 and P-glycoprotein appears to be the activation of the nuclear factor pregnane X receptor (PXR) by the hyperforin present in St John’s wort preparations. Hence reduced efficacy of CYP3A substrates should be anticipated when coadministered with St John’s wort.

Adverse drug reaction reports have indicated that a small number of women taking low-dose oral contraceptives and St John’s wort have become pregnant, and this has led to the sensationalized reporting of a “miracle baby” phenomenon in the lay press. It is unclear whether this phenomenon has a pharmacokinetic basis; however, the interactions between strong inducers of CYP3A enzymes (eg, rifampin [INN, rifampicin]) and oral contraception have been described in the “precaution” section of the labeling for oral contraceptives. Gorski et al examined the effect of St John’s wort (300 mg 3 times daily for 8 weeks) on menstrual cycle abnormalities and the serum concentrations of midazolam, norethindrone [INN, norethisterone], follicle-stimulating hormone, and luteinizing hormone during oral contraceptive treatment. After comparison with the control period, there were no changes in the serum concentrations of gonadotropins or progesterone and no evidence of ovulation during long-term St John’s wort consumption. In contrast, a significant 15% increase was observed in oral clearance of norethindrone, a drug thought to be eliminated at least in part by CYP3A-mediated hydroxylation.

St John’s wort treatment was also associated with breakthrough bleeding in 7 of 12 subjects, whereas only 2 of 12 subjects had this abnormality in the control phase. Thus a significant interaction exists between St John’s wort and oral contraceptives because breakthrough bleeding is the primary cause of discontinuation of oral contraceptives. This discontinuation in turn contributes to contraception failure, with 23% of women who discontinue treatment because of breakthrough bleeding having an unintended pregnancy after they abandon contraception or choose a less effective method. Interestingly, the oral clearance of midazolam was 215.9 ± 66.5 L/h in the 7 subjects who had breakthrough bleeding during St John’s wort treatment but was significantly lower (97.5 ± 37.2 L/h) in the 5 subjects who did not have this abnormality.

Echinacea, a dietary supplement used commonly to treat or prevent viral infections, is also capable of producing significant interaction with drug metabolizing enzymes. In a controlled study echinacea did not change the oral clearance of midazolam but caused a modest but significant reduction in the oral clearance of tolbutamide and caffeine, by 15% and 30%, respectively. The systemic clearance of midazolam was significantly increased by 42%, and the intestinal wall availability increased from 0.34 to 0.69. These effects are consistent with inhibition of intestinal CYP3A metabolism, inhibition of hepatic CYP2C9 and CYP1A2 activity, and induction of hepatic CYP3A activity. Thus caution should be exercised when echinacea products are consumed along with CYP1A2, CYP2C9, and CYP3A substrates of low therapeutic index (eg, theophylline, phenytoin, cyclosporine).

PREDICTING DIETARY SUPPLEMENT–DRUG INTERACTIONS: ST JOHN’S WORT AND PXR

Interactions of drugs with dietary supplements are difficult to anticipate because of the general lack of information characterizing the pharmacologic actions of these substances. A gene reporter assay to measure the activation of PXR by hyperforin can be used as an early indicator of drug interactions that are caused by induction of CYP3A4 by St John’s wort. The induction of CYP3A4 has been implicated in the loss of efficacy of various drug therapies as a result of coadministration with St John’s wort (Hypericum perforatum). Extracts of St John’s wort preparations and individual constituents were evaluated in the PXR assay. The extracts and the pharmacologically active component hyperforin were found to be potent activators of PXR. Hyperforin was a more potent activator of PXR (median effective concentration, 23 nmol/L) than the known CYP3A4 inducer rifampin. The induction of CYP3A4 expression in primary human hepatocytes by St John’s wort extracts and by hyperforin has also been demonstrated. In this assay system the difference between the potencies of hyperforin and rifampin was not as marked. This was likely a result of the greater lability.
of hyperforin over the course of a 30-hour incubation with hepatocytes. The clinical exposure to hyperforin associated with the ingestion of many available formulations of St John’s wort (eg, plasma concentrations of approximately 200–380 nmol/L) is sufficient to produce activation of PXR and, consequently, induction of CYP3A4. Thus the potential for clinically significant drug interactions between St John’s wort with many CYP3A4 substrates (eg, cyclosporine, tacrolimus, cisapride, midazolam, certain selective serotonin reuptake inhibitors, antineoplastic agents, antiretroviral agents) is a real possibility, one that may not be evident from routine “screening” for traditional drug-drug interactions.

