

# Natural Medicine Law™ Newsletter

## F&WS FINDING LIMITS GINSENG EXPORT

A new “finding” or determination published August 5, 2005 by the U.S. Fish and Wildlife Service (F&WS) has clamped down on export of ginseng from certain states. The document is a 12-page explanation of the new policy and the Service says it will review the situation in the spring of 2006 to see if any changes are needed.

Until further notice, export of wild American ginseng roots from plants 10 years of age (4-leafed) or older (i.e., with 10 or more bud-scale scars on the rhizome) harvested during the 2005 season in the following states will not be detrimental to the survival of the species: Alabama, Arkansas, Georgia, Illinois, Indiana, Iowa, Kentucky, Maryland, Minnesota, Missouri, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Vermont, Virginia, West Virginia and Wisconsin. “The export of wild-simulated and woodsgrown ginseng that is younger than 10 years of age, which is treated as wild for CITES export purposes, may be authorized on a case-by-case basis if applicants are able to document the origin [of] their roots (including source of seed or transplants.)”

Ginseng has declined from historic levels and continues to be under threat from over-exploitation because demand and price for its roots remain high, the F&WS report said. Since 1999, state data shows that implementation of a 5-year minimum-age

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## SALT CASE DISMISSED

The U.S. Court of Appeals for the District of Columbia dismissed the case filed in February by the Center for Science in the Public Interest (CSPI) against FDA for not acting on the regulations for sodium chloride in food. When we last reported on the case (*see NML* Vol. 9, No. 1, July 2005), the FDA had filed an opposition on June 3, 2005, but the Clerk did not place the item on the case web site. This was followed by a reply filed by the CSPI on June 13, a reply by FDA on June 28 along with a Motion for leave to file a surreply, and an opposition to the motion by CSPI on June 30.

Within two weeks, Circuit Judges Randolph, Rogers, and Tatel issued a *Per Curiam* Order on July 14, 2005 denying the FDA motion to file a surreply, and also dismissed the CSPI petition for lack of jurisdiction. The Court wrote: “FURTHER ORDERED that the petition be dismissed for lack of jurisdiction. Although the All Writs Act empowers federal courts to issue writs of mandamus to protect their ‘prospective jurisdiction,’ *Telecommunications Research and Action Center v. F.C.C.*, 50 F.2d 70, 76 (D.C. Cir. 1984), the Act itself does not ‘enlarge’ that jurisdiction, *see Clinton v. Goldsmith*, 526 U.S. 529, 534-35 (1999). Thus, a party seeking relief in an appellate court under the All Writs Act must be able to show that it has implicated the court’s prospective jurisdiction by instituting a proceeding in a lower court or agency that is subject to the

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## CHINESE NATURAL MEDICINE CHEMICAL FIGHTS MALARIA

An amazing new drug made from *artemesia* by the Guilin Pharmaceutical Factory, Guangxi, People’s Republic of China, was studied at the South East Asian Quinine Artesunate Trial Group. Artesunate is a derivative of artemisinin. It is an antimalarial agent extracted from the dry leaves of the Chinese herb *Artemisia annua* (qinghaosu or sweet wormwood). This plant is grown each year starting from seed and only yields artemisinin under specific agricultural and climatological conditions. Wormwood is cultivated only in China, Vietnam and pilot projects in Tanzania and India. It takes eight months to mature. ([www.medterms.com](http://www.medterms.com)).

The conclusion of the study reported in *Lancet* 2005; 366: 717-25 was that artesunate should become the treatment of choice for severe falciparum malaria in adults. The drug is more rapidly acting than qui-

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limit on ginseng roots, the number of wild roots harvested has steadily increased. But the five-year regulations are difficult to enforce in the field. The data also indicate that there is a growing trend in the harvesting of smaller roots, which indicates that fewer older plants are present in the wild.

Earlier this year, the status of Kentucky ginseng, where the largest amount of wild-collected ginseng is harvested, was changed from “apparently secure” to “vulnerable” by the Natural Heritage Program. And none of the Natural Heritage Programs in the 19 states approved for export have designated ginseng as “secure.”

Specialists have suggested that a removal rate of 5 to 8 % of a ginseng population per year is the sustainable rate if spread over each size-class of plants. But lack of state-wide data makes this extremely difficult to implement and monitor. Using non-local or “commercial” seed to replant wild ginseng is a great concern. Wild ginseng seed should be planted where they are harvested.

The entire report including background information and future actions is available on [www.fws.gov](http://www.fws.gov).

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court's appellate jurisdiction. *See In re Tennant*, 359 F.3d 523, 528 (D.C. Cir. 2004). Because petitioner ‘did not seek a remedy from the [agency] or initiate any proceeding in [the] agency before resorting to this court,’ the court lacks jurisdiction to consider its petition. *See id.* at 528.”

CSPI had argued that the *Telecommunications Research and Action Center v. F.C.C.* case was a basis for the Court of Appeal's jurisdiction to protect it's prospective action in a case. But CSPI did not mention *Clinton v. Goldsmith* or *In re Tennant*, that the Court of Appeals panel said requires seeking a remedy from the agency or initiating a proceeding in the agency before resorting to an appeal. Evidently, the 1983 lawsuit filed by CSPI and the two petitions CSPI filed at FDA were not a good enough seeking of a remedy. The prior case and petitions were discussed in the February 2005 CSPI petition.

This means that the CSPI must start over on its 22-year effort to get FDA to make decisions about limiting salt in food. The FDA may have disclosed some current strategy in the various court oppositions to the petition, but consumers will have to wait on the agency to do something outside of the courthouse.

An August 17, 2005 news release by CSPI states it is taking a new approach to the problem by urging Congress to create a new Division of Sodium Reduction within the FDA that could encourage—through bully pulpit and regulation—food companies to use less salt. In the United Kingdom, where salt reduction has been a major priority for that country's Food Standards Agency, some food products, such as Kraft's Lunchables, have less sodium there than they do in the United States.

## PHYTOLACCA TRADEMARKS

If you are looking for a word to use in a trademark that has not had much

play as a trademark, try “phytolacca,” as there are no current applications on file at the U.S. Patent and Trademark Office. Nor are there any marks on file for “Poke Weed.” But there are 97 live and dead marks on file for just plain “Poke.” None of them appear to be in the area of dietary supplements. And there are 434 trademarks on file using the word “weed” alone or in combination with other words. *NML* readers can get more information at [www.uspto.gov](http://www.uspto.gov).

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nine. Whether it will reduce mortality is unknown, but in this study mortality was 15% (107 of 730) for artesunate compared to 22% (164 of 731) for quinine, an absolute reduction of 34.7%.

According to J.F.S. Ferreira and Jules Janick, Purdue University School of Horticulture, in their 1996 article, “Distribution of artemisinin in *Artemisia annua*.” p. 579-584. In: J. Janick (ed.), *Progress in new crops*. ASHS Press, Arlington, VA, the plant is mentioned in the book *Chinese Handbook of Prescriptions for Emergency Medical Treatments* published in 340 A.D. Rediscovery of the chemicals in this plant in recent years has led to a large amount of research.

Patients in the reported study received artesunate “2.4 mg/kg body weight on admission, then at 12 h, 24 h and thereafter once daily until oral medication could be taken reliably. Each 60 mg vial contained anhydrous artesunic acid, which was dissolved in 1 ml of 5% sodium bicarbonate and then mixed with 5 ml of 5% dextrose before injecting in a bolus into

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## SECTION 403 LETTERS

Each month, *NML* includes more of the FDA's Letters of Rejection or Courtesy Letters that are designed to notify makers and distributors of dietary supplements about label claims that FDA determines are not permissible under current law. Readers should become familiar with these as this will help avoid using similar labeling phrases that will cause products to be inappropriately labeled and therefore in violation of law. Violation of the Food, Drug and Cosmetic Act, as amended, can result in criminal charges, seizure of products, and court injunctions with severe civil penalties for non-compliance. Persons giving notice have to be sure they have a product that is a dietary supplement and that there is not already an approved health claim that must follow specific regulations. A company could be asking for trouble if it has labeling on the Internet when the company asks FDA to review it, as well. Labeling should not be used if the law requires FDA review and this has not been done. Submitting a notice of such a product only results in FDA responding that the notice does not satisfy legal requirements.

**World Nutrition, Inc.** of Scottsdale, Arizona, wrote FDA on March 1, 2005 to notify the agency of a claim for Wang's Hokusotsu Blend, containing Chrysanthemum extract, Chameleon plant, Perilla, Chinese yam, Licorice root, Lily bulb and Cordyceps. The claim was "*Wang's Hokusotsu Blend contains a unique formulation that may help the immune system's sensitivity to pollens.*" FDA responded on March 28, 2005 to Ben Lewis, marketing manager, in a letter from Susan J. Walker, M.D., stating that the phrase "*may help the immune*

*system's sensitivity to pollens*" was a claim to treat the disease of allergy and therefore it does not meet the requirements of Section 403(r)(6), but rather makes the product subject to regulation under the drug provisions of the Act. Dkt. No. 97S-0163, Ltr. 823, received at the Dockets Office on May 12, 2005, Entered the file on May 16, 2005, and posted to the FDA Web site on May 20, 2005.

**Anabolic Laboratories, Inc.** of Lake Forest, California, wrote to FDA on April 4, 2005 with claims for two products. Mega Omega 3, containing 600 mg of fish oil per serving, would use the claim, "*May Reduce the Risk of Coronary Heart Disease,*" and CholestFighter, containing 900 mg plant sterols per two capsules, at least 88% combined phytosterols, meeting the content as required under 21 CFR 101.83, would use the claim, "*Clinically Proven to Reduce Cholesterol.*" The company claimed this was the same claim as used by the approved Nature Made® Cholest-off dietary supplement. FDA responded to Erin Silva, MS, RD, CNSD, by a letter of May 5, 2005 from Susan J. Walker, M.D. stating that these claims are claims for treatment of coronary disease. FDA reminded the company that it had issued conditions for using a health claim concerning the relationship between phytosterols and phytostanol at 21 CFR 101.83. [To see FDA letters defining the conditions of use of such claims see [www.cfsan.fda.gov/~dms/ds-ltr30.html](http://www.cfsan.fda.gov/~dms/ds-ltr30.html) and [www.cfsan.fda.gov/~dms/lab-qhc.html](http://www.cfsan.fda.gov/~dms/lab-qhc.html)—Ed.] Dkt. No. 97S-0163, Ltr. 824, received at the Dockets Office on May 13, 2005, Entered the file on May 16, 2005, and posted to the FDA Web site on May 20, 2005.

**KneeLife, LLC** of Santa Barbara, California, wrote to FDA on April 22, 2005 to give notice that it would use a certain page-long list of claims for its product, AM/PM Knee Packs, containing a number of vitamins, minerals, amino acids, other chemicals, including 1000 mg of glucosamine sulfate, and plant extracts. FDA responded on May 5, 2005 by a letter from Susan J. Walker, M.D. to John La Puma, CEO, stating that the following claims suggest that the product is for osteoarthritis treatment: "*[F]or pain and stiffness from osteoarthritis of the knee,*" "*[R]educe inflammation...*," "*[Q]uall inflammation in your knees,*" "*[T]o reduce inflammation,*" "*[C]omplete solution to your arthritis needs,*" "*[M]ay work to reduce your pain and stiffness...*," "*[L]et your knees recover from inflammation, and reduce your pain,*" "*[R]educe inflammation in your bloodstream and your knees,*" and "*Our goal is to treat arthritis pain.*" FDA said if these claims are used the product will be regulated under the drug provision of the Act. Dkt. No. 97S-0163, Ltr. 825, received at the Dockets Office on May 13, 2005, Entered the file on May 16, 2005, and posted to the FDA Web site on May 20, 2005.

