

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Petition to Require Cautionary Statements )  
On the Label of Dietary Supplements ) Docket No. \_\_\_\_\_  
Containing St. John's Wort )  
\_\_\_\_\_ )

Submitted by the  
Center for Science in the Public Interest

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Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

### **Citizen Petition**

The Center for Science in the Public Interest<sup>1</sup> submits this petition under sections 403(a), 201(n), and 701(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) to request that the Commissioner of Food and Drugs issue regulations requiring cautionary statements on the label of dietary supplements containing St. John's wort.

#### **I. Action Requested**

CSPI requests that FDA issue a regulation requiring a label statement warning of known risks of supplements containing St. John's wort, to prevent misbranding under FDCA § 403(a) and 21 U.S.C. § 343(a). Pursuant to the requirements of 21 C.F.R. § 10.30(b), CSPI proposes the following labeling statement for 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.**

This statement should be enclosed in a black box on the label, and should be prominently displayed and in a clear and conspicuous boldface typeface.<sup>2</sup>

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<sup>1</sup> CSPI is a non-profit consumer advocacy organization focused on health and nutrition issues that is supported by the more than 741,000 subscribers to its Nutrition Action Healthletter. Since 1971, CSPI has worked to ensure that consumers are given the information they need to make informed decisions about the food and supplements they consume.

<sup>2</sup> The proposed regulation would not prevent the manufacturer from voluntarily warning of other risks, either elsewhere on the label or inside the same ruled box following the required statement.

## II. Statement of Grounds

### A. Statement of Factual Grounds

#### 1. Labels for St. John's wort do not have adequate warnings of the multiple risks of this supplement.

Although there are a number of herbal supplements that should be required to display warning labels,<sup>3</sup> CSPI proposes that FDA address St. John's wort first because, in the National Center for Complementary and Alternative Medicine's (NCCAM) consumer publication *Herbs at a Glance: A Quick Guide to Herbal Supplements*, St. John's wort is the primary example of a supplement that can interact with several commonly used prescription drugs such as birth control pills.<sup>4</sup> St. John's wort was also the subject of an FDA advisory to health professionals<sup>5</sup> — a rare occurrence for a supplement.

NCCAM is the "Federal Government's lead agency for scientific research on complimentary and alternative medicine," which includes herbal supplements.<sup>6</sup> Con-

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<sup>3</sup> See CSPI, *Warning Labels on Dietary Supplements: A Patchwork Quilt of Confusing Messages* (Feb. 2009), [http://www.cspinet.org/new/pdf/supplements\\_warning\\_list.pdf](http://www.cspinet.org/new/pdf/supplements_warning_list.pdf) (last visited Sept. 15, 2011).

<sup>4</sup> U.S. Dep't Health & Human Serv., Nat'l Inst. Health, Publ'n No. 09-6248, *Herbs at a Glance* (2009) at 6. Updated information on supplements available at NCCAM's *Herbs at a Glance* web page, [http://www.nccam.nih.gov/health/NIH\\_Herbs\\_at\\_a\\_Glance.pdf](http://www.nccam.nih.gov/health/NIH_Herbs_at_a_Glance.pdf) (last visited Sept. 15, 2011).

The Office of Dietary Supplements (ODS) also directs consumers to the Herbs-at-a-Glance-fact sheets. Congress created ODS in 1994 to provide advice to the Director of the National Institutes of Health, the Director of the Centers for Disease Control and Prevention, and FDA Commissioners on issues relating to dietary supplements. *About the ODS*, [http://ods.od.nih.gov/about/about\\_ods.aspx](http://ods.od.nih.gov/about/about_ods.aspx) (last visited Sept. 15, 2011).

<sup>5</sup> See U.S. Food and Drug Admin., *Risk of Drug Interactions with St. John's Wort and Indinavir and other Drugs (Risk of Drug Interactions)*, FDA Public Health Advisory (Feb. 10, 2000), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/PublicHealthAdvisories/ucm052238.htm> (last visited Sept. 16, 2011).