GRAPEFRUIT JUICE–DRUG INTERACTIONS: MECHANISMS AND SIGNIFICANCE

The discovery that grapefruit juice can increase the oral availability of some medications was an accidental discovery made when grapefruit juice was used to mask the taste of ethanol in a study involving the calcium channel blocker felodipine.27 Since then, more than a dozen different drugs have been shown to enhance oral availability when consumed with grapefruit juice.16 Most of the drugs affected by grapefruit juice have poor and highly variable oral bioavailability. In addition, most of these drugs are chiefly metabolized in the body by CYP3A4, an enzyme present in the liver and intestine. The major effect of grapefruit juice appears to be to reduce “first-pass” metabolism by reducing CYP3A4 activity. Because grapefruit juice does not generally affect the systemic clearance of affected drugs, it appears that grapefruit juice selectively reduces intestinal CYP3A4 activity while having little effect on liver CYP3A4.

The assumption is that the active components in grapefruit juice do not reach the liver in sufficient concentrations to affect CYP3A4 activity. Although a variety of juice components have been implicated, the major active ingredients appear to be compounds termed furanocoumarins. The most abundant and probably the most important single furanocoumarin is 6,7-dihydroxybergamottin (DHB). DHB and other furanocoumarins appear to reduce CYP3A4 activity by 3 related but distinct mechanisms, as follows: (1) competitive or reversible inhibition, (2) mechanism-based inactivation (also called irreversible inhibition), and (3) actual loss of CYP3A4 enzyme. This latter mechanism was first noticed when small intestinal biopsy specimens were obtained in healthy volunteers before and after drinking grapefruit juice.25 With the use of antibodies specific for CYP3A4, it was noted that the intestinal content of CYP3A4 fell by more than 50% after consumption of even a single glass of grapefruit juice.26 It was then noted that this phenomenon could be reproduced with grapefruit extract or purified DHB in a human intestinal cell line (Caco2) modified to express CYP3A4.26 Standard pulse-chase studies performed in these cells have indicated that loss of CYP3A4 in response to a DHB exposure is exclusively caused by accelerated degradation of CYP3A4.38 This is consistent with the observation in humans that grapefruit juice–mediated loss of CYP3A4 protein is not associated with a reduction in CYP3A4 messenger ribonucleic acid.25

The clinical significance of grapefruit juice–drug interactions has been debated. Reports of cases of drug toxicity associated with grapefruit juice have been very rare. Although reporting is likely incomplete, there are 2 reasons why the true incidence of clinically significant grapefruit juice–drug interactions is probably low. First, drugs affected by grapefruit juice characteristically have highly variable apparent oral clearance, presumably because of well-established interpatient differences in activity of intestinal CYP3A4.25 For this reason, affected drugs must generally have a very wide therapeutic index (an exception is cyclosporine, for which blood level monitoring is generally used to guide individualization of dosing).

Second, the relative magnitude of response to grapefruit juice for a given patient appears to largely be a function of his or her relative intestinal CYP3A4 activity.25 After a standard oral dose of a “susceptible” drug, subjects with very low CYP3A4 activity in the intestine will tend to have a relatively high AUC. Grapefruit juice should have a relatively small effect on pharmacokinetics in these individuals because there is little intestinal CYP3A4 activity to inhibit. In contrast, subjects with high intestinal CYP3A4 activity will have a marked increase in AUC when affected drugs are taken with grapefruit juice. However, these individuals will tend to have unusually low AUCs from standard doses of affected drugs before grapefruit juice administration. This concept is supported by the data shown in Fig 1.

