Health Canada is very pleased to release the proceedings from the first-ever government sponsored International Symposium on Drug, Food and Natural Health Product Interactions. The Symposium took place on February 9-10, 2006 in Aylmer, Quebec. The goal of the Symposium was to increase awareness of potential drug/food/natural health product (NHP) interactions.

The Symposium brought together more than 260 attendees and included representatives from academe, industry, health care professionals, consumer groups and patient advocacy organizations from across Canada. Mr. Neil Yeates, the Assistant Deputy Minister of the Health Products and Food Branch and Mr. Omer Boudreau, Director General of the Therapeutic Products Directorate of Health Canada gave the opening remarks. They reiterated Health Canada’s willingness to work collaboratively with all stakeholders to identify strategies to reduce the risks to health associated with potential interactions.

Three scientific sessions were covered: adverse effects due to interactions between drugs, foods and natural health products; mechanisms of action and means to evaluate the data; and international surveillance strategies. The presentations emphasized that there is public knowledge that certain interactions can lead to serious life-threatening events; however, there is a great deal of uncertainty about the actual health risk of many other potential interactions. For the individual user, the level of risk will vary due to a number of factors including the person’s age, diet, gender, genetic make-up, health status, and the amount and length of time that drugs and NHPs are taken together. Individuals taking numerous products for serious health conditions (such as but not limited to: cancer, HIV/AIDS, or organ transplant) are at the greatest risk for an adverse interaction, because interference with the efficacy of their treatments can lead to drug resistance which could prove fatal.

Health Canada is appreciative of the contributions of the speakers and attendees for making this symposium successful.

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PROCEEDINGS
Drug, Food, Natural Health Product Interactions: The Health Canada International Symposium

Health Products and Food Branch
Drug, Food, Natural Health Product Interactions: The Health Canada International Symposium

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Summary
Health Canada hosted a symposium of internationally recognized experts co-chaired by Dr. B. Foster and Dr. E. Ernst to raise the awareness of drug, food and natural health product (NHP) interactions, on February 9 and 10, 2006. Raw herbs, herbal supplements and other related products will be referred to in this document as NHPs.

Three scientific sessions covered: adverse effects due to interactions between drugs, foods and NHPs; mechanisms of action and means to evaluate the data; and international surveillance strategies. The presentations emphasized that certain interactions can cause serious life-threatening events; however, there is a great deal of uncertainty about the actual risk posed to public health for many other potential interactions. For the individual user, the level of risk may vary depending on a number of factors, including the person's age, diet, gender, genetic make-up, health status, and use of other drugs and NHPs. Individuals receiving therapy for serious medical conditions (e.g. cancer, HIV/AIDS or organ transplant) are at greatest risk for an adverse interaction, given that interference with the efficacy of their treatments may lead to drug resistance which could prove fatal. A fourth session featured presentations by a consumer, a medical doctor and a naturopath as a lead into a general open forum.

The symposium addressed issues such as the belief that traditionally prepared medicines may have a lower risk than a commercially prepared formulation; the extent of the risk of grapefruit interactions with all drugs is not known and, as such, in order to err on the side of caution, grapefruit should be avoided when taking medication; and labeling should be improved for all products, especially those that present significant risk of interactions. The symposium stressed the importance of minimizing adverse events (AEs) through public education and awareness of any potential interactions of food, drugs and NHPs. Most of the studies to date on these interactions have examined the effect upon the metabolism enzyme cytochrome P450 3A4 and the P-glycoprotein transport protein. It is evident, however, that other metabolic enzymes and transport proteins can be affected by these interactions and that the actual risk has not been thoroughly determined for most products.

The symposium highlighted that the effectiveness of monitoring therapeutic products for their quality and of recording the occurrence of individual AEs, made these good tools in safeguarding the public against harmful interactions. The emerging consensus was that the individual user should consult with their health care professional (HCP) to determine if there is risk with their use of certain foods, or NHPs with drugs. Patients currently using drug-NHP combinations
should not curtail use of these combinations without direction from their HCP. It was also evident from the presentations and discussion that government, industry and HCPs should explore ways of taking more responsibility to address the potential for interactions among consumers. All participants agreed that more education is required to assist the user in making informed decisions.

1. Herb-drug Interactions: Issues and Risk Perspectives

1.1. Use/scope

Natural health products (NHPs) are from natural sources and there is a general perception of safety and benefit by the public. The global use of these NHPs is high and they are largely unregulated (Table 1). The pharmacological mechanism of action for most NHPs is generally unknown and it is likely that there are several active constituents in each product that can interact with other constituents to either increase their pharmacokinetic (PK) or pharmacodynamic (PD) activity. These interactions could be synergistic or antagonistic and may explain why different manufacturing processes or formulations have different activity.

Table 1. Use/scope

- Prevalence of use of NHPs is high;
- Amount of money spent on NHPs is high;
- Safeguards in NHPs are few;
- Many NHPs have potential for interactions;
- Many patients combine NHPs with drugs;
- Patients are both unaware of risks and uncommunicative that they use concomitant NHPs;
- Doctors are not much more knowledgeable than their patients about various interactions;
- Actual interactions require confirmation by in vitro or pharmacokinetic studies;
- Clinically noticeable interactions (limited quality case reports);
- Clinically relevant interactions.

There is potential to change the disposition and ensuing action of certain drugs. Although there is a long tradition of use for many NHPs and they have a wide therapeutic window with low toxicity and AEs, many NHPs are now available and used in non-traditional ways where there is insufficient information to make a risk/benefit determination.

Reasons for using NHP remedies instead of a prescription drug include preference for natural/organic products (43%), belief that there are fewer side effects (21%) and that they are more effective (14%), desire for self treatment (11%), cost (8%), and that they are more gentle/mild (6%) (Prevention Magazine’s 1999 National Survey of Consumer Use of Dietary Supplements, April/May 1999). Interestingly, this report also noted that about 51% of the consumers would use herbal remedies for about a month or longer without results. A survey on midlife and senior drug use determined that 76% of the respondents were currently taking at least one prescription drug regularly and those who say they are currently taking prescription drugs
regularly say they take on average four different prescription drugs daily (Prescription Drug Use Among Midlife and Older Americans, AARP, December 2004). More than 90% of the elderly were found to use at least one, 12% used over 10 medications per week (Kaufmann et al. 2002). Gurwitz et al. (2003) reported that in 1523 AEs in elders, 38% were serious, life-threatening or fatal. Of these 42% were preventable. Many patients combine NHPs with drugs (Peng et al. 2004; Smith et al. 2004), and there are risks of interactions (Clement et al. 2005; Ernst 2002; Mathews et al. 2003; Peng et al. 2004; Sparreboom et al. 2004). Ernst (2003), in a review of theoretically possible interactions of more than 200 NHPs (from acacia to yohimbe), concluded that it is hard to conceive of an herbal medicine that has not potential for interaction. Some reported interactions are very serious, but case reports can be misleading as controlled trials for NHPs are scarce (Fugh-Berman and Ernst 2001; Mills et al. 2005).