**InteMedica, LLC**, of Reno, Nevada, wrote to FDA on March 29, 2005 stating it would make certain claims for five separate products. Each of the products contains a long list of herbal ingredients identified by common names and Chinese names.

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The product, Supporter Constipation Herbal, containing Chinese Rhubarb Root and Rhizome, Bitter Orange, Flax Seed and Peach Seed, among other ingredients, had the claim: *Supporter Constipation Herbal is a herbal formulation designed to support healthy bowel function.*"

The product, Supporter Diarrhea Herbal, containing among other ingredients, Fragrant Angelica Root, Dolichos Seed, and Chinese Skullcap Root, had the claim: *"Supporter Diarrhea Herbal is a herbal formulation designed to support healthy bowel function."*

The product, Supporter Ingestion Herbal, containing, among other ingredients, Codonopsis Root, Ginger Fresh Rhizome, and Astragalus Root, had the claim: *"Supporter Ingestion Herbal is a herbal formulation designed to support healthy digestive system."*

The product, Supporter Irritable Bowel Herbal, containing, among other ingredients, Yin-Chen Wormwood Young Shoot, Schsiandra Fruit, and Job's Tears Seeds, had the claim: *"Supporter Irritable Bowel is a herbal formulation designed to support healthy bowel."*

The product, Supporter Soothing Bowel Herbal, containing, among other ingredients, Chinese Peony Root without Bark, Ligusticum Wallichii Rhizome, and Jujuba Seeds, had the claim: *"Supporter Soothing Bowel Herbal is a herbal formulation designed to support healthy bowel."*

FDA responded to W. John Diamond, M.D., chief medical officer, by letter of May 5, 2005 from Susan J. Walker, M.D., stating that the statements made for Supporter Constipation Herbal, Supporter Diarrhea Herbal and Supporter Irritable Bowel Herbal, were claims that these products treat, constipation, diarrhea, and irritable bowel by virtue of the names

of the products. If these claims are used, the products will be regulation under the drug provisions of the Act. Dkt. No. 97S-0163, Ltr. 826, received at the Dockets Office on May 13, 2005, Entered the file on May 16, 2005, and posted to the FDA Web site on May 20, 2005.

**Inverness Medical Nutritional Group** of Freehold, New Jersey, wrote FDA on April 27, 2005 concerning claims it would make for the product Daily for Woman, a multivitamin and mineral product. Included among the 11 claims made was one that stated: *"100% Daily Value of Folic Acid with a healthy diet may reduce the risk of having a child with neural tube birth defects."* FDA's Robert J. Moore, Ph.D., signed a letter for Susan J. Walker, M.D., dated May 10, 2005 to William J. Neumann, vice president of Quality and Regulatory Affairs, stating that FDA had published a health claim regulation on the relationship of folic acid and neural tube defects at 21 CFR 101.79 and this must be followed to make such a claim. FDA said if the company used the claim as stated, FDA would regulate the product under the drug provisions of the Act. Dkt. No. 97S-0163, Ltr.827, received at the Dockets Office on May 13, 2005, Entered the file on May 16, 2005, and posted to the FDA Web site on May 20, 2005.

**MD Drinks, Inc.** of Santa Monica, California, gave written notice to FDA in a letter of April 27, 2005 that the company would use certain claims for the product, Function Urban Detox, containing, Opuntia Ficus Indica, N-acetyl cysteine, Calcium carbonate, sodium [sic], Ascorbic Acid, Magnesium oxide, Riboflavin, Vitamin B6, Vitamin B12 and Folic Acid. The claim proposed



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was: *"FUNCTION is a physician-developed beverage that helps cure and prevent hangovers, helps protect your liver, helps reduce the effect of urban pollution on your lungs and sinuses, and boost your immune system."* FDA's Robert J. Moore, Ph.D., for Susan J. Walker, M.D. responded on May 10, 2005 to Alexander P. Hughes, president, stating the claim *"...beverage that helps cure and prevent hangovers"* was a claim suggesting the product was used to treat a disease such as the consequence of alcohol poisoning. FDA also said that the description of the product as a beverage indicates the product is not a dietary supplement. Beverages are conventional foods and must bear nutritional labeling in accordance with 21 CFR 101.9. Additionally, any ingredient added to a conventional food must be an approved food additive unless it is generally recognized as safe (GRAS) among qualified experts for

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## Natural Medicine Law Around the World

### NATURAL MEDICINE DEVELOPMENTS IN NIGERIA

Special Report from Austin A. Okwelle  
Nigeria is a developing West African country with over 120 million people. It is the largest country in Africa and the most populous black nation. It is estimated that about 40% of Nigeria's population are dependent on the use of herbs as an alternative remedy for their health care needs. In spite of the relatively large number of users and the long acclaimed effectiveness of natural medicine in the control of diseases and maintenance of healthy living, the practice of herbal medicine in Nigeria have regrettably remained largely underdeveloped.

Several factors account for the poor state of herbal medicine in Nigeria. One of such factors is the near absence of an enabling law on the practice of natural medicine. Unlike the conventional medicine where the federal government enacted a law that established the Nigerian Medical and Dental Council (NMDC) to register, regulate and license qualified medical doctors, there is no similar law for the registration, regulation and practice of natural medicine. This has over the years hindered direct budgetary allocations from government for the development of the natural health sector.

The ultimate consequences of all this is that the local practitioners faced lack of government recognition, their activities were neither harmonized nor the products standardized, and public acceptability of the herbal preparations was put to question. The lack of official recognition by government

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### AYURVEDIC WARNING FROM CANADA

Health Canada is warning consumers not to use certain Ayurvedic medicinal products because they contain high levels of heavy metals such as lead, mercury and/or arsenic. Health Canada is taking action to remove these products from the market and to prevent further importation into Canada.

Ayurvedic medicinal products are used in traditional Indian healing and are often imported from India. According to the principles of Ayurvedic medicine, heavy metals may be used because of their reputed therapeutic properties. However, improper manufacturing processes may result in dangerously high levels of heavy metals remaining in the final product.

For more information, please see the text of the full Advisory on the Health Canada Web site:  
[http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005\\_80.html](http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_80.html)

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Santé Canada avise les consommateurs de ne pas utiliser certains produits ayurvédiques étant donné leur teneur élevée en métaux lourds, notamment du plomb, du mercure ou de l'arsenic. Santé Canada prend les mesures nécessaires pour retirer ces produits du marché et prévenir toute nouvelle importation au Canada.

Les remèdes ayurvédiques sont utilisés en médecine traditionnelle

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### EU COURT SAYS FSD REALLY LIKE DSHEA

Initial reaction to the European Court of Justice decision on the Alliance for Natural Health's case challenging the EU Food Supplements Directive (FSD), is now interpreted by some to mean that vitamins and minerals will stay on the market unless the European governments prove that these products are unsafe. This is similar to the way the Dietary Supplement Health and Education Act in the United States works.

The Court of Justice cleared up this issue and many others in the details of its decision on July 12, 2005. In the 17-page Judgment of the Court, it was mindful that the preamble to the Directive 2002/46 concerned food supplements that are regulated in Member States by different national rules that may impede free movement, create unequal conditions of competition, and therefore have an impact on the internal market. Another recital in the preamble was to "ensure a high level of protection for consumers and facilitate their choice, the products that will be put on the market must be safe and bear adequate and appropriate labeling..."

After analyzing precedent cases, the Court said that the prohibitions taking effect on August 1, 2005 were such as could be adopted on the basis of Article 95 EC. Then following up it stated that restrictions on marketing vitamins and minerals not included on the August 1 positive lists are capable of restricting free movement of food supplements within the Community. The Court explained that the Member states' power is laid down in Article

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created the credibility question of professional competence on the part of the practitioners. And the non-compliance to any set guidelines or regulations gave way to quacks, fake and adulterated products.

Besides the lack of legislation for the establishment of a statutory body for natural medicine, there were also no laws for the establishment of schools to teach and train natural health professionals in Nigeria for a long period. The non-establishment of training institutions led to the development of misconceptions about the use of natural medicine. This is because over 80% of the practitioners who are mainly illiterates do not have any scientific knowledge of the formulations they administer to their unsuspecting patients. The practitioners who in some cases were alleged to operate under the cover of superstition and fetishness claim to have inherited the art of natural healing from their forefathers. These illiterate and untrained practitioners operate in secrecy and carry out their business under an unhygienic environment without regard for Good Manufacturing Practice (GMP) and Product Quality Control (PQC). There is also little consideration by the untrained hands for adherence to proper labeling specifications and good packaging of products.

Regardless of the longstanding absence of relevant laws, however, natural medicine in Nigeria seems to be changing for better in the past few years. Interestingly, the use of herbs is increasing in popularity and general acceptability. This positive trend stemmed from the achievement made by a few Nigerian born natural health practitioners who studied overseas but are practicing at home. More im-

portant is the success recorded by some foreign natural health products that were introduced into the Nigerian herbal product market. These include products made by Forever Living, Golden Neo-Life Diamite (GNLD) and Tianshi from USA to mention just a few. The effectiveness of the products from the stables of these companies in the control of some tropical diseases dramatically changed the previously held misconceptions, altered attitudes and perception, greatly shifted user interests and enhanced demand for herbal products in Nigeria. The media, both electronic and print, must equally play a leading role in the campaign for policy makers to enact appropriate legislative measures that will improve the practice of natural medicine in the county.

Realizing the increasing patronage of herbal medicine by Nigerians, the success of foreign herbal products, and the efforts made by the developed countries to encourage, promote and regulate the practice of natural medicine, the Nigerian government has started having a quick re-think on its earlier neglect of the industry. An indication to this effect came from the Health Minister, Prof. Eyitayo Lambo who revealed recently that the federal government has embarked on a comprehensive health reform program that will accord natural medicine practice its proper place. The minister stated that a draft policy on traditional medicine has already been prepared by a technical committee, and that a bill seeking to establish the Traditional Medical Council of Nigeria (TMCN) similar to the NMDC is to be forwarded to the National Assembly for passage into law.

The bill will provide the required legal framework for the implementation of the federal government's new National Traditional Medicine Policy in Nigeria. The draft policy spells out (i) the traditional medicine strategy; (ii) traditional medicine system management; (iii) traditional medicine manpower development ; and (iv) traditional medicine research and technology. When passed, the law will empower the TMCN to set up National Guidelines for the establishment of Boards of Natural Medicine in all the 36 states of the federation as is the case with orthodox medicine. Under the policy, intending practitioners will be required to undergo an intensive four year practical training for the award of a Diploma.

At the moment, the National Agency for Food and Drug Administration and Control (NAFDAC) is empowered by law to regulate the manufacture and sale of all food products and pharmaceuticals including herbal products. To speed up the process of development of natural medicine, the government has created a separate Nigerian Natural Medicine Development Agency (NNMDA). The agency is empowered by law to carry out research and currently runs the first Nigerian Natural Medicine College for the training of practitioners. There is also the law setting up the National Institute for Pharmaceutical Research and Development (NIPRD). The NIPRD equally liaises with individual local natural health operators to identify and extract the pharmacologically active component of an herbal preparation.