A situation in which toxicity could occur would be in patients who have been given higher than usual doses of a susceptible drug and then begin drinking grapefruit juice for the first time. This could occur if the physician increases the drug dose to a desired pharmacologic effect. The dose in a patient with very high intestinal CYP3A4 activity might then be titrated to an unusually high daily dose of drug. A sudden fall in intestinal
CYP3A4 activity, as would occur after drinking grapefruit juice, could then result in drug toxicity. An additional situation might be when a patient has severe liver disease such that the intestine is the major site for metabolism of the drug. Such a patient would be expected to have high systemic exposure to the drug at usual doses; loss of intestinal CYP3A4 activity would further increase the exposure. Finally, patients who have a peculiar susceptibility to toxic effects of a susceptible drug will be more likely to have toxicity when they consume the medicine with grapefruit juice, simply because systemic exposure to the drug would increase. In the future it should be possible to use grapefruit-derived furocoumarins as additives to certain drugs to improve the oral delivery of some drugs by reducing variability. Such formulations would obviously no longer be susceptible to grapefruit juice interactions. It should also be possible to remove furanocoumarins from grapefruit juice to reduce drug interaction potential.

ANALYTIC CHALLENGES AND STANDARDIZATION ISSUES

One of the biggest issues facing consumers and clinical researchers is the quality of herbal products, which could affect the magnitude of drug interactions. Standardization has been touted as the answer to the quality question, but relatively few persons in the United States know what the term means and how it relates to product quality. This is complicated by the fact that the concept is evolving around the world so that the term as understood in the United States is no longer synonymous with the term as used in the European Union. When performed properly, standardization is a “seed-to-shelf” process that ensures lot-to-lot consistency of botanical products. The process begins with careful control of raw material sources and continues throughout the manufacturing process. It includes selection of phenotype-cultivar in process controls (method of drying, preparation of extract, storage of herb and finished product, monitoring extraction, formulation, and encap-
sulting), finished product evaluation, and stability testing. The purpose of the process is to minimize batch-to-batch variation caused by seasonal conditions and chemotype. For certain ingredients and products, monitoring marker compounds provides a positive control for production and confirmation that the product contains the correct amount of extract. Manipulation of marker compounds (one or more constituents that occur naturally in the plant) ensures batch-to-batch consistency but not necessarily quality of a finished product. Hence the term standardization as used in the United States entails more than simple measurement and manipulation of marker compounds and can best be described as the continuum of steps necessary for production of a consistent product.

BOTANICAL PRODUCTS: REGULATORY AND SAFETY PERSPECTIVES

Botanicals have certain unique features and quality concerns that require special considerations in the regulatory approaches for further product development. Many herbal preparations are available on the market and have had a long history of human use with some accumulated safety experiences but lack of rigorous proof of efficacy or safety. They are mostly complex, variable mixtures with unknown mechanisms of action and unidentified active ingredients. The strength and potency of these products are not easily quantified, and their impurity and stability are often difficult to monitor.

In the United States botanicals are defined from a regulatory standpoint as products containing ingredients of vegetable matter or its constituents as a finished product. Botanicals may contain whole plants or plant parts, including plant materials—such as juices, gums, fatty oils, or scent oils—and include algae or macroscopic fungi and similar products. They do not include fermentation products (yeast, bacteria) or highly purified or chemically modified substances derived from botanical sources (eg, paclitaxel or homeopathic drugs or elixirs) because these products have different regulatory issues.

US regulation of a product is determined by its intended use, not by its source or origin, as defined by the label claims or indications and route of administration. Botanicals can be regulated as follows: foods (conventional foods, spices, food additives, dietary supplements), drugs (over-the-counter, prescription), biologics (eg, allergenic vaccines), cosmetics (eg, antiaging creams, shampoos), or devices (eg, dental alginates, poultries, adhesives). Some botanical ingredients may have more than one intended use. Although the ingredients may be identical, the require-

ments for a botanical sold as a food differ from those when it is sold as a drug. These requirements include differences in Good Manufacturing Practices (GMPs), labeling, and marketing and reporting requirements.