There are many confounding factors that can affect how interactions risk prevalence data can be interpreted (Bruno and Ellis 2005; McNaughton et al. 2005; Ness et al. 2005; Quandt et al. 2005; Roy-Byrne et al. 2005; Wheaton et al. 2005). Some of the major points to consider include: time span, regional or geographical location, age, health status, ethnicity, and author. Patients might not consider the possibility of risk with self-determined NHP intake during concomitant drug therapy or consumption of other NHPs or dietary items. Most prevalence reports state that patients might not feel the need to tell HCPs that they are consuming NHPs and conversely, that many HCPs do not routinely ask whether patients are ingesting NHPs (Giveon et al. 2004).

There are a limited number of published clinical cases (case reports) related to NHP-drug interactions. In the case reports examined to establish causality of NHP-drug interactions, it was found that 13% were well-documented, 18% possible, with 69% having insufficient information and were unable to be evaluated (Fugh-Berman and Ernst 2001). Of the interactions presented in these case reports, St. John’s wort (SJW) (54 cases, 78.7%) was the most common NHP, with ginkgo (3.7%) and ginseng (2.8%) being the next most common. Warfarin (18 cases) and cyclosporine were the most common drugs involved in NHP-drug interactions. HCPs should note that many drugs, foods, and NHPs may interact with warfarin; and that the International Normalized Ratio (INR) should be checked after a change in medications, drastic change in diet, and after starting or discontinuing phytomedicines. As examples, Dong quai, Danshen and Lycium barbarum increased INR; whereas, green tea and ginseng decreased the INR value.

The 2003 Gallup NHP Survey found that 49% of NHP consumers would hesitate to take certain herbal NHPs because of insufficient safety information. The survey also showed that 58% of those using NHPs expressed concern about side effects and harmful interactions from taking herbal NHPs. Only 16% described themselves as very knowledgeable about herbs, and 83% indicated that “I’d like to know more about herbal supplements.” Another survey showed that few serious problems actually occurred when mixing NHPs and conventional drugs (Peng et al. 2004).

Variability in response to drug therapy is impacted by genetics, disease and the environment. Interindividual differences in drug disposition also exist and are influenced by age, gender and body mass. Metabolic enzymes and transport proteins are under nuclear regulation. The main nuclear receptors involved in drug disposition are pregnane X receptor (PXR) and constitutive
androstane receptor (CAR). These receptors are present in the liver and kidney, and in other tissues responding to different ligands. These receptors mediate the same target genes (\textit{CYP 2B6, CYP2C9, CYP3A4, MDR1} and \textit{MRP2}).

Table 2. Why is there low prevalence or under-reporting?

- Lack of surveillance system for monitoring NHP adverse reactions in many countries;
- Reluctance of patients to inform their physicians that they take NHPs;
- Physicians do not always recognize the association between the adverse reaction and the NHP;
- Failure to write up the case;
- Uncertain causality.

Some herb-drug interactions involve inhibition and/or induction of drug metabolizing enzymes or transporters. Many NHPs interact with nuclear receptors to induce expression of drug metabolizing enzymes and transporters. Systematic studies are required to investigate the constituents in herbals for their potential to interact with drug metabolizing enzymes, transporters, and nuclear receptors.

1.2. Risk identification

Interaction prevalence is low in Europe and in North America, possibly due to under-reporting (Table 2). The WHO noted (2005) that of the WHO member states: 73% allowed herbals to make therapeutic claims; 54% had no post-market surveillance system for herbals; 35% had no law or regulations for herbals, and; 20% had no manufacturing control with 73% allowing medicinal claims. Potential for interactions is considerable but hard data are scarce. Standards are low for reporting AEs and interactions involving herbs. Reviews and commentaries often contain inaccurate information about NHPs and theoretical interactions. Guest- or ghostwritten articles also exist in the medical literature (>11% admitted) and represent only one example of hidden corporate influence that may be “fronted” by “medical education companies”. Such articles are difficult to identify, and may promote a product, denigrate a competitor’s product, or highlight AEs of competitive products, even NHPs. This underscores the importance of critical appraisal when reading published.

Risk identification and assessment requires that signals be identified and stratified in terms of evidence, probability and significance. There are a number of problems and challenges in interpreting the NHP safety literature. These include: poor documentation or characterization of the NHP in case reports and clinical studies; an AE may be based on only one case report; a pure compound being investigated may not be in the biologically active form but rather the whole extract or botanical, and; extrapolation of \textit{in vitro} tests to the clinical situation. The situation is further complicated by the question of phytoequivalence (Table 3) occurring when the results of one study specific to one product are extrapolated to all similar products, even though there may be significant differences between products.
To act on a safety concern, regulatory evaluators must first assess the signal through review of several types of evidence including: pre-market clinical trial data, registries, record linkage studies, and comparative observational studies which may rarely provide info regarding drug-NHP interactions. Passive surveillance spontaneous reaction case reports may either have triggered or can be used as supporting evidence in the assessment. The individual case assessment may require other evidence such as expert advice or hypothesis-testing studies. It may be difficult to quantify risk (determine frequency) as utilization data are scarce. After assessment of causality, the implications for public health (severity and seriousness, benefit-risk analysis) have to be determined. A prevention and communication strategy based upon the at-risk groups needs to be established and actioned. Regulatory action may be limited but all options should be identified and discussed with the companies involved.

### Table 3. Natural Health Product – Drug Interactions: Issue of phytoequivalence.

- Many proprietary products are chemically distinct and defined;
- Much clinical literature is based on proprietary extracts with known chemistry, known clinical pharmacology;
- Data from such trials may not be relevant to other botanical preparations.

Adverse reaction reporting has lead to products such as *Piper methysticum* and *Larrea tridentata* (Pishvaian et al. 2004; Kauma et al. 2004) being removed from the market. Not all interactions are negative, some combinations have positive benefits, for example: plavix and hesperidin (Granados 2003). This emphasizes the dilemma faced by regulators who have the duty to protect public health with limited information.

#### 1.2.1. Is it necessary to distinguish between PD and PK?

Human case reports achieve relevance to the degree they are supported by other evidence, such as *in vitro*, *in vivo* animals and/or human studies. Known active PD phytochemicals can be studied in isolation, if the PK of that isolate shows that it is bioavailable in active amounts after oral dosing.

Human oral intake studies of NHPs together with drugs to determine adverse PD effects are uncommon hence there is reliance on the PK data. However, knowing the action of the NHP and drug, one can make a reasonable prediction about the probable outcomes when combining agonistic or antagonistic agents. Data from studies of actual NHP-drug combinations are necessary, and these data needs to come from human studies. The most valid speculative PK interactions would be based on human studies that show influence of NHPs on substrates of transporters (e.g. P-glycoprotein) or specific CYP450 isozymes. Speculative PD interactions would be based on known pharmacological actions observed in *vitro* or *in vivo* in animals or in humans. *In vivo* effects found by combining NHPs in animals are more relevant when administered orally rather than parenterally.