Although the on-going policy initiatives by the federal government to put in place the necessary legislations required to sustain the development of

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natural medicine is highly commendable, it is nevertheless feared that inadequate funding, mismanagement and poor implementation of guidelines and regulations by the respective statutory establishment will continue to affect the use of natural medicine in Nigeria. Until the bill setting up the Traditional Medical Council of Nigeria (TMCN) is finally passed into law, the practice of natural medicine will continue to suffer a setback.



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indienne et sont souvent importés de l'Inde. Selon les principes de l'ayurveda, les métaux lourds peuvent être utilisés en raison de leurs soi-disant propriétés thérapeutiques. Un processus de fabrication inadéquat peut toutefois occasionner des concentrations dangereusement élevées de métaux lourds dans le produit final.

Pour de plus amples renseignements, veuillez voir la Mise en garde complete sur notre site Web à l'adresse suivante : [http://www.hc-sc.gc.ca/francais/protection/mises\\_garde/2005/2005\\_80.html](http://www.hc-sc.gc.ca/francais/protection/mises_garde/2005/2005_80.html)

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4(7) to impose national restrictions and bans in trade for food supplements containing vitamins and minerals not on the positive lists is

merely a corollary of the Member states ability under Article 4(6) to allow in its territory until December 31, 2009 the use of such constituents on the conditions there set out.

The Court then explained that the purpose of "Article 11(2) of Directive 2002/46, when that provision is read in conjunction with the 8<sup>th</sup> recital to the Directive, it becomes clear that its purpose is to preserve, until specific Community rules are adopted, the application, in compliance with the Treaty, of national rules concerning nutrients other than vitamins and minerals or other substances with nutritional or physiological effect used as ingredients in food supplements."

From the various preambles to Directive 2002/46, when read together, the Court concluded, "[I]t is apparent that the directive concerns food supplements containing vitamins and/or minerals derived from a manufacturing process using 'chemical substances' (11<sup>th</sup> recital), and not food supplements whose ingredients include 'amino acids, essential fatty acids, fibre and various plant and herbal extracts' (6<sup>th</sup> recital), whose conditions for use consequently remain 'until ... specific Community rules are adopted' within the scope of 'national rules', without prejudice to the provisions of the Treaty' (8<sup>th</sup> recital)."

The fact that certain substances at issue have not yet received favourable evaluation from the competent European scientific authorities does not preclude giving scope in Article 4(5) for obtaining a modification of the positive lists by reference to scientific and technological developments. The Court wrote that "a measure which, like that at issue in the main actions, includes a prohibition

on marketing products containing substances not included on the positive lists laid down in the applicable legislation must be accompanied by a procedure designed to allow a given substance to be added to those lists and the procedure must comply with the general principle of Community law, in particular the principle of sound administration and legal certainty." Going on, the Court said, "Such a procedure must be accessible in the sense that it must be expressly mentioned in a measure of general application which is binding on the authorities concerned. It must be capable of being completed in a reasonable time. An application to have a substance included on a list of authorized substances may be refused by the competent authorities only on the basis of a full assessment of the risk posed to public health by the substance, established on the basis of the most reliable scientific data available and the most recent results of international research. If the procedure results in a refusal, the refusal must be open to challenge before the courts (see, by analogy, Case C-24/100 *Commission v. France* [2004] ECR I-1277, paragraph 26, 27 and 36 and Case C-95/01 *Greenham and Abel* [2004] ECR I-1333, paragraphs 35, 36 and 50). [Editor's emphasis.]

The Court then mentioned a "comitology" procedure in the preambles to Directive 1999/468 intended to reconcile the requirement for effectiveness and flexibility arising from the need to regularly amend and update aspects of Community legislation in the light of developments of scientific understanding in the area of protection of human health or safety and, on the other hand, the

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the positive list, and the EC government cannot refuse to file or refuse to act on the request in a reasonable time. This is why the procedure can be compared to that in the United States where, under the Dietary Supplement Health and Education Act, requires FDA to prove the product is unsafe in order to exclude it from the market. The complete decision can be obtained at: <http://curia.eu.int/juris>. Look for Alliance for Natural Health and Nutri-Link, Ltd v. Secretary of State for Health, joined cases C-154-04 and C-155/04.

The European Consumer's Organization welcomed the decision, according to Jim Murray, director, in an article from Associated Press writer Paul Ames, posted on <http://businessweek.com/ap/financialnews/D&BA227701.htm>. In a statement from the Alliance for Natural Health, that uses Dame Judi Dench as a spokesperson, the organization said: "It seems that the ruling may have been a compromise gesture on the part of the Court. It has ensured that the European Institutions (notably the European commission, the Council of Ministers and the European Parliament) were able to avoid the embarrassment of an overturned Directive and that the clarification of the law avoided conflicts with EU law, which had been the key basis of contention in the case brought by the ANH."

**"Opinions still divided** — As you may know, this view is not shared by all and opinions seem to be particularly polarised in the UK, where the two trade associations, the Health Food Manufacturers Association (HFMA), the National Association of Health Stores (NAHS) and a consumer organisation, Consumers for Health

Choice (CHC) appear to be of the opinion that the legal challenge has failed dismally and confers no benefits to consumers, practitioners, retailers or manufacturers."

"In the latest issue of Health Food Business, a trade magazine that is widely distributed to the UK health industry, which hit the health food shops this week, it is clear that these UK trade and consumer organisations' present campaign strategy is to create a strong political lobby to push the Government towards national derogation (known legally as 'subsidiarity') for the UK, by using the influence of the British Prime Minister Tony Blair while the UK holds the 6-month rotating EU Presidency. It is the opinion of our legal team that there is no currently available mechanism for achieving this and it was actually the ANH that ran this 'subsidiarity' argument particularly strongly in its legal challenge but the argument unfortunately was lost for a number of reasons."

**"Derogation dossiers: just delaying the inevitable ban? —** Mainstream industry spokespersons continue to propound the 'doom and gloom' scenario about the ECJ ruling. They say that all the work on derogation dossiers has just bought some more time and the inevitable bans will come into place anyway, even if it's after 2009. The ANH argues that this need not be the case."

"The HFMA and NAHS, as well as companies and other trade associations, worked hard to file dossiers for the derogation provision within the Directive which allows ingredients that have been used prior to 2003 to continue to be used at

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need to take account of the respective powers of the Community institutions. The procedures set forth in Directive 1999/468 which are referred to in Article 4(5) of Directive 2002/46, will ensure that once an item is submitted, the process will be concluded in a reasonable time.

This means, according to the Court, there must be a binding legal act, subject to judicial review, when an application for inclusion on the positive lists is filed. And the Court added that only human-health protection is the relevant criteria to the exclusion of considerations of nutritional needs.

So, it has been interpreted by legal counsel for the Alliance for Health in the U.K. that what the Court has done has made it a EC responsibility to prove the substance being submitted as an addition to the positive list is unsafe. Makers and distributors must submit in the dossiers the information they believe allow the substance on

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 least until 31 December 2009, on the basis that dossiers are not given an unfavourable opinion by the European Food Safety Authority. Assuming that Member States support the principle of mutual recognition, dossiers filed in one country will provide derogation in another. These derogations, assuming they have met the required criteria for safety and bioavailability, will provide sufficient time for applications to be made to the positive list under the now much clearer and simplified procedures. Furthermore, the ECJ ruling makes it much more difficult for derogation or positive list submissions to be rejected as the burden of proof for lack of safety of a given nutrient has been firmly placed back in the regulator's court.

“The ANH therefore urges companies to make full use of the simplified dossier procedures pointed to by the ECJ – and so avoid the ban!” See more at: <http://www.alliance-natural-health.org/index.cfm?action=news&ID=183>.

The Health Food Manufacturers Association has been seeking help from American vitamin and mineral and other suppliers to assist in filing dossiers for a number of months. [See *NML*, Vol. 7, No. 4, Jan. 2004 and Vol. 7, No. 5, Mar. 2004.]

**CANADA REGULATES HOMEOPATHIC MEDICINES**

On July 27, 2005 Health Canada announced to persons seeking to

market homeopathic medicines that they are first required by law to obtain a product license, by submitting a product license application to the NHPD for assessment. This application must contain evidence supporting the safety, efficacy, and quality of the homeopathic product. Products meeting the required criteria will be authorized for sale and issued a product license (DIN-HM) that must appear on the label.

Assessment of product licence applications for HMs are conducted by the NHPD's Homeopathic Medicines Unit. The Unit currently numbers four assessment officers, all of whom are practitioners with training in homeopathy. Other members of the Directorate have similar training in homeopathy and are located in other key units within the NHPD.

Homeopathic medicines are treated differently than other natural health products in that they may contain Schedule 2 substances that are otherwise prohibited in natural health products.

Homeopathic Medicines are medicines that are manufactured from, or contain as medicinal ingredients, only those substances or sources referenced in homeopathic monographs and that are prepared in accordance with the following accepted homeopathic pharmacopoeia, as they are amended from time to time:

- Homeopathic Pharmacopoeia of the United States (HPUS)
- Homöopathische Arzneibuch (German Homeopathic Pharmacopoeia)(HAB)
- Pharmacopée française (French Homeopathic Pharmacopoeia) (PhF)
- European Pharmacopoeia (EuP)

- British Homeopathic Pharmacopoeia (BHP)

Providing that the following Schedule 2 substances are found in a recognized pharmacopoeia the Natural Health Products Regulations apply to homeopathic medicines manufactured from:

- Substances listed on Schedule D of the Food and Drugs Act
- Substances regulated by the Tobacco Act
- Substances listed on Schedule F of the Food and Drug Regulations
- Items on the restricted substances list in Part A of the Natural Health Products Compliance Guide
- Items on the prohibited substances list in Part A of the Natural Health Products Compliance Guide.

Other substances acceptable for inclusion in HMs are:

- Homeopathic medicines manufactured from any substance derived from an animal material.
- Nosodes, isodes, sarcodes, and allersodes provided they appear as monographs in at least one of the accepted homeopathic pharmacopoeia, as they are amended from time to time.

While HMs may include certain substances listed in Schedule 2 of the Natural Health Products Regulations, HMs manufactured from the following Schedule 2 substances are unacceptable as natural health products:

- Schedules I to V of the Controlled Drugs and Substances Act
- Schedule C in the Food and Drugs Act
- Homeopathic medicines intended for injectable use

The lists referenced above are all available on the NHPD's Web site at:

See HOMEOPATHIC MEDS-- on p. 10..

Natural Medicine Ties™  
[www.natmedlaw.com](http://www.natmedlaw.com)

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[www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/nhp\\_compliance\\_guide\\_parta\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/nhp_compliance_guide_parta_e.html).

IS THE NHPD ACCEPTING HM APPLICATIONS FOR SUBSTANCES SUCH AS KAVA, SYMPHYTUM AND ARISTOLOCHIA?

Yes. The NHPD will accept and assess all applications for products meeting the definition of a natural health product. These include applications for Kava, Aristolochia, and Symphytum (Comfrey).

While the NHPD will assess these applications, authorization for sale will only be granted if adequate evidence has been submitted to support the safety, efficacy, and quality of the product.

#### THE DIN TO DIN-HM TRANSITION.

Prior to the Natural Health Products Regulations, many HMs received market authorization as drugs and were issued Drug Identification Numbers (DINs). Under the Natural Health Products Regulations, homeopathic medicines issued DINs prior to January 1, 2004, will have until December 31, 2009 to obtain the appropriate DIN-HM. In the meantime, these products can continue to be sold as drugs with their DINs.