BOTANICAL NEW DRUGS

The FDA has published a draft “Guidance for Industry” to facilitate and encourage development of botanical new drugs. Under this guidance, previous uncontrolled human experiences (ie, “historical use”) can be used as the basis for presumed safety to expedite limited early-stage testing to assess the therapeutic potential of existing botanicals; further purification of the botanical or identification of the active ingredients would not be required. Regulatory requirements for clinical studies of botanicals would depend on the extent of past experiences, the degree of deviation from historical use, and the scale of proposed studies. The FDA will consider all types of existing data and, if deemed acceptable, may accept some of them as evidence of prior use. For certain widely used botanical preparations, preliminary clinical studies and nonclinical testing may be reduced or delayed. Chemistry, manufacturing, and control of botanical products have been extended to the control of raw materials. For final marketing approval, botanical preparations will be subjected to the same clinical standards as for nonbotanical products.

A botanical review team was established at the FDA’s Center for Drug Evaluation and Research to provide the necessary scientific expertise to ensure consistent interpretation and implementation of the “Botanical Guidance” and other related policies. As of March 31, 2002, 130 preinvestigational new drug applications and investigational new drug applications had been submitted to the Center for Drug Evaluation and Research (recently, 1-2 new applications per month). These submissions are approximately evenly divided into academic research projects and commercial developments. Oncology, antiviral, and dermatology are the therapeutic areas with the most botanical applications.

DIETARY SUPPLEMENTS

Currently, most botanical products in the United States are sold as dietary supplements. The 1994 Dietary Supplement Health and Education Act (DSHEA) created a new regulatory framework for the safety and labeling of dietary supplements. Under DSHEA, dietary supplements are products taken by mouth that contain a “dietary ingredient” intended to supplement the diet. Dietary ingredients may include vitamins, min-
erals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites.

Under DSHEA, the manufacturer is responsible for ensuring that its dietary supplement products are safe before they are marketed and that any representations or claims made about them are substantiated by adequate evidence to show that they are not false or misleading. A number of claims are permitted on dietary supplements, but any claims that suggest the product is intended to diagnose, treat, cure, or prevent any disease would make it subject to regulation as a drug. Unlike drug products that must be proved safe and effective for their intended use before marketing, there are no provisions in the law for the FDA to “approve” dietary supplement ingredients or products for safety or effectiveness before they reach the consumer.

Except in the case of a new dietary ingredient, for which premarket review for safety data and other information is required by law, a firm does not have to provide the FDA with the evidence it relies on to substantiate safety or effectiveness before or after it markets its products. In addition, unlike drug products, manufacturers and distributors of dietary supplements are not currently required by law to register their firms or products with the FDA\(^1\) or to record, investigate, or forward to the FDA any reports they receive of injuries or illnesses that may be related to the use of their products. Under DSHEA, once the product is marketed, the FDA has the responsibility for showing that a dietary supplement is “unsafe” before it can take action to restrict the product’s use or remove it from the marketplace. Dietary supplement–specific GMP regulations have been proposed but have not yet been implemented.\(^2\) Consequently, dietary supplements are only subject to the current GMPs that apply to all foods, which emphasize sanitation requirements rather than contaminant or quality characteristics.\(^3\)

**OFFICE OF DIETARY SUPPLEMENTS AT THE NATIONAL INSTITUTES OF HEALTH: PROGRAMS RELATED TO HERBAL PRODUCTS**

The Office of Dietary Supplements (ODS) was established at the National Institutes of Health (NIH) in 1995 as an outcome of DSHEA. Its mission is to support and coordinate research in dietary supplements at the NIH, as well as to inform scientists, the public, and practitioners about the benefits and risks of these ingredients. The NIH supports a variety of research projects on dietary supplements, including those funded by the ODS or in collaboration with other institutes and centers. These include a network of Dietary Supplement Research Centers whose focus is botanical and herbal supplement ingredients; their activities include botany, pharmacognosy, and analytic chemistry, as well as preclinical and clinical studies.