In 1998, Eisenberg et al. reported that one in five Americans take prescription medications concurrent with at least one NHP, a high-dose vitamin, or both. Hence, at least fifteen million US citizens could be at risk for potential adverse interactions (including 3 million people 65 years or

These tools were found to be appropriate for food or NHP interactions with drugs, as the three essential questions for drug-drug interactions, once the terminology has been slightly modified, are just as critical for dealing with other interactions (Table 4). Figure 1 presents a comparison of the efficacy and safety curves for most products, and these are dependent on a number of genetic (intrinsic) and environmental (extrinsic) factors, including adverse interactions. The safety curve for most products is normally associated with adverse events; however, in situations where the exposure is markedly shifted in either direction from the distinct therapeutic range, the curve could also have an inverse relationship to decreasing exposure. The graphics are more complicated with prodrugs or conjugated botanicals that require metabolic transformation to the biologically active form.

**Table 4. Modified Key Questions To Ask About NHP-Drug Interactions.**

- Will an NHP alter exposure to other drugs?
- Will other drugs alter exposure to the NHP?
- Are these alterations in exposure significant enough to warrant dose adjustment?

Answers to the questions in Table 4 will help determine if the drug or NHP has moved outside of the therapeutic range where there could be a concomitant shift of the efficacy and safety (AE) curves. Evaluation of NHP-drug interactions is required through systematic assessment of case reports, in addition to specific studies to elucidate the NHP’s effects on specific drugs or specific probes for enzymes and transporters (in vitro and in vivo studies). A single exposure may inhibit one or more of the enzymes or transporters allowing for more drug and active NHP constituent to enter into the blood. This may enhance the therapeutic effect but also may potentiate any AR associated with these compounds. Repeated administration may induce these enzymes and transporters and result in lower blood levels with a decrease in efficacy and ARs. However, this decrease may lead to the development of therapeutic failure such as cardiac rejection noted with St. Johns wort (SJW) (Ruschitzka et al. 2000), or increased health care costs associated with drug resistance or increased hospitalization.

Metabolism and interaction information for the active constituent and any active metabolite is key to benefit/risk assessments (active clearance pathways need to be well-defined). An integrated approach may reduce the number of unnecessary studies and optimize knowledge. There is a need to establish “therapeutic equivalence boundaries” such as no effect boundaries with a well-defined exposure-response. Study design and data analysis are necessary to determine this exposure response, and for subsequent proper labeling with useful and consistent language. With the understanding that many factors can influence clinical trial design, exclusion criteria need to be re-evaluated along the line of “For at least two weeks prior to the start of the study until its conclusion, volunteers will not be allowed to use prescription or over-the-counter (OTC) products including NHPs, or eat any food or drink any beverage containing alcohol,
grapefruit or grapefruit juice (GFJ), apple, orange juice or cranberry juice, vegetables from the mustard green family (e.g. kale, broccoli, watercress, collard greens, kohlrabi, brussel sprouts, mustard) and charbroiled meats.”

![Diagram of pharmacokinetic (PK) exposure relationships to pharmacodynamic (PD) response for most products. AUC, area-under-the-time-concentration curve. Adapted from Huang et al. 1999.](image)

**Figure 1.** Pharmacokinetic (PK) exposure relationships to pharmacodynamic (PD) response for most products. AUC, area-under-the-time-concentration curve. Adapted from Huang et al. 1999.

### 1.2.2. Drug Interactions: Clinical evidence

*Hypericum perforatum* (St. Johns wort, SJW) has been used as an antidepressant for the treatment of mild-to-moderate depression (Linde et al. 1996, Linde et al. 2005, Linde and Knuppel 2005). SJW contains numerous compounds but the main active constituents include hyperforin, hypericin and flavonoids which block the uptake of neurotransmitters. SJW treatment is not commonly associated with serious ARs, and is considered by some to be safer than conventional antidepressants. However, SJW’s safety has been questioned because of multiple cases of drug interactions namely with immunosuppressants, oral contraceptives, anticoagulants, cardiac inotropic drugs, antihyperlipidaemic drugs, anti-AIDS drugs, anti-cancer drugs, anxiolytics, and antidepressants. Repeated use of SJW leads to PXR activation with subsequent
induction of CYP3A4 leading to lower blood levels of these drugs (Johne et al. 1999, Kliewer and Willson 2002, Sugimoto et al. 2001, Wentworth et al. 2000). Other cytochrome P450 isoymes, and thus additional drug categories can also be affected by SJW.

**Grapefruit juice** (GFJ) has been extensively studied after the initial reports to identify the active flavanoid and furanocoumarin (psoralen) constituents that inhibit CYP 3A4. The total clinical effect likely depends on combined action of all the furanocoumarins and the site of exposure. Furanocoumarins are chemical defense products found in many botanicals (Guo and Yamazoe 2004). The major furanocoumarins include bergamottin, dihydroxybergamottin, and related dimers and trimers, and have high *in vitro* mechanism-based (also known as suicide substrate) inhibition of 3A4. P450 isoymes 2A6, 2A13, 2B1, 2B4, 2B6, 3A5 are also affected by psoralen-mediated mechanism-based inhibition (Fontana et al. 2005). Other NHP-related mechanism-based inhibitors include: capsaicin (peppers; 2E1), glabridin (licorice; 2B6 and 3A4), resveratrol (red wine, 1A1 and 3A4), and silybin (milk thistle; C9 and 3A4). GFJ can also inhibit 1A2, 2C9/19 and 2D6-mediated metabolism (Guo and Yamazoe 2004). Pummelos and more than one of its crossed varieties also contain furanocoumarins (Guo and Yamazoe 2004).

GFJ can also inhibit drug transport. P-glycoprotein (P-gp) is an outward (efflux) transporter commonly found in the gut and other tissues. Inhibition of this protein may lead to higher blood levels of compounds that are also substrates for this transporter. Organic anion transporting polypeptides (OATPs) are another family of uptake (influx) transporters present in gut, liver and other tissue locations. Inhibition of enteric OATP-A (OATP1A2) will generally decrease oral bioavailability of compounds transported by this isozyme. *In vitro*, GFJ is a more potent inhibitor of OATP-A than P-gp. Inhibition of OATP-A has also been shown to be inhibited by other dietary substances such as orange juice and apple juice (Dresser and Bailey. 2003).