Since January 1, 2004, many stakeholders have already begun the process of transferring their HMs from DIN to DIN-HM rather than waiting until the December 31, 2009. Given this situation, the NHPD, in collaboration with the Canadian Homeopathic Pharmaceutical Association (CHPA) is exploring options and approaches to help facilitate this process and ensure that the transition from DIN to DIN-HM is as smooth as possible. It is anticipated that a final approach will be in place by September 2005.

#### AVAILABLE RESOURCE TOOLS FOR HMs.

The NHPD currently has two documents relating to HMs:

1. THE EVIDENCE FOR HOMEOPATHIC MEDICINES GUIDANCE DOCUMENT: provides detailed information on the safety, efficacy, and quality requirements for HMs. This document is currently available at:

[www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/guidance\\_documents\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/guidance_documents_e.html).

2. GOOD MANUFACTURING PRACTICES - SUPPLEMENTARY GOOD MANUFACTURING PRACTICES FOR HOMEOPATHIC MEDICINES: provides an outline of the specific requirements related to the people, places, and processes involved in the manufacture, packaging, labeling, and/or importation of homeopathic medicines. There are also requirements for product specification and stability. These supplementary guidelines are outlined in Chapter 2 of the Good Manufacturing Practices guidance document, which is available at: [www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/gmp\\_e.html#2](http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/gmp_e.html#2).

NHPD is currently reviewing all its guidance documents, including the two mentioned above. It is anticipated that the revised version of the EVIDENCE FOR HOMEOPATHIC MEDICINES GUIDANCE DOCUMENT will be available in fall 2005. There is no anticipated timeline as of yet for the SUPPLEMENTARY GOOD MANUFACTURING PRACTICES FOR HOMEOPATHIC MEDICINES.

For further questions regarding the regulations of HMs, do not hesitate to contact the NHPD's toll-free line at 1-888-774-5555. For more information go to: [www.healthcanada.ca/nhpd](http://www.healthcanada.ca/nhpd).

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#### NEW DIETARY INGREDIENTS

There is no end in sight for sponsors who submit notices of New Dietary Ingredients (NDIs) to FDA. But *NML* is slowly closing the gap for reporting on the most recent submissions. These current reports remind us of some lessons learned long ago — that submissions for multiple ingredient products must include information about all of the new ingredients, that test materials used must be related to the ingredients, and that previously marketed pharmaceutical products may not be dietary supplements. Lawyers are routinely cautioned in law school classes that if you mislead a judge in your pleadings or arguments, by citing erroneous cases or information, this will taint your future dealings with the court, even if you are correct in most everything you state. Law school professors explain that such behavior has a chance of caus-

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NEW DIETARY INGREDIENTS -- Continued from page 10...

ing trouble even for new and innocent clients. And *NML* readers should keep in mind that these notifications are eventually public information. A notification should not be submitted if it is incomplete, resulting in delays in obtain FDA "approval," as your competitors may learn what you are doing before your product is ready to market. Here are additional NDI summaries.

**SK Pharma Co., Ltd.**, a client of Rakesh M. Amin, Esq. of Chicago, Illinois, submitted an NDI on July 26, 2004, according to a letter from Amin dated October 18, 2004, in which a later letter certain portions of the earlier submission were requested to be kept confidential, including the general description, product description, product labeling information, and summary of all testing results. The October 18, 2004 letter also comments that the client was misidentified as Ztis, Inc. in the July 26 submission. However, there is a letter from Amin to FDA dated July 19, 2004 as well that identifies the client as Ztis, Inc. The public file contains the general description, product description and product labeling information and in this the reader learns that the ingredient is *Clematis mandshurica*, also called Wei Ling Xian, in the Chinese pharmacopeia. "The product SK1306X is marketed in Korea and Australia as JOINS® tablet and Cararthon®, respectively, and it is a purified extract from a mixture of three oriental herbal medicines that have been widely used to support healthy joints and cartilage in far East Asia." Under product labeling the public record includes a statement that "SK1206X is marketed as a 20 mg tablet and contains about 100 mg of *Clematis mandshurica* extract." Another statement is "Suggested Use: As a dietary supplement to support healthy joints and cartilage, take one tablet, 2-3 times daily." FDA responded to Rakesh M. Amin, Esq., concerning its client Ztis, Inc., on September 29, 2004, by a letter from Susan J. Walker, M.D., stating that the agency has significant concerns about the evidence upon which the company relies to support its conclusion that a dietary supplement containing "*Clematis mandshurica* extract" will reasonably be expected to be safe. FDA said the notification failed to explain the composition and manufacturing process and according to the notification, the product contains two other botanical extracts, namely, *Trichosanthes kirilowii* and *Prunella vulgaris*. Moreover, FDA said the composition and weight of the dietary supplement SK1306X is unclear. For example, on page 18 the notice states the tablets weigh 430 mg and contain 25% "*Clematis mandshurica* extract," whereas

on page 4 the notification states, the amount of "*Clematis mandshurica* extract" in 200 mg tablets should be 50%. Among other FDA comments is one that states that JOINS® tablet and Cararthon® are not described and therefore the relationship to the new ingredient is unclear. FDA wrote that the product may be adulterated and introduction in interstate commerce is prohibited. Dkt. No. 95S-0316, RPT. 250, sent to the Dockets Office October 22, 2004, and posted to the FDA Web site on December 2, 2004.

**American Research Institute of World Traditional Medicine**, of Rockville, Maryland, wrote FDA on July 19, 2004 through its attorney, Runan Zhang, Esq. of Washington, D.C., to give notice that it was going to market Shuanghuanglian – Healthy Respiration, containing extracts of Chinese herbs, honeysuckle, forsythia and root of skullcap, with latin binomials of, *Lonicera Japonica Thunh*, *Forsythia Suspensa (thumh) Vahl*, and *Scutellaria Baicalensis Georgi*. The product will be packaged in small bags with a mixture of 5 g of three ingredients, 1.5 g each of honeysuckle and skullcap and 2 g of forsythia. The condition of use will be chewing or making drinks with hot/cold water. Adults are recommended to take 1-2 bags, three times a day. Children under 2 should not take more than one-half bag a day. FDA responded on October 20, 2004 to Runan Zhang, Esq. by letter from Susan J. Walker, M.D., signed by Linda S. Pellicore, Ph.D. stating that FDA had concerns about the evidence upon which the company relies to support its conclusion that a dietary supplement containing Shuanghuanglian – Healthy Respiration will reasonably be expected to be safe. FDA said the notification did not contain documentation of the long history of use of the product. The notification fails to clearly identify the composition and manufacturing process for the new dietary ingredient. There is no mention of the source of raw materials, levels of active ingredients, product specification, methods of analysis, and purity. Moreover, FDA said the information submitted concerns the intravenous administration of a product whose relationship to the new dietary ingredient is unclear. It appears evident that the test substances are not the same as Shuanghuanglian – Healthy Respiration. For these reasons, FDA said the

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Photo Courtesy of Lloyd Library and Museum

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product may be adulterated and introduction of such a product into interstate commerce is prohibited. Dkt. No. 95S-0316, RPT 251, sent to the Dockets Office on November 4, 2004, and posted to the FDA Web site on December 2, 2004.

**Gencor Pacific, Inc.** of Virginia Beach, Virginia, wrote FDA on August 24, 2004 through its attorney, Steven Shapiro, Esq., of Ullman, Shapiro & Ullman of New York City, to give notice that it would market a new dietary ingredient, *Caralluma fimbriata* extract, made by Gencorp Pacific of Austin, Texas, a 20 year old company. The product will be marketed in powder form with a recommended dose of 500 mg twice a day. The product is proposed as a dietary supplement in weight management strategies. The file contained a report by Henry G. Preuss, M.D. of Georgetown University Medical Center. FDA responded to Steven Shapiro, Esq. and Vanessa Riviere,

Esq. by letter of November 10, 2004 from Susan J. Walker, M.D., signed by Robert J. Moore, Ph.D. stating that FDA has concerns about the evidence upon which the company relies to support its conclusion that the ingredient will reasonable be expected to be safe. FDA wrote it was unclear how the history of use of the plant, *Caralluma fimbriata*, related to the extract. According to the notification 100 g of raw plant is equivalent to 1 g of the new dietary ingredient, but this claim is not substantiated. And FDA said the materials used in the various tests reported and the ingredient called *Caralluma fimbriata* extract is unclear. Further, FDA said there were discrepancies in the descriptions of the solvents used to extract in Exhibits 3, 5, and 7. There was no information on the testing for residual hexane in one extraction procedure. For these reasons, and others, FDA told the company that the submission does not provide an adequate basis to conclude that the product will reasonably be expected to be safe. FDA advised that the product may be adulterated and is prohibited from interstate commerce. Dkt. 95S-0163, LTR 252, sent to Dockets Office on November 29, 2004, and posted to the FDA Web site on December 22, 2004.

**Kyowa Hakko Kogyo Co., Inc.** of Tokyo, Japan, through the American Institute for Biosocial and Medical Research, Inc. of Tacoma, Washington, wrote FDA on September 2, 2004 to give notice that it was submitting information about N-Acetyl-L-Hydroxyproline, to be supplied in tablets or capsules of 50 to 100 mg each. The conditions of use are not more than 300 mg daily with single servings of 50 mg to 100 mg each. The structure/function claim proposed is "A dietary supplement for

healthy joints." On November 22, 2004, FDA responded by a letter signed by Linda Pellicore, Ph.D. for Susan J. Walker, M.D. to Richard Conant, V.P. of AIBMR Life Sciences, Ind. stating that it is not readily apparent that the new ingredient is a dietary supplement. Therefore, FDA cannot determine whether it may be lawfully marketed at this time. Nevertheless FDA stated that the ingredient is not a natural product and it is not a constituent of human or animal cells and is not a product of mammalian proline or hydroxyproline metabolism. Moreover, FDA's letter stated that the ingredient appears to involve test materials previously described as the pharmaceutical AHYP 200, a product of Chem.-pharm Fabrik, GmbH, Germany; a trademarked product of Merrell-Pharma, Germany; and Oxaceprol 200, a product of Chephasaar, Germany; and Jonctum. The relationships among these materials is not stated. For these reasons the information submitted does not provide an adequate basis that the ingredient will reasonably be expected to be safe. Therefore, the ingredient may be adulterated and introduction into interstate commerce is prohibited. Dkt. No. 95S-0316, RPT 253, sent to the Dockets Office December 3, 2004, and posted to the FDA Web site on December 22, 2004.

**ArtJen Complexus, Inc.** of Windsor, Ontario, wrote FDA on August 27, 2004 that it would market a new dietary ingredient,  $\alpha$ -cyclodextrin that is trademarked as FBCx™. The supplement will be in the form of tablets containing 1.0 g of  $\alpha$ -cyclodextrin or chewable tablets containing 1.0 or 2.0 g of  $\alpha$ -cyclodextrin. Recommended use is two 1 g tablets or chewable tablets

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or one 2 g chewable tablets be consumed within one hour, before, after or during the consumption of a fat containing meal. The notice was based in part on information from the Joint FAO/WHO Expert Committee on Food Additives. FDA responded by letter of November 22, 2004 to Joseph D. Artiss, Ph.D., from Susan J. Walker, M.D., and signed by Linda S. Pellicore, Ph.D. The FDA letter states the agency has concerns about the evidence upon which the company relies because there is no information about the product specifications. According to the Joint Committee report there is no established ADI for the ingredient's "use as a carrier and stabilizer for flavours, colours, sweeteners, as a water-solubilizer for fatty acids and certain vitamins, as a flavour modified in soya milk, and as an adsorbent in confectionary." The Joint Committee did not consider exposure from dietary supplements when making there conclusions about exposure levels and safety of a food additive. Because of this, FDA said it could not make an assessment of safety because the notice fails to include adequate identify information to characterize the specific  $\alpha$ -cyclodextrin intended to be marketed in the new ingredient. Moreover, the statement that the ingredient is GRAS under the conditions of use in foods, not as an additive. The proposed use is for a dietary supplement, a different use, which is not GRAS. See 21 CFR 170.30(i). For these reasons, FDA stated that the product may be adulterated and it is prohibited from interstate commerce. Dkt. No. 95S-0316, RPT 254, received at the Dockets Office on December 3,

2004 and posted to the FDA Web site on December 22, 2004.