Another major emphasis of ODS research is the development and validation of analytic methods and reference materials for dietary supplement ingredients. This program, initially concentrating on herbal and botanical ingredients, is a collaboration among Federal agencies, nongovernmental organizations, academia, and industry. ODS programs are still emerging. Its approach is to use the principles of evidence-based medicine—including systematic review of literature and meta-analysis where appropriate—to guide the development of new research initiatives. A recent example in which this strategy was used involved the evaluation of efficacy and safety of ephedra-containing products for weight management and athletic performance enhancement. Results of this evaluation are currently being used by the Department of Health and Human Services in its assessment of how best to deal with the safety issues associated with the use of ephedrine alkaloid–containing dietary supplements.

**PRODUCT LABELING AS A RISK MANAGEMENT STRATEGY**

Potential drug-drug interactions can often be predicted by use of information about the drug’s active ingredients, by use of general pharmacologic knowledge regarding “drug class,” and from preclinical, animal, and human experience. Botanicals have special features that in most cases have the potential either to hamper or to have an adverse impact on the evaluation of botanical-drug interactions. Unlike chemically defined drugs, botanicals are complex mixtures with multiple or unknown active ingredients. Their natural heterogeneity may enable them to alter human physiologic characteristics through more than one mechanism of action, making it difficult to relegate these products to any one drug class. Finally, because the process defines the product, extrapolation of scientific data across products from different manufacturers or sources is not possible. Proper identification of the plant is the first step in defining a potential botanical-drug interaction. This includes the Latin binomial and authority, identification of the plant part(s) used in the preparation of the botanical product, and the processes used to extract and isolate the purported active ingredients from plant sources.
Determination of whether a botanical is “safe” depends on the intended use or indication for which it is being marketed. Botanicals are regulated as drugs in most countries except the United States, and studies conducted in those countries have been directed toward treating disease conditions or symptoms. In contrast, dietary supplements sold in the United States are marketed to the healthy general public. Thus it is important to scrutinize the published literature carefully in considering what safety data are really pertinent to the particular use.

RECENT FDA EXPERIENCES WITH DRUG INTERACTIONS

At first glance, the explicit criteria used by the FDA to determine that a drug’s benefits outweigh its risk and the drug is, therefore, suitable for marketing are simple. These criteria are contained in Section 505 of the Food, Drug and Cosmetic Act and read “...safe and effective under...proposed labeling.” It should be remembered that safety is a relative concept, weighing benefits and risks is complex, and the analysis is a judgment that must be placed in the context of the disease being treated and the availability of alternative acceptable therapies.

The issue is made more complex by the emerging awareness that product labeling may be a relatively ineffective risk management tool in limiting predictable adverse reactions and maintaining a favorable benefit/risk balance. The FDA’s recent experiences with effective and commercially important drugs that have been withdrawn from the US market because of preventable adverse drug-drug interactions (eg, terfenadine, astemizole, mibefradil, and cisapride) have catalyzed the FDA’s introspection on the role of labeling and labeling changes in completely managing the risks of pharmaceuticals in the marketplace. These experiences have led to the perception that labeling and other traditional risk communication strategies (eg, “Dear health care professional” letters) are ineffective means of communicating risk with the intention of changing behavior. The root cause of the lack of translation from knowledge into practice regarding preventable drug interactions is not understood and raises many researchable questions.

Three fundamental questions are as follows: (1) Did the prescriber receive and read the message? (2) Did the prescriber understand and believe the information? and, ultimately, (3) Did the prescriber incorporate the knowledge into practice?