GFJ has provided new information about how common foods can affect important mechanisms that determine the disposition of ensuing clinical drug effects in humans. Clinically relevant GFJ issues are linked to the loss of patient compliance, and changes in drug treatment efficacy. Additionally, serious overdose toxicity of drugs to treat serious medical conditions include amount-effect relationships, variability and reproducibility within individuals, and duration of the inhibitory effect. The return of enteric CYP3A4 activity requires enzyme synthesis and can be referred to as enterocyte cell replacement. GFJ produces prolonged inhibition of enteric CYP3A4 activity with a 50% recovery time of approximately 12 hours with a single 200 ml dose. Hence, GFJ consumed yesterday can increase drug bioavailability today. Repeated GFJ ingestion over time will continually deplete the isozyme. It has been noted that the elderly have reduced capacity to taste, have a preference for stronger flavours such as GFJ and are considered to be the prime purchasers of GFJ. The risk is compounded as the elderly commonly consume affected drugs and are less able to compensate for elevated drug concentration. The Health Canada warning on GFJ mentions potential interactions with certain drugs and health products used in the treatment of: angina, anxiety, cancer, convulsions, depression, erectile dysfunction, gastrointestinal reflux, high blood pressure, high lipid (cholesterol) levels, HIV/AIDS, infections, irregular heart rhythms, organ graft rejections, and psychotic problems. The major feature of most of the drugs associated with GFJ interactions, include low to moderate bioavailability, where an interaction could markedly increase blood concentration of drug. GFJ is a complex product that can affect several systems affecting drug disposition. The variable nature of the
product and the clinical issues help explain the uncertainty in the literature. Many drugs are affected by GFJ and not all have been studied to date for potential interaction; hence, the precautionary principle would suggest that GFJ be avoided with all drugs and NHPs. Clinically, if there is a concern about a drug interaction, grapefruit should be avoided entirely. The risk of interaction may be exacerbated by use of other foods or juices that could potentiate these actions.

**Confounding events for consideration.** In one case report involving GFJ (normally ingested at breakfast) and lovastatin (dosed in the evening), the interval was not specified but may in a 10-14 hour range. Clinically this may not be considered relevant except that the mechanism-based inhibition caused by GFJ constituents has a replenishment half-life of about 50% in 12 hrs. Hence, in 24 hrs the body has recovered about 75% of the previous daily level. This imbalance can lead to higher plasma levels of active drug or NHP constituents. Is the interaction greater and riskier with less time interval (co-administration)?

2. **Risk Evaluation and Management**

Several risk evaluation models exist. Brinker (2001) developed an evidence-based system to rank NHP-drug interactions using four categories according to their probable pertinence based on the strongest degree of evidence available (Table 5).

**Table 5. Evidence-based Ranking of Herb-Drug Interactions.** Categorization of I, II, III and IV is used to rank potential herb-drug interactions.

I. **human studies** – published research on healthy individuals, **clinical studies** - published research from therapeutic trials on patients being treated for a condition, **empirical** - traditional knowledge or consensus based on experience from extensive use, **case reports** – published individual response to using herbs;

II. **in animals** (types listed) – laboratory tests using live animals (*in vivo*) and various modes of administering the NHP or herbal component(s);

III. **ex vivo** – laboratory interaction finding on cells, tissue, or organs from animals or humans who were administered herbal agent (*vs. in vivo* when studies are done on living organism themselves), **in vitro** - laboratory interaction findings in cell or tissue samples from animals or humans, **speculative** – using pharmacological evidence from *in vitro* research, animal studies, or human studies to infer probable or potential interactions or effects in humans;

IV. **(dubious interactions)** shown in brackets with the drugs underlined rather than in bold type are based on preliminary findings, speculation, inaccurate information, and/or false assumptions that have been contradicted by established evidence.

http://www.eclecticherb.com/emp/updatesHCDI.html

A Dutch clinical risk management system requires that hazards be identified and stratified in terms of evidence, probability and significance. The classification system for the structured risk assessment of drug-drug interactions is a two-part system based upon categories for quality of evidence (Table 6) and clinical relevance (Table 7) with the outcome being reported as an alpha numeric, such as 3E. This is complemented with incidence information and risk factors increasing the seriousness of the incident.

0 Animal studies, *in vitro* studies, data on file;
1 Incomplete or otherwise poor case reports, posters;
2 Well-documented case reports/case series;
3 Controlled studies in patients or healthy volunteers with surrogate endpoints;
4 Controlled studies in in patients or healthy volunteers with clinically relevant endpoints.

Table 7. Categories of clinical relevance. Modified from Van Roon et al. (2005).

A No or insignificant clinical effect;
B Transient inconvenience (less than 2 days) without residual symptoms;
C Prolonged inconvenience (2-7 days) without residual symptoms;
D Prolonged (greater than 7 days) or permanent residual symptoms or invalidity. Failure of therapy for a serious but non-fatal diseases;
E Increased risk of dying, failure of life saving therapy, increased risk of pregnancy (without risk factors for mother or child);
F Death, potentially fatal adverse effects, increased risk of pregnancy (with risk factors for mother or child).

Table 8. Caveats in computerised screening for drug-drug interactions. Know what programme can and cannot do.

- How is it established that the prescribed drug information is still current;
- Alert for adding CYP inhibitor/inducer easier than for moment of withdrawal;
- (In)consistent recording of OTCs and herbs;
- Account for risk modification (e.g. age, organ dysfunction, pharmacogenetic status, etc.);
- Univariate versus multivariate analysis.

As with all classification systems there are caveats that need to be considered in order to avoid false sense of security (Table 8). The codes should always be considered in combination with assessment of incidence and risk factors increasing seriousness of the incidence. An adequate and robust system is required for collecting and assessing new emerging evidence without unnecessary delay. Negative controlled study versus case report with positive challenge and rechallenge should allow for more than 1 code. In the event where there is a probable interaction without actual report/study, it is encouraged that the review not refrain from careful extrapolation. A case-by-case (one-to-one) risk assessment examines risk factors such as dosage, duplicate medication, drug-drug interactions, drug-disease interactions, etc. individually with the patient (De Smet 2005). A plural risk assessment looks at all factors together and then relates this assessment to the patient who can then be categorized at low, moderate or high risk.
2.1. Risk Reduction and Management Strategies

As with product variability, there are several risk reduction strategies which should be considered in parallel as no single strategy will reach or even relate to all individual users (Table 9).

There is consumer demand for more information on product safety, but risk communication is complicated by the need to get the correct message across without creating undue alarm as some but not all consumers are at risk, and not all products are involved in interactions. Current strategies have not yet reached maturity but nevertheless hold promise for future (Edwards et al. 2004).

Risk reduction strategies must be continually evaluated to determine if they have actually worked effectively and efficiently. Questions inherent to this evaluation include: Do pharmacists continue to dispense NHP-drug combinations that should be avoided (e.g. SJW + SSRI)? Do patients receive appropriate and up-to-date information about herb-drug interactions in pharmacies and health food stores?

Table 9. Risk reduction strategies.

- Risk communication;
- Clear-cut information in package inserts or labels;
- More conspicuous warning on products with special risks;
- Improved patient healthcare records;
- Reclassify and restrict access to NHPs with serious risk of interactions;
- Education and training;
- Post-approval surveillance;
- Continually evaluate the risk reduction strategies.