**Anatanais Corp (Suisse) SA** of Geneva, Switzerland, wrote FDA on August 29, 2004 giving notice that it would market Argan Oil, extracted from *Argania spinosa* (L.), Skeels. The product will be marketed as softgels composed of 47.3% Gelatin, 17.2% Glycerin, and 35.5% water containing 300 mg of Argan Oil each. The company states that Argan Oil is rich in Tocopherols and Vitamin E. FDA replied by letter of November 30, 2004 to Lorens Safavi, General Manager, from Susan J. Walker, M.D. stating that FDA has concerns about the evidence upon which the company relies to support its conclusion that the supplement containing Argan Oil will reasonably be expected to be safe. FDA stated that the notification fails to identify the ingredient, its composition and manufacturing process. Also, FDA said that none of the material submitted in support of the notice appears to be related to the product. For these reasons, there is not an adequate basis to conclude that the product will reasonably be expected to be safe and since there is inadequate information, it may be adulterated. Therefore the product may not be introduced into interstate commerce. Dkt. No. 95S-316, RPT 255, sent to the Dockets Office on December 15, 2004, and posted to the FDA Web site on January 4, 2005.

**Naturasol** of Bogata, Columbia, wrote FDA on September 21, 2004 to give notice that it would market a product named, Vira Vira, containing dehydrated plant material of *Achyrocline satureioides* (Lam.) DC. English translations were sent September 24, 2004 and on Octo-

ber 11, 2004 additional material was submitted in response to FDA's telephone call. FDA responded on December 6, 2004 by letter to Ms. Tomasina Uboldi from Susan J. Walker, M.D., signed by Robet J. Moore, Ph.D., stating that FDA carefully considered the information and has concerns about the evidence upon which the company relies to conclude the product will reasonably be expected to be safe. FDA specifically stated that English translations of various articles and pages of botanical handbooks were not provided. Further, that there was no documentation of the history of use of the product. And the notice fails to identify the composition of Vira Vira and to clarify the relationship of the substances used in various tests with the ingredient. The notice does not explain how the studies are relevant to evaluating the safety of the ingredient. Because of these reasons, the product may be adulterated and it may not be entered into interstate commerce. Dkt. No. 95S-0316, RPT 256, received at the Dockets Office December 21, 2004, and posted to the FDA Web site on January 4, 2005.

**Naturasol** of Bogata, Columbia, wrote FDA on September 21, 2004 to give notice that it would market a product named, Anamu, containing dehydrated plant material of *Petiveria alliacea* (L.). English translations were sent September 24, 2004 and on October 11, 2004 additional material was submitted in response to FDA's telephone call. This product will be sold in 500 mg tablets with suggested use of 2 to 3 tablets three times a day. FDA responded on December 6, 2004 by letter to Ms. Tomasina Uboldi from

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Susan J. Walker, M.D., signed by Robert J. Moore, Ph.D., stating that FDA carefully considered the information and has concerns about the evidence upon which the company relies to conclude the product will reasonably be expected to be safe. FDA specifically stated that English translations of various articles and pages of botanical handbooks were not provided. Further, that there was no documentation of the history of use of the product. And the notice fails to identify the composition of Anamu and to clarify the relationship of the substances used in various tests with the ingredient. The notice does not explain how the studies are relevant to evaluating the safety of the ingredient. Because of these reasons, the product may be adulterated and it may not be entered into interstate commerce. Dkt. No. 95S-0316, RPT 257, received at the Dockets Office December 21, 2004, and posted to the FDA Web site on January 4, 2005.

**Syntech (SSPF) International, Inc.** of Walnut, California, wrote FDA on September 17, 2004, to give notice it would market, Betaphrine, a chemical known as Isopropyl octopamine hydrochloride, that is a derivative of the natural substance, octopamine. The ingredient is included in dietary supplements for the purpose of supporting the maintenance of normal weight. The recommended use is 80 mg per day with a warning that persons with low blood pressure should not take the product. FDA requested additional information and responded to Narsh B. Zhu, president, by letter of December 6, 2004 from Susan J. Walker, M.D., signed by Robert J. Moore, Ph.D., stating that FDA concludes this product is not a new dietary ingredient under 21 USC 321(ff)(1), since it is a chemically synthesized substance. Betaphrine is not a concentrate, metabolite, constituent, extract, or combination of any ingredient described in the law. FDA stated that this product is a new drug requiring FDA approval under 21 USC 355(a) prior to marketing. Introduction of a new drug without approval is prohibited by the Act. FDA did not review the information submitted because of it is a new drug. Dkt. No. 95S-0316, RPT 258, sent to the Dockets Office on December 23, 2004, posted to the FDA Web site on January 4, 2005.

**MTC Industries, Inc.** of Great Neck, New York, notified FDA by letter of September 27, 2004 that it would market a new dietary ingredient, L-Arginine alpha-ketoglutarate, supplied in 1,000 mg tablets. Suggested use for adult men is 2 tablets in the morning be-

fore breakfast and 2 tablets in the afternoon on an empty stomach. For adult women the suggested use is 1 tablet before breakfast and 1 tablet in the afternoon on an empty stomach. The notification included web pages about Nitrox Extra Strength capsules and NoX<sub>2</sub> capsules. FDA responded to Mr. Dini Philip, Sales Manager, by letter of December 10, 2004, signed by Robert J. Moore, Ph.D. for Susan J. Walker, M.D., stating that the notification does not include any basis for the conclusion that the product is an amino acid within the meaning of 21 USC 321(ff)(1)(D). Nevertheless FDA has evaluated the information provided and FDA was unable to determine the identity of the "L-Arginine alpha-ketoglutarate (2:1)" product. Therefore, FDA cannot conclude that the product you are selling is quantitatively and qualitatively similar to the products referenced on the web pages. For these reasons, FDA said that the information provided does not provide an adequate basis to conclude that the product when used as suggest will reasonably be expected to be safe, and therefore, introduction of the product in interstate commerce is prohibited. Dkt. No. 95S-0316, RPT 259, sent to the Dockets Office December 27, 2004, and posted to the FA Web site on January 4, 2005.

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### DIETARY MANIPULATION CHANGES BIOMARKERS AS INDICATORS OF CANCER RISK REDUCTION

**F**DA, the National Cancer Institute (NCI) and Office of Dietary Supplements (OSI) held a joint workshop on July 12-13, 2005 at the NIH campus in Bethesda, Maryland. The two-day program brought together scientists to discuss the current status of knowledge of biomarkers when diets and exercise are modified to reduce cancer risk. Participants included about 60 top researchers, including people like Bruce Ames, Ph.D. at Children's Hospital Oakland Research Institute, Margot Cleary, Ph.D. of the Hormel Institute, Mary Hager, Ph.D. of the American Dietetic Association, Gary Stoner, Ph.D. of Ohio State University, and many others from private research organizations and the government agencies. Here is a brief summary of points made at the workshop.

Ross L. Prentice, Ph.D. of the Fred Hutchinson Cancer Research Center in Seattle spoke about the ongoing work to link biomarker changes to chronic disease risk in the Women's Health Initiative, already shedding much light on the need for diet and exercise modification.

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DIETARY MANIPULATION -- Continued from page 14...

Padma Maruvada, Ph.D. of the NCI spoke about early detection of cancer and validating biomarkers. He reviewed the July 2004 workshop sponsored by FDA and NCI on statistical approaches to validate biomarkers.

Arthur Schatzkin, M.D., Dr. P.H., M.P.H., of the NCI spoke about surrogate end points in observational and intervention studies of malignant disease. An example of surrogate end points is epithelial cell proliferation. Surrogate end points may not be valid for all exposures. And complications arise when a single biomarker (a pro-inflammatory cytokine, for example) has contradictory effects on carcinogenesis. This requires an understanding of the casual structure underlying the interrelations of exposures, surrogate, and cancer.

Robert D. Vardiff, M.D., Ph.D. of the University of California at Davis spoke about histological markers, saying that histological criteria of malignancy are used for the diagnosis of cancer. Any other marker of cancer must be confirmed by histopathology. Grading of neoplasms is not perfect. There is hope that molecular techniques will supplement, or even supplant, the microscopic exam. The discovery of protein specific antigen (PSA) has been a great triumph to this approach.

Karen Aubron, Ph.D., of North Shore LIJ Institute for Medical Research spoke about whether Indole-3-Carbinol changes in cervical Intraepithelial Neoplasia (CIN3) can be extrapolated to other food components. She mention four possibilities for food components to decrease pathology in the cervix.

Michael J. Wargovich, Ph.D. of the University of South Carolina School of Medicine spoke about what diet-induced alterations in colorectal polyps and abberant crypts indicate for risk. Crypts aid in the process of absorption of water and nutrients. Crypts are composed of four or more cell types held together by connective tissue and interlaced with contact with cells of the immune system. The system is intricately constructed and disruption of the intercellular network quickly results in the death of colonocytes, so that it is almost impossible to culture and maintain normal epithelium. Two types of preneoplastic lesions in crypts have been identified and the trick is to know which might progress to cancer and this is a rich area for biomarker development.

Roderick H. Dashjwood, Ph.D. of the Linus Pauling

Institute at Oregon State University spoke about xenobiotic metabolism relevance to cancer, saying since L. C. Wattenbergs's classification scheme of chemoprevention of categorized cancer in 1985, the possibility that dietary factors might inhibit carcinogen-activating enzymes has become highly attractive for development of chemotherapeutic agents. More than 250 papers have described modulation of mutagenicity and carcinogenicity of one chemical class alone – the cooked meat heterocyclic amines. He said that most chemopreventive agents probably work by more than one mechanism.

James S. Felton, Ph.D. of the Lawrence Livermore National Laboratory questioned what do diet-induced changes in Phase I and II enzymes tell us about prevention. Cooked protein contains PhIP, now classified by the National Toxicology Program as a “reasonably anticipated human carcinogen.” This and other heterocyclic amines are metabolized by cytochrome P4501A2 to N-hydroxy or ring-hydroxy intermediates that can then be either detoxified by conjugation to phase II enzymes, like UDP-glucuronosyltransferase or activated by other phase II enzymes, which presumably act as leaving groups. The reactive free radicals formed during the activation bind almost exclusively to the C-8 of guanine causing DNA adducts, mutations, chromosomal abnormalities, and cancer. Changes in ratios of PhIP and other metabolites are continuing to be studied.