It must be emphasized that even a patient under the care of a fully and appropriately educated prescriber who practices evidence-based prescribing may have a preventable drug-induced injury. The presence in the consumer marketplace of herbal therapies or dietary supplements with significant drug interaction potential heightens the potential for injury.

An FDA guidance published in November 1999 provided detailed case studies on the labeling language that may result from certain types of interaction data. A recently proposed FDA rule on labeling recommends prominent drug interaction information in the highlighted area. The 1999 drug interaction guidance is being revised to propose the use of a classification system for CYP3A inhibitors in the labeling in an effort to improve the consistency of labeling language and to highlight key drug interactions. Additional risk management tools have been proposed or implemented to communicate risks to patients regarding serious adverse events (eg, medication guides with the use of alosetron hydrochloride [Lotronex; GlaxoSmithKline, London, United Kingdom]; mifepristone [RU486]). In addition, as part of the Prescription Drug User Fee Act (PDUFA III) initiatives, the FDA has proposed various risk management tools in recently published concept papers.

Labeling decisions for interactions with St John’s wort or grapefruit juice can be based on the metabolic and dispositional characteristics of the drugs being labeled without conducting actual in vivo studies to characterize the interaction. If a drug is a substrate for either CYP3A or P-glycoprotein, or both, and reduction in the activity of these pathways may significantly alter (eg, lower) systemic drug exposure and, by doing so, alter drug safety and efficacy, cautions regarding the use of St John’s wort are added to the labeling. For example, labeling for mifepristone (Mifeprex; Danco Laboratories, LLC, New York, NY), lopinavir-ritonavir (Kaletra [Abbott Laboratories, North Chicago, Ill], and imatinib mesylate [Gleevec; Novartis AG, Basel, Switzerland]) have warnings about St John’s wort use. Kaletra’s labeling states “Concomitant use of Kaletra and St John’s wort (Hypericum perforatum), or products containing St John’s wort, is not recommended.” In addition to being a CYP3A substrate, if the drug also has a low oral bioavailability, warnings regarding concomitant ingestion of grapefruit juice may be added to the labeling. Depending on the potential clinical consequences of an interaction, information in the product labeling may be stated in the “Precautions/Warnings, Drug Interactions, Contraindications, Dosage and Administration” sections, in addition to the “Clinical Pharmacology” section. For example, labeling for cyclosporine (Neoral; Novartis AG) and simvastatin (Zocor;
Merck & Co, Inc, Whitehouse Station, NU) have warnings about grapefruit juice use. The labeling for Neoral states “Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, and thus should be avoided.”

**SUMMARY**

Drug interactions with herbal products and food are an evolving knowledge base. Recent examples of protease inhibitors and St John’s wort provide compelling evidence of the necessity of adequate pharmacovigilance in ascertaining heretofore unanticipated but preventable drug-herbal interactions. Clinical pharmacology studies of potential significant interactions in phase 1 and phase 2 trials, as well as phase 3 trials, will require a heightened awareness of possible herbal product usage by patients and consumers in the intended study population. Ultimately, better mechanisms are needed to encourage communication among patients and physicians about dietary supplements and, in particular, herbal drug and food interactions. Patients whose current prescription regimens do not provide complete symptomatic relief are study populations likely to use supplemental herbal products. Such patient populations might include those with cancer, persistent pain, and other refractory long-term diseases. Drug development study protocols, as well as postmarketing risk assessments, are needed to maintain a high level of alertness to potential drug and food interactions and manage patient risk.

We acknowledge Dr Christine Taylor for her participation in the workshop.

The following authors have no conflict of interest: Shiew-Mei Huang, Stephen D. Hall, Paul Watkins, Lori A. Love, Cosette Serabjit-Singh, Joseph M. Betz, Freiddy Ann Hoffman, Paul M. Coates, Jonca Bull, Shaw T. Chen, Gregory L. Kears, and Michael D. Murray. Peter Honig is an employee of Merck & Co and holds stock options.

**References**

45. Food and Drug Administration Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology Subcommittee meeting. Issues and challenges in