<sup>6</sup> NCCAM *Facts-at-a Glance and Mission*, available at <http://nccam.nih.gov/about/ataglance/> (last visited Sept. 16, 2011).

gress established NCCAM as a component of the National Institutes of Health in 1999.<sup>7</sup> Its purpose is to “conduct and support . . . basic and applied research . . . with respect to identifying, investigating, and validating complementary and alternative treatment, diagnostic and prevention modalities, disciplines and systems.”<sup>8</sup>

NCCAM’s *Herbs at a Glance* summarizes uses for a supplement, how it is used, scientific support, and, most importantly, side effects and cautions.<sup>9</sup> FDA should rely on this comprehensive resource to establish standardized warning labels for St. John’s wort.

In addition, an article by former FDA Commissioner Jane E. Henney, published in the *Journal of the American Medical Association* warned that “health care providers should alert patients about these potential drug interactions” because St. John’s wort interacts with many drugs that are used to treat heart disease, depression, seizures, certain cancers, as well as drugs that prevent transplant rejection and pregnancy.<sup>10</sup>

Both the Canadian<sup>11</sup> and British<sup>12</sup> governments have already issued warnings to their healthcare professionals, advising them of St. John’s wort’s potential to interact with certain drugs.

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<sup>7</sup> See Omnibus Consolidated and Emergency Supplemental Appropriations Act of 1999, Pub. L. 105-277. NCCAM was preceded by the Office of Alternative Medicine, which was part of the Office of the Director. Pub. L. 103-43 (1993).

<sup>8</sup> 42 U.S.C. § 287c-21(a).

<sup>9</sup> See generally *Herbs at a Glance*.

<sup>10</sup> Jane E. Henney, Comm’r of Food and Drugs, *Risk of Drug Interactions With St. John’s Wort* (hereinafter “Henney”), 283(13) JAMA 1679 (2000).

<sup>11</sup> *Risk of Important Drug Interactions between St. John’s Wort and Prescription Drugs*, available at [http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/medeff/hypericum\\_perforatum\\_hpc-cps-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/hypericum_perforatum_hpc-cps-eng.pdf) (last visited Sept.16, 2011).

<sup>12</sup> *Important Interactions Between St. John’s Wort (Hypericum Perforatum) Preparations and Prescribed Medicines*, available at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2015756> (last visited Sept.16, 2011).

## **2. St. John's wort interactions with many prescription medications endanger consumers.**

St. John's wort is a potential danger to consumer health<sup>13</sup> because it is known to interact with a number of drugs, both prescription and over-the-counter.<sup>14</sup> A recent study indicated that among prescription medication users, more than half were concurrent users of dietary supplements.<sup>15</sup> When surveyed on actual use of specific drugs and supplements, 4% of older adults were at risk for a major potential drug interaction based on the drugs and supplements they used.<sup>16</sup> Of the known potential interactions for which the surveyed adults were at risk, 61% of the potential interactions were of moderate severity and 24% were of major severity.<sup>17</sup> Thus, a large segment of the population is unnecessarily at risk of having an adverse supplement–drug interaction. In addition, factors such as the proliferation of pharmaceutical drugs and an aging baby boomer population indicate that the risk of public harm may be growing.

### **a. St. John's wort interacts with oral contraceptives.**

Oral contraceptives are the leading method of contraception in the United States. Recent statistics indicate that approximately 10.7 million women in the United States use oral contraceptives as their primary method of birth control.<sup>18</sup> As both NCCAM<sup>19</sup>

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<sup>13</sup> *Id.*

<sup>14</sup> See *Risk of Important Drug Interactions*.

<sup>15</sup> Dima M. Qato, et al., *Use of Prescription and Over-the-counter Medications and Dietary Supplements Among Older Adults in the United States*, 300 JAMA 2867, 2867 (2008).

<sup>16</sup> *Id.* at 2874.

<sup>17</sup> *Id.*

<sup>18</sup> Mosher WD, Jones J. *Use of contraception in the United States: 1982–2008*. National Center for Health Statistics. Vital Health Stat 23(29), 2010.

<sup>19</sup> *Herbs at a Glance* at 83.

and former FDA Commissioner Jane E. Henney<sup>20</sup> have recognized, St. John's wort<sup>21</sup> can interfere with the action of oral contraceptives and thus cause unwanted pregnancy. That means that women are disproportionately put at risk of having to make life-altering choices. Supplements containing St. John's wort should be required to provide a warning to women taking an oral contraceptive.