Lynnette R. Ferguson, D. Phil (Oxon), D.Sc. of the University of Auckland spoke about DNA (oxidative) damage and repair, saying that when such damage is repaired, a slow steady state of oxidized DNA remains  
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#### PHOTOGRAPHS FROM LLOYD LIBRARY AND MUSEUM

Page 4 - Goldenseal (*Hydrastis canadensis*) from AMERICAN MEDICINAL PLANTS by Charles F. Millsbaugh, M.D. 1887

Page 8 - Valerian (*Valeriana officinalis*) from MEDICAL BOTANY by John Stephenson, M.D. and James Morss Churchill, F.L.S. 1829

Page 12 - Ginseng (*Panax quinquefolium*) from THE FAMILY FLORA AND MATERIA MEDICA BOTANICA by Peter P. Good 1847

Page 16 - Evening Primrose (*Oenothera biennis*) from AMERICAN MEDICINAL PLANTS, *supra*, 1887

MANIPULATION -- *Cont'd from p. 15.*

and may lead to mutations. Persons with high risk for chronic pancreatitis, uncreative colitis, and Crohn's disease, for examples, show elevated levels of modified DNA bases as compared to the normal population. Measuring urine excretion of the accepted biomarker 8-hydroxy-2'-deoxyguanosine (8OhdG) could show reduced formation of oxidized DNA bases or reduced repair of such damage. Other assay measures may be more informative.

Robert M. Russell, M.D. of the Jean Mayer Boston USDA Human Nutrition Research Center on Aging spoke about the clinical significance of diet and changes in oxidative markers. He said studies of beta-carotene and alpha-tocopherol demonstrate a paradox of a protective effect of dietary antioxidants against DNA damage versus the procarcinogenic effects of antioxidants seen in certain intervention studies could also indicate that the DNA damage is not a good biomarker to follow. He said there have been no prospective epidemiological or intervention studies performed showing that modification of oxidative DNA damage by antioxidant correlates with lower incidence of invasive cancer. The problem is measuring true antioxidant capacity or performance *in vivo*.

Henry J. Thompson, M.D. of Colorado State University spoke about the common sites of action in oxidative damage. Products of guanine oxidation have been most extensively investigated and characterized. 8-hydroxy-2'-deoxyguanosine can give rise to G to T transversion mutations in key genes known to be involved in the development of cancer. These observations provide a basis for using

this compound as a biomarker. But evidence that diet and physical activity can modulate steady state levels of this and other DNA oxidation products. There are still problems in collecting samples, what amount to use, and there is a need for additional methodological work before using this analyte as a cancer biomarker.

Leonard H. Augenlicht, Ph.D. of the Albert Einstein Cancer Center spoke about cell proliferation, saying that the effect of diet modulating the development of human intestinal cancer can be studied in the mouse. He and others have demonstrated that the Western Diet mimics risk factors for colon cancer and that targeted inactivation of *p27<sup>Kip1</sup>* is sufficient to initiate tumor formation, but not if the mice are fed a standard chow diet. This and other models of intestinal cancer can be useful in dissecting cellular and molecular pathways, and their interactions, that are involved in intestinal cancer. Other diet research has shown changes with additional calcium and vitamin D.

Lenna Hilakivi-Clarke, Ph.D. of Georgetown University talked about cell differentiation in mammary epithelium in the rat, specifically when terminal end buds appear that play a role in mammary gland development. They contain cap cells interpreted to represent a pluripotent stem cell population that potentially gives rise to breast cancer. She said pregnancy reduces breast cancer only if the woman is under 18 when she has her first child and it increases breast cancer risk in women over 30 at the time of first pregnancy. It is not clear why pregnancy-induced mammary epithelial differentiation is not sufficient to reduce breast cancer in all women. Studies have recently showed that excessive pregnancy weight gain or



Photo Courtesy of Lloyd Library and Museum

an exposure to a high-fat diet increases pregnancy estradiol and leptin levels and breast cancer risk. Other times when hormonal changes occur are being studied as well. Expression of cavolin-1 in differentiated epithelial cells may be closely linked.

Priscilla A. Furth, M.D. of Georgetown University spoke of apoptosis and the markers being used currently. Routine processing with hematoxylin and eosin staining, with an experienced observer is one method. Electron microscopy can be used, but is expensive and laborious. DNA can be isolated and fractionated through a gel and the DNA will appear as a ladder if a significant number of cells are undergoing apoptosis. The sensitivity of the technique can be improved by using an isotope or other labeling of the DNA. A third approach relies on identification of the activation of specific enzymes during apoptosis. In tissue culture cells, DAPI staining can be used to enhance

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visualization of fragmented nuclei, and annexin V staining can be used to detect the increase in externalized phosphatidylserine residues as the cell membranes are disrupting during the apoptosis but these techniques are less useful for recognition of apoptotic cells in intact tissue.

Ian M. Thompson, M.D. of the University of Texas Health Science Center, spoke of PSA and Prostate Cancer as a case study, saying that PSA was discovered in the early 1970's and began to be used clinically in the 1980's, it is now used as a screen test in about 50 percent of men over 50 years of age. It is the most common test used for diagnosis of prostate cancer. Thompson's group discovered that 15 percent of men with PSA under 4.0 ng/ml had prostate cancer and 15 percent of these had high-grade cancer. So now it is not the value of the PSA that is diagnostic of a disease free state. Data now suggests that dietary manipulation may affect PSA in the absence of cancer risk. PSA stepwise decreases with increasing quintile of body mass index. Obesity is associated with lower testosterone and higher estrogen, therefore this suggests that obese men may have suppressed PSA production. Dietary manipulations that affect androgens, estrogens, and other modulators of PSA production could affect this marker without affecting disease status. Studies may have to rely on biopsy correlations.

Carol J. Fabian, M.D. of the University of Kansas Medical Center, spoke about the links between mammary density and cancer risk. She said mammary density is reflective of the relative amount of epithelium, stroma, and fluid compared to fat. It

is apparent that stroma plays a major role in visualized density. Mammary density could be measured at the time of annual mammary exams with no additional risk and little extra cost. Histologic examination of tissue sections corresponding to high vs low density in a predominantly postmenopausal population showed no significant difference in the frequency of ductal and lobular structures but significantly higher collagen content, extent of fibrosis, and expression of two stromal proteoglycans, lumican and decorin. Expression of these can be positively associated with the development of breast cancer. Mammary density is also associated with other risk factors, including family history, serum IGF-1 in premenopausal women, serum prolactin, sex hormone binding globulin in postmenopausal women, and hormone replacement therapy. Several methods to measure density have been developed. Patterns identified on films, the BIRADS system and the continuous density measurement system assessed by planimetry.

Stephen Barnes, Ph.D. of the University of Alabama at Birmingham, spoke about genomics, proteomics and metabolomics. To address how a complex system responds, he said we currently have DNA microarrays to measure gene expression, proteomics methods to identify proteins, examine protein abundances and protein modifications and metabolomics to determine how metabolite levels change. Each of these methods is a *tour de force* within the context of analytical chemistry available in the 21<sup>st</sup> century. Barnes explained how each of these processes worked and concluded that slices of a complex system are like what Einstein considered in developing theories about relativity. We photo-

graph a moment in the system and assume it must be related. We need ways to know the time and spatial domains. We assume that concentrations of chemicals produce biological effects, but it is more likely that the changing, wavelike variation in concentration are the real signals in a cell. Measuring those changes is the challenge.

[NML has included this summary of the workshop to allow non-scientists and basic scientists to get a glimpse of what research is being done in these measurement methods that may be affected by dietary and exercise modification. If you want to measure the affects of a new dietary ingredient, these speakers may be a good place to ask your questions and focus your attention in order to develop appropriate methods.

For those who use natural remedies with hundreds of ingredients and compounds, the science is complex and sometimes a mystery. We are learning more, but much more inquiry must take place for us to understand cancer. More information about this can be obtained from Peter Greenwald, Division of Cancer Prevention at NCI, Paul Coates at ODS, and Kathleen Ellwood at FDA. – Ed.]

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#### NEW CANADIAN WEBSITE

The new intergrated Health Canada web site is now online. Take a look and start surfing [www.healthcanada.gc.ca](http://www.healthcanada.gc.ca).

The section pertaining to natural health products can be found at: [www.healthcanada.gc.ca/nhp](http://www.healthcanada.gc.ca/nhp).

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its intended use in foods. Otherwise, the product would be adulterated under 21 USC 341(a)(2)(C). Adulterated foods may not be marketed in the U.S. Dkt. No. 97S-0163, Ltr. 828, received at the Dockets Office on May 13, 2005, Entered the file on May 16, 2005, and posted to the FDA Web site on May 20, 2005.

**Lidtko Technologies Corporation** of Tempe, Arizona, wrote FDA on May 11, 2005 giving notice that it would make certain claims for the product, DiabeStat™, namely, *“Introducing a patented product for the lowering of peak, postprandial blood glucose levels, the reduction of urea formation, and the lowering of cholesterol, triglycerides, and homocysteine levels among individuals with elevated levels. This revolutionary product is a natural blend of nutrient, available in convenient capsule form, and is supported by three patents. In preliminary tests, the consumption of one capsule before each meal has resulted in very significant reduction in glucose, BUN, cholesterol, triglycerides, and homocysteine among individuals with high initial levels.”* There was no information about the content of the product, but the three patents listed were No. 6,602,909, No. 5,559, 142, and No. 3,080,234. FDA responded by a letter, dated, May 24, 2005, from Susan J. Walker, M.D., to Ronald G. Sturtz, stating that the claims: *“for the lowering of peak, postprandial blood glucose levels ... lowering of cholesterol, triglycerides, ... among individuals with elevated levels”* and *“consumption of one capsule before each meal has resulted in very significant reduction in glucose ... cholesterol, triglycerides, ... among individuals with high initial levels,”* were claims for treating diseases and that if these claims are used the product will be regulated under the drug provisions of the Act. Dkt. No. 97S-0163, Ltr. 829, received at the Dockets Office, Entered in the file, and posted to the FDA web site, all on June 22, 2005.

**Market American, Inc.** of Greensboro, North Carolina, wrote FDA on May 4, 2005 to give notice that the company would use seven statements of claim about its new product, Glucosatin®, that is composed of vitamin C, vitamin D3, zinc sulfate, copper gluconate, manganese sulfate, glucosamine HCl, *Scutellaria baicalensis* root, oleanolic acid, boswellia gum resin extract, hops strobile extract, and other ingredients. FDA responded on May 24, 2005, by letter from Susan J. Walker, M.D, to James L. Wilmer, Ph.D., director, scientific affairs,

stating that three of the seven claims were claims to prevent or treat arthritis. These claims were: *“ [M]ay help control joint inflammation and assist in the regeneration of cartilage ... control bone loss and joint pain,” “ [A]ssist you in pain-free movement,”* and *“[A]nti-inflammatory and help regenerate healthy cartilage.”* FDA’s letter further stated that if these claims were used the product would be regulation as a drug under the Act. Dkt. No. 97S-0163, Ltr 830, received at the Dockets Office, Entered in the file, and posted to the FDA web site, all on June 22, 2005.

**MD Drinks, Inc.** of Santa Monica, California, wrote FDA May 27, 2005 in response to FDA’s letter of May 10, 2005 concerning the product, Function Urban Detox, stating it would eliminate the claim concerning hangovers and state only that: *“FUNCTION is a physician-developed beverage that fights hangovers, helps protect your liver, helps reduce the effect of urban pollution on your lungs and sinuses, and boost your immune system.”* FDA responded on June 14, 2005 with a letter signed by Susan J. Walker, M.D. to Alexander P. Hughes, stating that the revised claim is a claim that continues to be a claim that subjects the product to regulation as a drug. The disease claim does not come solely from the use of the words “cure” or “prevent,” FDA said, but rather from the fact the product is being represent for use for hangovers. FDA pointed to the January 6, 2000 preamble to the final rule on structure/function claims (65 FR 1000) as a place where FDA described “alcohol intoxication” as a disease. FDA said use of the claim would result in regulation of the product as a drug. Dkt. No. 97S-0163, Ltr. 831, received at the Dockets Office, Entered in the file, and posted to the FDA web site, all on June 22, 2005.