2.1.1. Pharmacovigilance

Signals should not be missed, found early, and the ‘false’ signals kept to a minimum; however, there are several challenges associated with NHP pharmacovigilance (Table 10). To the inexperienced collector of safety and efficacy information, it is possible to confuse closely related plants such as *Piper methysticum* G. Forst (the true kava) with the false kavas *P. aduncum*, *P. wichmannii*, *P. auritum*, or *P. puberulum*. In order for NHPs to maintain the safety/efficacy profiles associated with their traditional use, it is also important that the formulated product is dosage-correlated with the traditional form. Kava was traditionally prepared as a water extract but formulated commercially as an organic extract that differs chemically from the traditional product. Similar inconsistencies with traditional use also exist with respect to SJW, where there are numerous related species that share the common name. Products can be chemically very different. *H. perforatum* L. has a numerical designation (such as 9022700000) and there are 5 other designations depending upon whether the preparation is a root or an extract. Other nomenclature issues can occur when Latin pharmaceutical names are used. An example is *Aesculus hippocastanum* L. (syn. *A. procera* Salisb., *A. castanea* Gelib., *Hipposcastanum aesculus* Cav. and *H. vulgare* Gaert.). The Latin name Flos Hippocastani
designates the organ used. The common names include horse chestnut, Suo Lou Zi, Rosskastanie, marron d’Inde and morrone amaro. The situation can be further confounded when a common name such as ginseng is used to designate several different botanical genera that are chemically unrelated.

Table 10. Major challenges in pharmacovigilance.

- Inexperienced collectors;
- The authenticity of the manufacturer;
- Diversity of herbal terminology;
  - Use of only common or pharmaceutical name
- Not using the Latin binomial names + authority + parts;
- Complex mixture of various NHPs;
- Need for global herbal checklist;
- Dosage and usage correlation with traditional form
- What’s on the label may not be what is in the bottle;
- Almost any substance can be toxic in large doses.

2.2.2. Package Inserts and Labels

While consumers want more safety information on NHP labels, there are challenges in interpreting NHP safety literature, such as poorly documented botanical identification of NHPs in case studies and clinical trials. Pharmaceutical companies must include food and NHP interaction warnings on prescription drugs when applicable, and this applies to most regulatory jurisdictions. In the US, NHP manufacturers are not constrained to this regulation but may do so where product liability concerns require appropriate label warning of materially known, not theoretical, interactions. Failure to warn may result in increased liability. A warning does not eliminate liability, but may mitigate the risk (Rubin 2002). Clear information in package inserts of conventional drugs and NHPs with simple language and general terms such as “increase or decrease the activity of CYP 3A4” are critical to reduce confusion. More conspicuous warnings are required on the conventional/herbal product which present special risks that provide direction on what to do, or in some instances, what not to do until advice has been obtained from a HCP.

In determining whether to include a NHP-drug warning on product labelling, a variety of issues should be evaluated, including but not limited to: the likelihood of a potential interaction; the potential severity of the interaction; whether the interaction is well known by the general population or scientific community; whether drug product labelling already warns against ingestion of the NHP; and the level of the NHP present in the product (Rubin 2002).

The American Botanical Council (ABC) safety assessment program provides expanded safety information on contraindications, pregnancy and lactation warnings, AEs and interactions on product labels to guide responsible use by consumers. This system has merit and needs to be examined further by regulatory bodies and industry to help promote responsible use of NHPs.
2.2.3. Education and Training

Educational material needs to reach many different stakeholders (Table 11). Each stakeholder group will have different needs and the information will need to be provided through undergraduate, graduate and continuing education courses; conferences, workshops, association/society journals, etc.; the internet and consumer magazines.

Table 11. Stakeholders who should be targeted with educational material.

- Health care professionals (doctors, healers, naturopaths, nurses, pharmacists, etc.);
- Public (consumer, friend or family member of the consumer, media);
- Policy-makers (Health Canada and other regulatory authorities);
- Researchers and educators (including granting bodies such as Alberta Heritage Foundation for Medical Research, Canadian Institutes of Health Research, National Science and Engineering Research Council).

Consumers require specific, unbiased information to make the appropriate decision (risk-benefit analysis) concerning the use of some foods, with specific NHPs or drugs (Table 12). The information should be clear as to what is known concerning the potential risks. As a public health issue, the consumer should not be inundated with conflicting, complicated information; it must be kept simple when lives are at risk. An example of straightforward messaging is GFJ, where some product labels or monographs state that GFJ should not be used with a prescribed drug that has low to moderate bioavailability and has a narrow therapeutic index.

Table 12. Changes/Needs

- Cross cutting research in developing public health policy and on the interactions among food, drugs and NHPs;
- Better understand PK and pharmacogenomics (host genetics) and the role of micronutrients;
- Discovering natural inducers and inhibitors;
- There is a need for more Phase IV trials and data collection for prescription drugs;
- Stronger links between research and policy;
- Create more opportunities for dialogue between potential users and with researchers.

The issue of harm/risk reduction is important to the average consumer and everyone must recognize the complexity of the issues. This is confounded by an underlying belief that all products have been adequately tested and that HCPs have sufficient NHP-drug-food interaction information to advise patients accordingly. Examining the issue from the perspective of an informed consumer living with HIV, offered valuable insights. HIV presents an interesting lens through which to examine the issue: due to the need for >95% treatment compliance being required for successful anti-retroviral therapy [and possibly other therapies]; and the importance of bioavailability resulting in dietary restrictions. Any issue that affects treatment compliance can influence the long-term health of this patient. The importance, was emphasized, of recognizing that everything one ingests – whether a synthetic or “natural” product has the potential to cause an unwanted effect. It was highlighted that a great deal of importance is
focused on the potential for serious interactions among food/drugs/NHPs, but that a post-approval surveillance system is also necessary to advise about less serious ARs. Presently, only the well informed consumer is likely to be aware of the potential for these ARs.

Better provision of information to consumers through awareness campaigns is required. The challenge is to understand producer-push / user-pull technologies in a “wired” world and how to reach “unwired” people. With regards to risk communication, if the web is to be used effectively, the information provider must find a way to connect with the consumer, who is bombarded with information but also wants to know more about a specific safety issue. For those who live in a less wired world, it is helpful to have a dialogue in person, with experts that include one’s peers. The medical community needs to learn more about CAM, and the role of alternative health providers. as well as In this regard, it would also be constructive to increase interdisciplinary curricula to include naturopathic doctors, medical doctors, doctors of traditional Chinese medicines, pharmacists/pharmacologists, nurses and nurse practitioners, etc. Consumers need help make to informed decisions about what treatments to take and how to incorporate them into daily life with food. To make those decisions, the consumer needs to understand the potential for side effects, interactions, and how to avoid them. Providing the necessary tools, for the consumer to achieve this level of understanding, is a shared responsibility between consumers, health professionals, regulators, and industry.

A recent survey found that 54% of consumers relied on pharmacists for drug safety information. As such, community-based pharmacists, particularly those in locations which also sell NHPs, have a vital role in providing safety information. It is critical that pharmacists inquire about NHP use with each prescription given, in order to identify and communicate the potential for interactions and their consequences to the patient. It is important for post-market surveillance, that ARs, including those suspected as being interactions, be reported to Health Canada. However, Charrois et al. (2007) reported that one out of two pharmacists had been advised of NHP-related ARs, but that only two had reported the AR to Health Canada.

It is important for physicians to know: the NHPs used by the patient; the NHPs which may be used as alternative treatment to prescribed medications; the NHPs with demonstrated safety and effectiveness in this patient population; and the predictors, signs and symptoms of the ARs associated with the NHP.

