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January 5, 2012

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket ID: FDA-2011-P-0819. Citizen Petition to Require Cautionary Statements On the Label of Dietary Supplements Containing St. John's Wort.

The Council for Responsible Nutrition (CRN)[1] appreciates this opportunity to provide comments regarding the Citizen Petition requesting FDA to issue regulations requiring a black box warning label for dietary supplements containing St. John's wort.[2] Disclosure of potential interactions between medications and dietary supplements should occur between healthcare professionals and their patients. In addition, there is no factual or legal basis to require a black box warning on a dietary supplement, which is reserved for medications with a significant risk of serious or life-threatening adverse effects. Therefore CRN opposes this petition, and we urge the FDA to deny the petitioner's request for the reasons stated below.

[1] CRN, founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands, as well as the store brands marketed by major supermarket, drug store, and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. In addition to complying with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control, and safety, our 75 plus manufacturer and supplier members also agree to adhere to additional voluntary guidelines, as well as CRN's Code of Ethics. Learn more about us at www.crnusa.org.

[2] On November 10, 2011 the Center for Science in the Public Interest (CSPI) submitted a petition to FDA requesting the Agency to issue regulations requiring cautionary statements on the label of dietary supplement containing St. John's wort under Sections 403(a), 201(n), and 701(a) of the Food, Drug, and Cosmetic Act (FDCA).

I. Healthcare professionals should consult with patients about all possible drug interactions when prescribing medication, and nearly every supporting reference cited within the petition takes this position.

The petitioner suggests that FDA require the following statement in a black box on the label of all dietary supplements containing St. John's wort:

> **CAUTION: St. John's wort interacts with some commonly used prescription and over-the-counter drugs. DO NOT USE this supplement if you are taking contraceptives, antidepressants, immunosuppressants (such as cyclosporine), anticoagulants, Digoxin, HIV medicine, blood thinners, seizure-control medicine, cancer medicine, or any other medications.**[3]

CRN does not dispute that St. John's wort may interact with some prescription drugs in some individuals. Individuals taking prescription medications should always consult with their healthcare professionals about all of the products they are taking, including non-prescription drugs and dietary supplements. This is CRN's position, and the recommendation of several other organizations including FDA[4] and the National Center for Complementary and Alternative Medicine (NCCAM)[5], the federal government's lead agency for scientific research on complementary and alternative medicine.

In noting the various articles and advisories regarding St. John's wort (several of which are over a decade old), the petitioner interprets these sources as supporting a need for its suggested warning label. In fact, these sources share CRN's view that it is the responsibility of the healthcare professional to discuss potential interactions with a patient when prescribing a medication. With regards to St. John's wort specifically, CRN is not aware of any organization

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[3] CSPI Petition, page 1.

[4] U.S. Food and Drug Administration, *FDA 101: Dietary Supplements*, available at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm050803.htm (last visited January 4, 2012).

[5] National Center for Complementary and Alternative Medicine, *Herbs at a Glance, St. John's Wort*, available at http://nccam.nih.gov/health/stjohnswort/ataglance.htm (last visited January 4, 2012).

or governmental agency -- international or domestic -- that has taken the position that an enhanced warning label is needed for supplements containing St. John's wort. The FDA Public Health Advisory cited by the petitioner states that "it is important that health care professionals ask patients about concomitant use of products that could contain St. John's wort" with regards to those taking indinavir and other antiretroviral agents.[6] For patients taking oral contraceptives or other prescription drugs for heart disease, depression, and other specified conditions, FDA suggests that "healthcare providers should alert patients about these potential drug interactions to prevent loss of therapeutic effect…"[7] The petition also cites advisories issued by Canadian[8] and British[9] health agencies, which again recommend that healthcare professionals consult with patients about the use of herbal remedies. Similarly, the NCCAM fact sheet on St. John's wort cautions users to inform "all your health care providers about any complementary and alternative practices you use."[10]

In addition, the petition grossly overstates the danger to consumers from a potential interaction with St. John's wort. The number of adverse event reports (AERs) from the use of

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[6] U.S. Food and Drug Administration, *Risk of Drug Interactions with St. John's Wort and Indinavir and other Drugs*, FDA Public Health Advisory (Feb. 10, 2000), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm052238.htm (last visited January 4, 2012).

[7] *Id*.

[8] Health Canada, *Risk of Important Drug Interactions between St. John's Wort and Prescription Drugs*, available at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2000/hypericum_perforatum_hpc-cps-eng.php (last visited January 4, 2012).

[9] The Medicines and Healthcare products Regulatory Agency, *Important Interactions Between St. John's Wort (Hypericum Perforatum) Preparations and Prescribed Medicines, Message from Professor A Breckenridge, Chairman of Committee on Safety of Medicines*, 29 February 2000, available at http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con019563.pdf (last visited January 4, 2012).

[10] NCCAM, *Herbs at a Glance, St. John's Wort.*

prescription and OTC drugs vastly exceeds those associated with dietary supplements.[11] In fact, CRN is not aware of any reported AERs for St. John's wort products. Moreover, the petition alludes to but fails to provide any actual clinical data demonstrating that St. John's wort significantly increases the risk of a life-threatening or serious complication with oral contraceptives or anti-depressants. It even goes so far as to suggest that the lack of a black box warning label could threaten the supply of human organ transplants. The petition warns of "the potentially disastrous consequences" from St. John's wort interactions, but given the lack of clinical data and reported AERs, these consequences are unlikely to be realized. Further, conjecture and speculation should not serve as the basis for new warning labels for St. John's wort supplements or any FDA-regulated product.