**Organix-South, Inc.** of Clearwater, Florida, wrote FDA on April 22, 2005 to give notice that it would use certain descriptive claims on the products, Ajay, Anita, Kama, Manish, Narsimha, Nartana, Neem, Nirmal, Nisha, Pavan, Sahana, Thera Neem, Thera Neem Leaf, Usha, and Vijay. Attached to the letter in the FDA public file is a label for the product Narsimha. No other labels were present. The label is essentially illegible because the type is so small, but under the product name, the words “Heart Cholesterol Support” are visible. The supplement facts box indicates ingredients are Commiphora mukul SC02 Extract 1:100, Tumeric extract and other ingredients.

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On this company's web site the following statements are made about this product: "TheraVeda's Narsimaa Formula was developed using unique herbs to support the heart by regulating lipid metabolism and promoting healthy cholesterol levels."

*Narsimha*, in the Indian language, means the lion among men, or Lionhearted. Always speak the truth. Do not hold anger. Do not be cruel. Ayurvedic medicine teaches two types of rasayanas, prescriptions of herbs, and prescriptions of behavior, such as these recommendations for maintaining the health of the heart."

"Commiphora mukul, also known as guggul or guggulu, is a resin collected from the bark of the myrrh tree. The "guggullipid" extracted from the herb is widely reported to lower levels of LDL and raise levels of HDL, helping the arteries remain flexible in the early stages of high blood pressure. Turmeric is a source of the antioxidant curcumin. Exactly how curcumin affects high blood pressure is not entirely understood, but scientists theorize that it keeps the white blood cells known as granulocytes from causing inflammation in the lining of the arteries. Tinospora is a bitter, stimulating good digestion - thorough digestion of food shortens the time bloodstream concentrations of fats are elevated after a meal of fatty foods. Defatted fenugreek is a mild diuretic, relieving fluid without depleting minerals, and provides beneficial fibers, helping to prevent fat accumulation."

"Ayurveda teaches that almost any heart condition benefits from a calm, orderly, planned lifestyle. Avoiding heavy meals, getting a good night's sleep, and patiently dealing with stress will make any treatment for the heart work better. Following the ethical rasayanas while taking the herbal rasayanas always is best for the heart. \*These statements have not been evaluated by the Food and Drug Administration (FDA). These products are not intended to diagnose, treat, cure, or prevent any disease." – <http://www.theravedaherbs.com/narsimha.html>, accessed July 26, 2005 — Ed.]

FDA responded to the notice on June 14, 2005, by letter from Susan J. Walker, M.D. to Robert S. Rister, Consultant, stating that the statements, among others, "Heart Cholesterol Support" and [S]upport healthy LDL ... levels..." were statements that made people believe the product is intended to affect blood cholesterol that is already in the normal range and this makes them implied

disease claims. Other claims on the label also imply the product will also prevent coronary heart disease, including, "[H]elping the arteries remain flexible," and "[K]eeps the white blood cells known as granulocytes from upsetting balance in the lining of the arteries." FDA's letter stated that if these claims are used, the product will be regulated as a drug. Dkt. No. 97S-0163, Ltr. 832, received at the Dockets Office, Entered in the file, and posted to the FDA web site, all on June 22, 2005.

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### WORKSHOP ON THE SAFETY OF BLACK COHOSH IN CLINICAL STUDIES

Last November 22, 2004, the National Center for Complementary and Alternative Medicine and the Office of Dietary Supplements, both agencies of the National Institutes of Health, held a workshop on the safety of black cohosh in Bethesda, Maryland. Also participating in this meeting were representatives from the Office of Research on Women's Health, NIH; the National Cancer Institute; the National Institute on Aging; the Food and Drug Administration (CDER and CFSAN, FDA); American Herbal Products Association; and Center for Science in the Public Interest. The report was recently made available by NIH.

This meeting was called in response to several case reports of hepatotoxicity in the medical literature and an abstract referencing data from a murine model of breast cancer that raised questions about the safety of black cohosh. Because NCCAM and other Institutes and Centers at the NIH support clinical studies on black cohosh, the workshop was convened to reflect on what is currently known about risks associated with this dietary supplement ingredient. First and foremost was the concern for the safety of research subjects. Given ambiguity and uncertainty in the scientific information available when viewed in aggregate, it was not clear what additional actions if any NIH should take to protect human research subjects. Thus, the meeting was convened to:

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[www.NatMedLaw.com](http://www.NatMedLaw.com)

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- Gain a better understanding of the nature of the reported hepatotoxicity in humans;
- Understand what might be warranted to better understand the effects of black cohosh on metastatic processes reported in a mouse model; and
- Clarify steps that investigators might take to continue to protect participants in studies of black cohosh.

The desired outcomes for this meeting were focused on issues related to the mandate of the NIH and its role in supporting biomedical research. The meeting was not expected to produce a definitive statement on the safety of this botanical. That would certainly be beyond the scope of a one-day workshop. Similarly, the meeting was not expected to address questions concerning efficacy, which await the findings of several ongoing studies supported by the NIH. Finally, participants were not expected to develop an extensive research agenda. Rather, this interactive forum was to provide a better understanding of:

- the nature of the reported hepatotoxicity in humans;
- what approaches might be warranted to better understand the effects of black cohosh on metastatic processes reported in a mouse model; and
- what investigators and sponsors could do to further protect participants in studies of black cohosh if warranted.

Participation and ideas were solicited from a group of scientists representing a broad range of disciplines (e.g., pharmacology, pharmacognosy, toxicology, endocrinology, hepatology, oncology, gastroenterology, and medicine) that reflect the multidisciplinary nature of the topic.

“This report summarizes the presentations and discussions from the November 22 workshop and is organized into three general areas: 1) background information on safety and efficacy of black cohosh; 2) data from a murine model of breast cancer and metastases to lung associated with black cohosh; and 3) case information on suspected toxicity associated with use of black cohosh products.”

“Meeting participants were asked to address the question that catalyzed the development of this workshop, namely what, if anything, should NCCAM and other

Institutes and Centers at NIH supporting clinical studies on black cohosh, do to ensure the protection of subjects? The following summarizes this discussion. The group was unanimous in its support for characterizing and standardizing botanical products used in research. The group recognized that control of commercially available products is beyond the purview of the NIH, since it is not a regulatory agency. In cases of adverse events associated with black cohosh or other botanical substances, it is critical to obtain as much information about the product taken or, better, a sample of the product for subsequent analysis. Non-standardization of product presents an enormous barrier to understanding the safety and efficacy of botanicals, including black cohosh.”

“With respect to preparation, possible adulteration, and contamination, investigators should be required to conduct an independent verification of content of material used in research, noting such things as disintegration time, presence of heavy metals, microbial and pesticide analysis, and the like - even in cases where the preparation comes from a reputable source. Verification should be done for in vitro studies as well as studies involving animal and human subjects. The group noted that it would be extremely helpful if publications included more information on the extraction procedures and chemical characterization of products used in studies. Similarly, they noted that study sections reviewing grant applications should be alerted to problems associated with verification of black cohosh and other botanicals. Verification costs should be allowable as part of the research grant budget.”

“NCCAM’s policy on the quality of natural products addresses many of the aforementioned issues. (See <http://nccam.nih.gov/research/policies/naturalproducts.htm>). NCCAM is continuing to strengthen its policies with respect to quality of botanical products used in research supported by the Center. Applicants will be required to submit documentation supporting verification of substance(s) under study prior to any award being made. NCCAM is also planning to conduct random tests of products used in research projects. Investigators will be required to save and store specimens for such testing. The group noted that the conditions of storage are important to preserve the integrity of study material. This may require storing samples at -20 degrees to slow degradation.”

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“Meeting participants noted that it is critical for NCCAM to communicate these expectations clearly to the field. Recently NCCAM modified its website to make it easier for investigators to find policies and requirements associated with NCCAM-funded and NIH-funded research. We will continue to work on improving communication. The discussion then turned to Dr. Davis’ presentation of data from the murine model of breast cancer. The abstract from this study had raised questions concerning safety of black cohosh because of increased incidence of metastatic lesions in lung among animals fed black cohosh. Participants reported that the results of this study were difficult to interpret, given no difference in overall survival or numbers of tumors when animals fed black cohosh were compared with animals fed the control diet. Moreover, Dr. Davis indicated that work remains to complete the histology component of the research. The study has not yet been published in a peer-reviewed journal. Nevertheless, the workshop participants believed that the study should be replicated and that other research on the effect of black cohosh on different stages of tumor genesis should be pursued using different approaches, as suggested by Dr. Green.”

“With respect to black cohosh and human breast tissue, there is scant evidence that black cohosh will harm healthy women. Data were presented indicating that black cohosh is not estrogenic. Thus, there appears to be little reason to do mammography on healthy female research subjects participating in studies of black cohosh. However, the use of black cohosh to treat hot flashes associated with treatment for breast and prostate cancer raise additional safety concerns. For women who have been treated for breast cancer, it would seem reasonable to screen for recurrence and metastases, actions that are consistent with standard care. Too little is known about the effect of black cohosh on prostate tissue to say anything more at this time.”

“The workshop participants expressed interest in ongoing efficacy studies of black cohosh for a range of symptoms and health problem, many of which are associated with menopause. The group noted that there are few long-term clinical studies of this dietary supplement. They also noted that several studies had deficiencies in design that made interpretation of findings difficult. For example, many studies use a cross over design, but it is not clear that all such studies have used a sufficiently long washout period. Discussions at the workshop noted the number

of organ systems with which black cohosh interacts. This raised additional interest in the underlying mechanism(s) of action of this dietary supplement ingredient. For example, the effect on vasomotor symptoms may not be due to any estrogenic properties but rather dopaminergic and/or serotonergic properties. More research is clearly needed to understand the pharmacological mechanisms of action for this botanical.”

“Hepatotoxicity and black cohosh were topics of extensive discussion. Ultimately, the workshop participants concluded that a balanced approach be taken with respect to this issue. On the one hand, millions of people have taken black cohosh with very few adverse events reported. On the other hand, those cases of hepatotoxicity associated with products that are known to contain black cohosh and believed to be free from other substances of known toxicity raise concern. Thus, the workshop recommended that appropriate safety parameters should be used in clinical studies of black cohosh. Such measures would include monitoring liver function throughout the study period, specifically looking at alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin. And depending on what is being studied, investigators should consider screening potential subjects for liver function to exclude individuals with pre-existing liver problems.”

“At this time, there is no known mechanism with biological plausibility that explains any hepatotoxic activity of black cohosh. Studies using mass spectrometry show that black cohosh contains catechols and phenols, which can be activated to quinone-type intermediates and trapped by glutathione or other sulfhydryls. These phenolic compounds, however, do not appear to be absorbed in animal models, and the conjugates are not detected in blood or urine. However, the possibility cannot be ruled out that such intermediates are generated in vivo. Animal models might provide useful information about what causes idiosyncratic liver damage. It would be helpful to understand the human metabolism of various black cohosh components, to see if these are replicated in specific animal models. And it is likely that we need to look beyond the usual mechanisms to understand how liver damage occurs. Use of genomic microarrays may be useful in exploring such mechanisms.”