The retailer industry has to adopt a precautionary approach rather than a general “non-issue” attitude. The ABC notes that consumer education is important but that unlike pharmaceuticals where pharmacists require extensive training, little if any training is required for the sale of NHPs. ABC has a 6-hour herbal information specialist program course (www.herbretraining.com) for distributors, practitioners and retail clerks. The two-part certification online course is based upon the ABC Clinical Guide to NHPs and provides understanding of the issues. The course is revised with new modules added annually.
2.2.4. Complementary and Alternative Research and Education Program (CARE)

CARE is a novel integrative approach housed in the Stollery Children’s Hospital, University of Alberta, Edmonton (Canada), with an emphasis on research and education, which aims to promote evidence-based safe and informed pediatric CAM use, based on patient/family’s choice. The goal of the CARE is to empower patients and their families to enable informed choices about their treatment. The program promotes open communication and monitor ARs using a research-based approach (every patient seen is a potential research subject). The Education arm comprises specific expertise, and tries to reach as many different stakeholders as possible. The NHP research – efficacy side of the equation works on producing systematic Reviews [e.g. melatonin for sleep (Agency for Healthcare Research and Quality)], randomized controlled trials [e.g., echinacea and ginseng for pediatric upper respiratory tract infection], and N-of-1 trials.

The treatment approach is multi-disciplinary and comprises joint proactive medical and naturopathic doctor cooperation

3. Surveillance

3.1. Health Canada’s approach to communicating drug-NHP interactions

The Natural Health Products Regulations, implemented January 1, 2004, mandate that market authorization holders, submit to Health Canada serious AR reports associated with use of their authorized natural health product (NHP) (Part 1 section 24 of the NHP Regulations). In order to maximize the amount of relevant safety information available to consumers, to enable making an informed choice about the NHPs they use, Health Canada capitalizes on the various communication vehicles available directed both at health practitioners and the public. These include: the Canadian Adverse Reaction Newsletter, published quarterly in the Canadian Medical Association Journal; communications sent through the newswire including public advisories and warnings, information updates, foreign product alerts; and, “It’s Your Health” fact sheets. All of these communications are posted on the Health Canada website, and sent automatically, to MedEffect subscribers (http://www.hc-sc.gc.ca/dhp-mps/medeff/subscribe-abonnement/index_e.html).

In terms of satisfaction with Health Canada’s risk communications, consumers and health professionals indicated that their expectations and demands were largely met regarding drug safety information via Health Canada’s standard communication processes. As with over-the-counter and prescription drugs, consumers indicated being most likely to approach a pharmacist for NHP information, with doctors and the Internet serving as important secondary sources. In addition to these sources, however, consumers indicated also relying on the media (television, print), health food stores, and friends/family, specifically for NHP information (Marketed Health Products Directorate Risk Communication Survey, 2003). As such, increasing consumer access to NHP safety information, requires innovative communication strategies and increased engagement with stakeholders concerning safety information and the importance of AR reporting.
In order to increase awareness of the importance and process of AR reporting among health care practitioners, Health Canada implemented electronic training modules, earmarked to be accredited continuing education requirements, of both conventional medical and naturopathic doctors, as a result of collaborative initiatives with the Canadian Medical Association (CMA) and the Canadian Association of Naturopathic Doctors, respectively. Additionally, Health Canada is working to incorporate AR educational materials and content into the naturopathic core curricula, via collaboration with the Canadian College of Naturopathic Doctors. Health Canada is also collaborating in studies to increase the active monitoring and reporting of NHP ARs and NHP-drug interactions at the pharmacist level (Charrois et al. 2007), as these health care professionals are often the consumer’s first point of contact, upon experiencing an NHP-associated AR. Since NHPs are often used by consumers, without health professional intermediaries, Health Canada anticipates posting electronic modules on AR reporting for use by the public as well as health professionals (www.healthcanada.gc.ca/medeffect).

3.2. The spontaneous reporting system in the United Kingdom (UK)

As in Canada, pharmacovigilance in the UK focuses on: (1) Hypothesis-generating, and (2) Hypothesis-Testing methods.

In Hypothesis-Generating, suspected adverse drug reactions (ADRs), including drug interactions are identified, by means of literature reports and spontaneous reporting schemes e.g. UK’s “yellow card” scheme, and the UK’s Prescription Event Monitoring (PEM).

The PEM system is a non-interventional method developed by the Drug Safety Research Unit (DSRU), Southampton, UK. Adverse event (AE) data are collected from general practitioners (GPs) for certain newly marketed prescription drugs. The Prescription Pricing Authority identifies all prescriptions for drugs of interest, as well as the GPs and patients who have prescribed/used the drug, respectively. These data are sent to the DSRU, which in turn, sends a “green form” to the prescribing GP six months after initial prescription, for submission of AE information. Each PEM study aims to collect data on 10,000 patients who have been prescribed the drug, and the analysis calculates incidence densities for each AE. Unfortunately, this method is not suitable for monitoring herbal medicines since these are most often not prescribed, hence modified PEM schemes have been designed for herbal medicines. These studies are being piloted via herbalists and pharmacies (see New Zealand discussion).

Additionally, the UK-herbal-sector has initiated various schemes for spontaneous reporting of suspected ADRs associated with herbal medicinal products. For instance, Phytonet was set up by the European Scientific Co-operative on Phytotherapy. The password protected system is internet-based and designed for conventional healthcare professionals, herbal practitioners and the public. The system feeds reports, where appropriate, into the World Health Organization (WHO) Uppsala Monitoring Centre. The National Institute of Medical Herbalists scheme was set up in January 1994. There is also the Register for Chinese Herbal Medicine scheme, and for manufacturers, the British Herbal Medicine Association voluntary code of practice. Finally, the Medical Toxicology Unit at Guy’s and St. Thomas’ Hospital Trust, London also carries out ADR
reporting. It is important that all ADR reports are fed into the common CSM/MHRA Adverse Drug Reactions On-line Information Tracking (ADROIT) System, in order to prevent signal dilution.

There are limitations to these methods for herbal medicines, due to: some ADR reporting forms not being tailored to herbal medicine information (Barnes and Aggarwal 2005, Table 13); under-reporting by consumers (Barnes et al. 1998) and health professionals (Barnes and Abbot 1999), and poor quality of reports. Also, as with any spontaneous reporting system, the AR incidence cannot be estimated from the number of reports, because of the lack of denominator (exposure) data, and significant under-reporting.

In the Hypothesis-testing method, there is an attempt to confirm or refute the suspected association between a medicine and an ADR, by means of analytical pharmacoepidemiological studies. Case-control studies involve a retrospective analysis of exposure to health products among patients with a particular medical condition compared with controls. Cohort studies prospectively follow individuals exposed to a particular health product to determine health outcomes relative to controls. However, the pharmacoepidemiological methods used for conventional medicines have important limitations when applied to herbal medicines, due mainly to the inability to accurately estimate herbal medicine exposure, and incomplete record-keeping concerning e.g. brand, dosage. The use of computerized health record linkage databases such as the General Practice Research Database can also be used in the pharmacovigilance of herbal medicines. These, however, are subject to biases which may be more pronounced with herbal medicines, since herbal medicines are rarely prescribed, and their use is often not documented in medical records. Finally, hypothesis-testing methods also include intervention studies such as clinical trials, and Phase I drug interaction studies, and are steadily increasing in the area of herbal medicine (Barnes 2003).