Finally, the petitioner claims that existing labels for St. John's wort supplements are inconsistent and fail to adequately warn consumers of the known risks. Many manufacturers already provide warning statements on the labels of products containing St. John's wort. As evidenced by the petitioner,[12] most labels direct consumers to consult with their physician or healthcare practitioner before use -- echoing the current recommendations discussed above. St. John's wort is safe when used as directed, and there is no scientific evidence demonstrating that an enhanced warning label would provide any additional safety benefit to consumers.

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[11] From January 2008 through October 2008, FDA received 948 adverse event reports for dietary supplements. By contrast, in the same year drug-related adverse outcomes were noted in nearly 1.9 million inpatient hospital stays and 838,000 emergency department visits. *See* U.S. Government Accountability Office, GAO-09-250, *Report to Congressional Requesters, Dietary Supplements, FDA Should Take Further Actions to Improve Oversight and Consumer Understanding* (January 2009), available at http://www.gao.gov/assets/290/285372.pdf (last visited January 4, 2012) and Agency for Healthcare Research and Quality, *Healthcare Cost and Utilization Project (HCUP), Statistical Brief #109* (April 2011), available at www.hcup-us.ahrq.gov/reports/statbriefs/sb109.jsp (last visited January 4, 2012)

[12] CSPI Petition, Attachment: Chart, Current Statement on St. John's Wort Products.

II. There is no legal basis for requiring a black box warning label for supplements containing St. John's wort. Moreover, this type of warning is unwarranted and unsupported by precedent.

CRN agrees that FDA has the authority to require certain information on dietary supplement labels and to determine whether a product is misbranded. One aspect the Agency must consider is "the extent to which the labeling or advertising fails to reveal facts material…with respect to consequences which may result from use of the article…under the conditions of use prescribed in the labeling" or under "customary or usual" conditions.[13] The Agency may also "require disclosure of material facts either by regulation or court enforcement action".[14]

Based on a misapplication of these statutory provisions and a misinterpretation of past Agency actions, the petition incorrectly concludes that FDA should require its suggested warning label for St. John's wort products. FDA has never exercised this authority with respect to herbal dietary supplements, or any natural foods that are known to interact with drugs. For example, grapefruit has significant interactions with many prescription drugs. In addition, leafy greens such as broccoli, spinach and turnips can interact negatively with the anticoagulant Warfarin, and dairy products such as milk and cheese can interact with tetracycline antibiotics. However, FDA has not required any of these foods to bear a warning label. Dietary supplements are regulated as food. And as with these other food products, the appropriate communication vehicle for informing consumers about potential interactions between a food and a drug is for the *prescriber* of the drug to convey these risks to the patient. This responsibility has never been, nor should it be, placed on the label of the food.

[13] FDCA § 201(n).

[14] 21 CFR 121 (a), (b).

The petition also cites the "special labeling" for the food additive olestra.[15] However, FDA regulates food additives differently than dietary supplements; these substances are subject to premarket approval by FDA unless "there is a reasonable certainty that the substance is not harmful" [16] or they meet a statutory exclusion.[17] Comparisons to the mandatory warning labels for iron-containing products and high-protein products are also misguided. These labels warn of the potential consequences of *misuse* of the product rather than potential drug interactions.[18] Therefore, the comparison to this group of warning statements is inappropriate and out of context.

Finally, the petition suggests that a "black label" or "boxed" warning is necessary for St. John's wort products. A black box warning is the strongest form of warning issued by FDA and is reserved for prescription drugs and biologic drugs with serious adverse reactions (fatal, life-threatening, or permanently disabling) or drugs approved by FDA on the condition that distribution or use is restricted.[19] FDA's drug labeling requirements also state that "[t]he boxed warning ordinarily must be based on clinical data" or "serious animal toxicity"[20] – neither of which is applicable to St. John's wort. FDA has never required a black label or boxed warning for a dietary supplement, and this type of label is not warranted in this case.

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[15] 61 Fed. Reg. 3117 (Jan. 30, 1996).

[16] 21 CFR § 180.1(a).

[17] FDCA § 409(a).

[18] 21 CFR § 101.17(e); 21 CFR § 101.17(d)(1).

[19] See FDA, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*, Guidance for Industry (October 2011), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf (last visited January 4, 2012).

[20] 21 CFR § 201.57(c)(1).

III. The petition references interactions with over-the-counter medicine but fails to provide evidence thereof.

The petition also contains inaccurate information regarding interactions between St. John's wort and over-the-counter (OTC) medications. Although the suggested warning label indicates that St. John's wort interacts with "commonly used" OTC medicines, the petition fails to provide any evidence or documented case of an interaction. In addition, CRN is not aware of any potential interactions between St. John's wort and OTC medicines. Therefore, this argument is baseless and should be rejected by FDA.

Conclusion

In conclusion, CRN urges FDA to deny this petition on the grounds that the current system effectively informs and protects consumers, and there is no factual or legal basis to support the petitioner's arguments. As demonstrated above, no governmental agency or organization shares the petitioner's view that an enhanced warning label is necessary for St. John's wort products, and no data or reports exist to verify that such a label is warranted. Agency precedent further supports this conclusion and a finding that the petitioner's arguments are without merit.

Sincerely,

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Regulatory Counsel