“From an ethical perspective, potential subjects should be told about known risks and benefits from study participation. But the risks and benefits of black cohosh are

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yet to be determined on several levels. For example, workshop participants were not clear about the relevance of data from the murine model to humans. Metastatic disease was increased in the mice, but it did not alter survival time. As more information is accrued on the efficacy and potential risks of black cohosh, the information included in informed consent can be revisited and revised. The evidence of risk remains equivocal but certainly warrants continued monitoring. The workshop concluded that informed consent should inform potential subjects about known risks and benefits and note conflicting information on rare risks, such as hepatotoxicity, and steps to be taken during the study to monitor for those events. New information should also be shared with the study's Data Safety Monitoring Board (DSMB). And the need to re-consent subjects should be reviewed as new data and publications come forth."

The entire 40-page report was posted to the NIH website in July 2005 and may be found at: [http://nccam.nih.gov/news/pastmeetings/blackcohosh\\_mtngsumm.htm](http://nccam.nih.gov/news/pastmeetings/blackcohosh_mtngsumm.htm).

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### ECHINACEA INEFFECTIVE IN NEW STUDY USING LOW DOSES

**F**irst the National Institutes of Health studied St. John's Wort and concluded that it was not good for major depression. After criticism, NIH started another study to see if the herb was good for mild or moderate depression. That study is still proceeding and will not be finished for a couple of years.

Now a *New England Journal of Medicine* reports that *Echinacea augustifolia* root is not effective for the common cold. See *NEJM* 353:341-348, July 28, 2005. This study, led by Ronald Turner, M.D. at the University of Virginia School of Medicine in Charlottesville, used three extract preparations, with different properties, in 437 college student volunteers assigned to received a prophylaxis or treatment with one of the three preparations or a placebo. Type 39 rhinovirus was dripped into their noses, the students were "secluded" in a hotel room for five days, while scientists examined and looked for symptoms.

Those students with the 7-day prophylaxis before the virus challenge and those with treatment beginning at the time of the virus challenge, did no better than a placebo. The scientists measured nasal secretions, polymorphonuclear leukocytes, or interleukin-8 concentrations in nasal-lavage specimens, or on a quantitative-virus titer.

According to Dr. Stephen E. Straus, director of the National Center for Complementary and Alternative Medicine, the dose was a 300 mg does determined by Dr. Rudolph Bauer, at the Karl-Fanzens University in Graz, Austria. That dose had been previously studied and one that the World Health Organization said was the most often used by consumers.

In response to the study results, the American Botanical Council concluded that the study doses were too low. And, ABC said the study materials do not correlate with commercially available products available to consumers. At higher doses and more frequent dosing levels, the

preparations used might have shown some effects.

Mark Blumenthal of ABC said that the WHO monograph has a dosage level of 3 grams per day of dried root. And this is the dosage level acknowledged in the monographs on *Echinacea* from the Canadian Natural Health Products Directorate. This dosage level would be 330% higher than that used in the *NEJM* study. Blumenthal said that a conclusion from this study that *Echinacea* is ineffective would be incorrect.

Bruce Barrett M.D., Ph.D. of the University of Wisconsin School of Medicine, pointed out that college students are immunocompetent. He said it might have been better to test old people to see how they reacted. And he added that you generally want about 100 people in each treatment group for more statistical significance than were used in this trial.

Two year ago, the *Journal of the American Medical Association*, 290: 2824-2830, December 3, 2003, reported that *Echinacea purpurea* was determined to be ineffective for upper respiratory infections in children 2 to 11 years old. Only 79 children completed that study. An increase of rash was prevalent in the children.

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### NEW ZEALAND ACTS ON CLASSIFICATIONS

**A**t the June 9, 2005 meeting of the Medicines Classification Committee, the New Zealand government group took several actions of interest to *NML* readers. **Kava** (*piper methysticum*) was classified as a prescription drug unless it meets cer-

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NEW ZEALAND -- Continued from page 22...tain conditions which included for oral preparations the labeling of a daily dose of less than 250 milligrams or less of kavalactones, and with a warning statement when more than 25 milligrams: "WARNING: Not for prolonged use. Not recommended for use by pregnant or lactating women. May harm liver." A tablet or capsule cannot contain more than 125 milligrams and a tea bag cannot contain more than 3 grams of dried whole or peeled rhizome. Other conditions allowed its use in topical preparations for use in the rectum, vagina, or throat and in dermal preparations. The Committee is expecting a report from the Kava Evaluation Group in Australia and will reschedule this for further review when the report is available.

**Stramonium** will have a cut-off point between restricted medicine and pharmacy-only medicine and this will be amended from 1 milligram to 1.2 milligram per recommended dose. **Strychnine and nux vomica** should be classified as a prescription drug except in medicines containing one milligram or less per liter or kilogram. **Melia azedarach** should be classed as a prescription medicine at all strengths. **Hyoscine butylbromide** classification should not be changed from restricted medicine and the Committee did not want to harmonize with Australia. **Juniperus Oil** will replace Savin Oil as a restricted medicine at all strengths. **Copaioiaba balsam** should be removed from the New Zealand schedule. **Aconitum** species were recommended for harmonization with the New Zealand classification. **Stimulant laxatives** (including Quassia) were recommended for pharmacy-only scheduling. **Sabadilla** was not classified as a prescription medicine.

For other classifications see <http://www.medsafe.govt.nz/Profs/class/mccMin9June2005.htm>.

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an indwelling intravenous cannula. When the patient had recovered sufficiently to take tablets, we administered oral artesunate 2 mg salt per kg per day to complete a total course (including parental treatment) of 7 days, providing a total cumulative dose of 17—18 mg/kg."

For more information, see the article in *Lancet* or contact Professor N.J. White, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400 Thailand or [nickw@tropmedres.ac](mailto:nickw@tropmedres.ac). The trial was funded by the Wellcome Trust and was conducted as part of the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Program funded by the Wellcome Trust of Great Britain.

### FDA WARNS MAKERS OF DIETARY SUPPLEMENTS

In the past few months FDA has used "warning letters" to enforce laws and regulations against makers of dietary supplements. Since the passage of the Dietary Supplement Health and Education Act in 1994, FDA usually issued "Courtesy Letters" or "Letters of Rejection" in response to notices of structure function claims. In response to health claims, FDA has merely responded that the products would be regulated as drugs if the claims were used as planned. But FDA has not forgotten its enforcement tool, called the "warning letter." FDA always demands a written response to the warning letter and al-

ways advises that further action can be taken without notice. Some FDA personnel would prefer to turn all "Courtesy Letters:" into warning letters, particularly where the products are on the market when the notices of claims are filed. If this happens, distributors and manufacturers should be prepared. Here are three examples of such letters issued in 2005.

The Maitland, Florida office of FDA wrote to James Jimenez of Cell Quest, Inc., Tampa, Florida on March 1, 2005 concerning the marketing of the products CellQuest Liquid and CellQuest Gel on the website, [www.cellquest.com](http://www.cellquest.com). Both products are promoted for "preventing or hafting (sic) abnormal cell divisions and growths which are known to weaken the immune system and cause disease."

Several label claims indicate the products are intended to prevent, treat, or cure serious disease conditions. FDA said these claims make the products drugs. Further FDA said these products are not dietary supplements because of the content of the claims. FDA advised that "the intended uses of a product may be established through product labels and labeling, catalogs, brochures, audio and videotapes, internet sites, or other circumstances surrounding the distribution of a product."

The CellQuest Gel cannot be a dietary supplement because it is not used by ingestion. And FDA wrote that the conditions for which these products are offered (treatment and prevention of cancer) are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners. Therefore, adequate directions for use cannot be written so that a layman can use these products safely. And because the labels fail to bear adequate directions for use, they are misbranded.

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**WARNING LETTERS** -- from page 23...

FDA said the violations must be corrected immediately and the company was subject to further enforcement measures without notice. FDA asked for a response within 15 days but has not posted the response on its web site. See the entire letter at [www.fda.gov/foi/warning\\_letters/g5268d.htm](http://www.fda.gov/foi/warning_letters/g5268d.htm).

The Parsippany, New Jersey office of FDA wrote to Clyde Rockoff of University Nutrition Services of New Brunswick on March 7, 2005 following a September 2, 2004 inspection of the company facility. At that time the company was distributing Universal Naturals Daily Caps, a daily multi-vitamin and mineral supplement, Muscle Pro-24™, a bodybuilding supplement, and Uni-Syn MRP2™, a meal replacement powder.

FDA made analyses of the Universal Naturals Daily Caps product and found it claimed to contain 5750 IU of Vitamin A and contained none. It purported to contain 400 mcg of folic acid and contained none. FDA analysis of the Muscle Pro-24™ product concluded that it contained only 22% of the labeled amount of Vitamin B6, 10 % of the labeled amount of folic acid, 8 % of the labeled amount of Vitamin C, and none of the labeled amount of Vitamin A and Vitamin E.

This led FDA to the conclusion that these products are adulterated because the labels are false and misleading. And FDA said this is not an all-inclusive list of deviations from regulations for these products. FDA advised that failure to correct these violations may result in further regula-

tory action (seizure of legal action to stop sales) without further notice.

In the case of Uni-Syn MRP2™, represented as a meal replacement powder and as a nutritional supplement, FDA said it is not regulated as a dietary supplement, but rather as a conventional food. The product contains no nutritional labeling and is therefore misbranded. The label also bears the claim "Low in Sugar" and a comparison of the sugar content of this product to comparable products reveals they contain the same or similar amounts of sugar. Consequently, FDA said, "Low in Sugar" is a false and misleading claim.

The company was ordered to respond within 15 days from receipt of the letter about how it would correct these violations. The company response was not posted by FDA to its website. See [www.fda.gov/foi/warning\\_letters/g4236d.htm](http://www.fda.gov/foi/warning_letters/g4236d.htm).

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## HARVESTING HEALTH

Scientific research is really moving fast in the area of dietary supplements. We have given readers a look at some of the things going on in the field in this issue. This science will be a basis for changes in the law.

Pharmacognosy used to be a plant physical identification science, but it is now a molecular analysis science, using high pressure liquid chromatography, and mass spectrometry. Most other fields of bio-science research are advancing steadily as time goes on.

With obesity and metabolic syndrome taking over the U.S. population, new efforts have to be made in measuring health parameters and finding ways of encouraging people to make lifestyle changes in the area of diet and exercise. The CSPI "Salt Assault" may help, too.

With the Texas jury awarding more than \$250 million for a death they determined was caused by the pain killer drug Vioxx, and several thousand more trials to be held, drug makers are going to have to look for safer drugs and do more and better testing before going on the market.

Post marketing surveillance and easy-upfront or midway-researched drug approvals may not cut it in the future. Besides FDA keeps raising the price for its doing drug reviews.

Natural medicine is still depended upon by many people in the world. Austin Okwelle of Nigeria brings us up to date on what is needed there to help improve the status of natural medicine. Mr. Okwelle began pursuing a doctorate degree in microbiology this summer after several years of publishing *The Natural Cure News* in Lagos. Who knows, maybe

he will be another Norman Farnsworth, Ph.D., who started off with his degree in microbiology, as I understand it, and became an accomplished and respected pharmacognosist, researcher and educator. Farnsworth received the American Society of Pharmacognosy Research Achievement Award for 2005 at the annual meeting held in July at Corvallis, Oregon.

Many readers have never met your editor, so here is a photo view from



*William J. Skinner, R.Ph.,  
Attorney at Law, Editor*

Florida, where we are awaiting the next hurricane of the season. Thanks to all of our readers who find *NML* helpful in staying up to date.