In the UK, safety concerns associated with herbal medicines are communicated at the international level using the Signal publication (WHO-Uppsala Monitoring Centre). Communications at the national level comprise: ‘Dear Doctor/Pharmacist’ letters; publication in Current Problems in Pharmacovigilance, sent to all doctors and practising pharmacists; press releases; and postings on the MHRA website as Herbal Safety News.

### Table 13. International spontaneous reporting of suspected ADRs associated with herbal medicines in a cross-sectional study a structured questionnaire sent to all official and associate member countries of the WHO-UMC program (n = 84); April to Dec 2004 (Barnes and Aggarwal 2005).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>National scheme accepts herbal ADR reports (n = 62)</td>
<td>87%</td>
<td>11%</td>
</tr>
<tr>
<td>National scheme has separate herbal ADR reporting form</td>
<td>4%</td>
<td>93%</td>
</tr>
<tr>
<td>Recognized reporter groups are specifically encouraged to report ADRs associated with herbal medicines (n = 54)</td>
<td>31%</td>
<td>67%</td>
</tr>
</tbody>
</table>
3.3. The spontaneous reporting system in New Zealand (NZ)

NZ has one of the highest ADR reporting rates in the world. There are currently more than 50,000 reports (1 per 80 people versus 1 per 150 people in the UK). The system, established in 1965 and run by the Centre for Adverse Reactions Monitoring (CARM), Dunedin, operates under contract to Medsafe (Medicines Regulatory Agency). The Agency receives reports of suspected ADRs to medicines. The ADR reports are generated by doctors, nurses, hospital and community pharmacists and dentists, while consumers are not formally encouraged to report. Pharmacists are encouraged to report ARs for herbal and complementary healthcare products, but the reporting rate is low (less than 2%). Decisions on action are made by the Medicines Adverse Reactions Committee.

The PEM system in NZ is a prospective, observational, cohort study on selected new medicines undertaken by CARM (Intensive Medicines Monitoring Programme, IMMP). Data are collected on all clinical events during medicine use, including suspected ADRs, deaths, accidents, abnormal laboratory test results, possible interactions, and are reported using the same form as spontaneous reports. The process is similar to the UK’s PEM, and measures incidence of ADRs, identifies previously unrecognized ADRs, and constructs a risk profile for each medicine e.g. high-risk populations. Medicines currently on the IMMP include: clozapine, olanzapine, and Coxibs, but studies for herbal medicines have not yet been conducted.

New Zealand communications concerning herbal medicines are disseminated via the Medsafe website, as ‘Hot topics’, Safety Alerts for Consumers, Prescriber Update Articles, as well as media releases, Director-General’s Privileged statements under Medicines Act 1981. It should also be noted, however, that New Zealand will introduce a new regulatory framework for herbal and complementary medicines when Medsafe joins Australia’s Therapeutic Goods Administration, to form the Trans-Tasman Agency, known as the Australia New Zealand Therapeutic Products Authority. This framework will likely reflect Australia’s existing complementary medicine’s framework.

3.4. Traditional Chinese Medicine control and risk communication strategies (Singapore’s Health Sciences Authority)

The Singapore traditional medicine control and risk-based approach centers on the belief that Traditional Medicines (TMs; Traditional Malay Medicine, Traditional Indian Medicine and Homoeopathic Medicine) are inherently ‘safer’ than western medicines. However, the level of clinical/scientific evidence meeting regulatory standards is often lacking, and some products may have intrinsic toxicity (e.g. Aristolochic spp.). There is also some confusion concerning nomenclature – botanical names, common names which are similar in appearance. The principles adopted in Chinese Proprietary Medicines (CPM) control take into consideration the conceptual differences between Traditional Chinese Medicine (TCM) and Western medicines. Additionally the contribution of TCM to primary healthcare services is recognized and while the efficacy of CPM is not currently assessed, regulatory control focuses on safety and quality of the product. As such, Singapore’s regulatory framework for CPMs, does not restrict CPM development, but meets the objective of safeguarding the consumer. The control
requirements include licensing of CPM dealers, listing of CPM products, submission of test reports for every consignment at point of import, and approval of advertisements and sales promotion (Table 14).

Singapore’s risk communication strategies aim to: enhance the safe use of drugs and related health products and minimise their associated risks; and, update and inform intended audience of safety issues in a timely, transparent and unbiased manner. One of this system’s strengths includes the detection of adulteration and non-compliance with heavy metal limits, through periodic sampling and AR monitoring. As with other regulatory agencies, this system’s limitations include the potential for unknown inherent toxicity of herbal medicines, and herb-drug interactions. Proactive regulatory action depends on the level of knowledge concerning a substance’s adverse event profile. In the case of unknowns, the premise is to wait for more signals to enable further analysis. This is achieved by pre-emptive targeting of professional groups with a subsequent re-evaluation of approval decisions. In cases of product non-compliance, regulatory actions may include fines, product suspension or withdrawal (e.g. kava kava, Slim 10®). Communication vehicles comprise Dear Health Professional letters, public advisories issued via web-postings, television, newspaper or via Health Sciences Authority email alert or ADR bulletin. Signals are obtained from case studies and from Adverse Drug Reaction Reports i.e., Adulteration of Jamu, adulteration of traditional Indian medicines, adulteration of Slim 10 (with nicotinamide, fenfluramine, thyroid gland and nitrosofenfluramine).


A. **Chinese Proprietary Medicines (CPM)**
   - Absence of Western drugs and toxic substances;
   - Toxic heavy metals and microbial counts within stipulated limits;
   - Labeling in English and other suitable language(s);
   - No claims on serious medical conditions and diseases e.g. cancer, diabetes, impotency;
   - Licensing status of manufacturer;
   - Free sale status of product in country of manufacture;
   - Testing of certain CPM are assessed to have higher risks of adulteration by accredited laboratories.

B. **Regulation of Other Traditional Medicines (Traditional Malay Medicine, Traditional Indian Medicine and Homoeopathic Medicine)**
   - Currently no licensing requirements;
   - Compliance with certain legislative requirements - absence of prohibited substances, toxic heavy metal limits;
   - Conduct risk based approach of sampling for compliance.

It is anticipated that future challenges will result from the rising popularity of TCMs, for which regulatory control will require strengthening, risk communication strategies will need revisiting, and there will be additional need for forging closer ties and cooperation with international regulatory counterparts.
3.5. Adverse Reaction (AR) Reporting issues

There is a general belief amongst consumers, that NHPs are “natural and therefore safe”, as a result of which, consumers may fail to associate ARs with the use of NHPs. Additionally, if using pharmaceuticals concurrently with NHPs consumers may attribute an AR to the pharmaceutical product. Consumers may also report NHP-related ARs to individuals not familiar with the formal AR reporting system, such as to health-food store staff, and as a result, the AR may go unreported either to the manufacturer or Health Canada.

HCPs’ knowledge of herbal medicines, their record-keeping for patients’ herbal medicine use, and knowledge of AR reporting schemes, are issues that need to be further addressed. Additionally, herbal practitioners may not be aware that they are encouraged to utilize AR reporting schemes, however, they may be reluctant to report suspected ARs. Pharmacists, in turn, may not be aware that the AR reporting system applies equally to herbal medicines as it does to conventional medicines.

Improvements are needed in manufacturer reporting of NHP-suspected ARs, and, given the emphasis placed on safety, more funding is required to conduct research relating to safety aspects of NHPs. This could lead to the development of new tools and modified methods of signal detection used for conventional health products, such as the efforts in the UK and New Zealand to tailor PEM strategies to NHP requirements.

4. Discussion

NHPs are different from conventional pharmaceuticals (Table 15) and there are many theoretical reasons for potential concern with NHP-drug interactions, but theory has not always translated to clinical events.

Table 15. Herbal versus synthetic drugs – a comparative summary.

<table>
<thead>
<tr>
<th>Herbal</th>
<th>Synthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Several active constituents</td>
<td>One active ingredient</td>
</tr>
<tr>
<td>Active constituents often not known</td>
<td>Active ingredient known</td>
</tr>
<tr>
<td>Pure compound not always available</td>
<td>Pure compound available</td>
</tr>
<tr>
<td>Raw material often limited</td>
<td>Raw material unlimited</td>
</tr>
<tr>
<td>Quality variable</td>
<td>Quality constant</td>
</tr>
<tr>
<td>Mechanism often unknown</td>
<td>Mechanism known</td>
</tr>
<tr>
<td>Toxicology often unknown</td>
<td>Toxicology known</td>
</tr>
<tr>
<td>Long tradition of use</td>
<td>Short tradition</td>
</tr>
<tr>
<td>Therapeutic window wide</td>
<td>Therapeutic window narrow</td>
</tr>
<tr>
<td>Adverse effects rare</td>
<td>Adverse effects frequent</td>
</tr>
<tr>
<td>Promoted by professionals</td>
<td>Promoted by professionals</td>
</tr>
</tbody>
</table>

Health Canada, the FDA, other regulatory bodies and clinical pharmacologists are interested in applying lessons learned from drug-drug interactions and food-drug interactions with regard to CYP450 probes and predicting AEs. However, laboratory analysis does not always predict...
clinically relevant NHP ARs, underscoring that the effects may be multi-factorial. Passive surveillance is associated with under-reporting. Many of these reports do not contain enough information to allow meaningful assessments of causality. This raises several questions of whose responsibility it is to collect these data, and should industry be asked to help pay for phase IV surveillance? Is it the sole responsibility of the regulatory agency? Do HCPs recognize NHP ARs when confronted with one? Several proposals were put forward. There is a need for active surveillance to complement, not replace, passive surveillance; and there is a vital role to be played by community-based pharmacists who are heavily relied upon for drug safety information. Because NHPs are different, the approach may need to be reversed from bedside to bench, rather than bench to bedside. For instance, there could be sentinel sites that are community- and hospital-based, with emphasis on pharmacists to inquire, recognize, and report suspected NHPs ARs. This would require a strengthened partnership with the patient. Pharmacists would require additional education regarding necessary patient information to be obtained, and product information to be provided (potential ARs, interactions) with each prescription. Such pharmacist monitoring could assist in generating numerator and denominator data on NHP use among prescription drug users. In-depth follow-up telephone surveys to ascertain details necessary to complete a quality AR report, would then maximize the information necessary for a meaningful causality assessment. Such systematic monitoring would allow for clinically relevant NHP ARs to be identified, in order to provide evidence to support or refute theoretical predictions. An important issue to be clarified is clinically relevance. What may not be relevant in a non-ambulatory patient, such as light headedness (dizziness), may be serious in an individual driving a vehicle or operating heavy equipment.

How could this be done? For serious ARs, examine the potential mechanism of action, adulteration/contamination phytochemical constituents (e.g. if not prepared/used according to traditional use), and look for multiple PK and PD NHP-drug interactions. Consider complex solutions for complex problems that would include improving the quality of case reports à la CONSORT, standardizing the vocabulary and language used in this field, improving labeling for consumers and strategies for informing HCP. For NHPs with potentially serious ARs, consider moving the product behind the counter, improving strategies to identify NHPs ARs, and understanding better the mechanism of ARs. When we don’t fully understand what to measure, we still can assess clinical efficacy versus safety (the AUC vs. safety).

Much of the symposium can be summarized in Table 15. Foods and NHPs are complex and their potential for interactions are not well understood when used in a non-traditional manner or together with other products. NHP-drug interactions may be uncommon but serious ARs can and do occur. The public has the right to choose which treatment to accept; HCPs and regulatory bodies must however be vigilant and remain proactive when public health may be at risk.

Glossary

**Adverse Events (AE):** Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal
product, whether or not considered related to this medicinal product [International Conference on Harmonisation, Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2D) (2003)].

**Adverse Reaction (AR):** For the purpose of this document, means a noxious and unintended response to a marketed health product, and includes "adverse drug reaction" as defined in the *Food and Drug Regulations* and "adverse reaction" as defined in the *Natural Health Products Regulations*. "Adverse drug reaction" as defined in the *Food and Drug Regulations* means a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function [*Food and Drug Regulations*, Part C, Division 1, Adverse Reaction Reporting (C.01.016), C.R.C., c. 870]. "Adverse reaction" as defined in the *Natural Health Products Regulations* means a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function. [*Natural Health Products Regulations*, Section 24, Reaction Reporting, C.R.C., SOR/2003-196].

**Chinese Proprietary Medicines (CPM):** Preparations in finished dosage forms containing NHPs animal parts or minerals used in the practice of Traditional Chinese Medicines (TCM).

**Drug:** any substance or mixture of substances manufactured, sold or represented for use in: the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, restoring, correcting or modifying organic function (Health Canada) [*Food and Drugs Act*, Revised Statutes of Canada, Interpretation, 1985, c. F-27, as amended].

**Functional food (FF):** has been defined as being similar in appearance to a conventional food, consumed as part of the usual diet, able to demonstrate physiological benefits, and/or able to reduce the risk of chronic disease beyond basic nutritional functions (Health Canada).

**Natural Health Product (NHP):** A substance set out in Schedule 1 of the *Natural Health Products Regulations* or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1 of the *Natural Health Products Regulations* (which include homeopathic preparations, substances used in traditional medicine, a mineral or trace element, a vitamin, an amino acid, an essential fatty acid, or other botanical-, animal-, or micro-organism-derived substance), that is: manufactured, sold or represented for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans; restoring or correcting organic functions in humans; or modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health. (Health Canada) [*Natural Health Products Regulations*, Interpretation, C.R.C., SOR/2003-196].

**Nutraceutical:** a product that has been isolated or purified from foods and is generally sold in medicinal forms not usually associated with food (Health Canada). Nutraceuticals would exhibit a physiologic benefit or provide protection against chronic disease. Nutraceuticals are encompassed within the NHP regulations.
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