**b. St. John's wort interacts with antidepressants.**

Antidepressant drugs were not only used by more than 10% of the entire U.S. population in 2003, but were also the "most commonly prescribed class of medications in office-based and hospital outpatient-based medical practice in 2005."<sup>22</sup> As NCCAM has recognized,<sup>23</sup> St. John's wort can interfere with the action of various classes of antidepressants and other drugs used in the treatment of psychiatric disorders.<sup>24</sup>

Ironically, St. John's wort is often taken for the treatment of mild to moderate depression.<sup>25</sup> Therefore, there is a distinct possibility that individuals who take antidepressants might also turn to St. John's wort, unwittingly counteracting the very treatment they are seeking.

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<sup>20</sup> See Henney at 2.

<sup>21</sup> For a review more recent than the *Herbs at a Glance* publication, see Francesca Borrelli & Angelo A. Izzo, *Herb-Drug Interactions with St. John's Wort (Hypericum perforatum): an Update on Clinical Observations*, 11 *Am. Ass'n Pharm. Scientists J.* 710, 712 (2009) (reviewing cases of intermenstrual bleeding, reduced efficacy, and unwanted conception when St. John's wort was taken with oral contraceptives; reviewing studies that measured and described the biochemical mechanism of interaction).

<sup>22</sup> Mark Olfson & Steven C. Marcus, *National Patterns in Antidepressant Medication Treatment*, 66 *Archives Gen. Psychiatry* 848, 848 (2009).

<sup>23</sup> *Herbs at a Glance* at 83.

<sup>24</sup> Borrelli & Izzo, at 722-23.

<sup>25</sup> See generally Greeson JM, *St. John's Wort (Hypericum perforatum): A Review of the Current Pharmacological, Toxicological, and Clinical Literature*. *Psychopharmacology (Berl)* (2001);153: 402-14.

Given the widespread use of antidepressants in the United States, and in light of NCCAM's advisories on the subject of drug-supplement interactions, labels on supplements containing St. John's wort should warn that these supplements should not be used by persons taking antidepressants.

**c. St. John's wort interacts with immunosuppressants and other life-saving medications.**

Immunosuppressant drugs can be medically necessary.<sup>26</sup> For example, cyclosporine is an immunosuppressant that is often used to prevent an organ transplant recipient from rejecting the new organ.<sup>27</sup> However, as NCCAM has recognized,<sup>28</sup> St. John's wort can interfere with the action of cyclosporine.<sup>29</sup> Such interference may result in damage to the transplanted organ, total rejection of the organ, or potential death of the patient.<sup>30</sup>

Given the scarcity and value of organs, the high cost and high risk of procedures, and the life or death consequences of drug interaction, the preventative action of requiring warning labels seems indisputable. With about 28,000 people receiving organ transplants in the United States each year,<sup>31</sup> this interaction poses a substantial risk to consumers.

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<sup>26</sup> See generally Thomas E. Starzl et al., *The Use of Cyclosporin A and Prednisone in Cadaver Kidney Transplantation*, *Surg Gynecol Obstet.* 151:17–26 (1980), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727074/> (last visited Sept. 16, 2011).

<sup>27</sup> See Thomas E. Starzl et al., *Liver Transplantation with Use of Cyclosporin and Prednisone*, 305 *New Eng. J. Med.* 266 (1981).

<sup>28</sup> *Herbs at a Glance* at 83.

<sup>29</sup> Borrelli & Izzo, at 712.

<sup>30</sup> *Id.* (citing many case reports).

<sup>31</sup> United Network for Organ Sharing, *UNOS Facts and Figures*, available at [http://www.uwhhealth.org/files/uwhhealth/docs/pdf3/UNOS\\_Facts\\_and\\_Figures.pdf](http://www.uwhhealth.org/files/uwhhealth/docs/pdf3/UNOS_Facts_and_Figures.pdf) at 1 (last visited Sept. 16, 2011).

The three common drug interactions that we have highlighted are serious, but they are not the only ones. *Herbs at a Glance* states that St. John's wort can interact with other potentially life-saving treatments: heart medication, drugs used to control HIV infection, drugs used to treat cancer, and seizure-control drugs.<sup>32</sup>

Given the potentially disastrous consequences that can be incurred by a consumer taking St. John's wort and then suffering an adverse drug interaction, it is imperative that FDA require warning labels on supplements containing St. John's wort so that consumers would be informed of this critical information.

### **3. CSPI examined 11 products containing St. John's wort, and their cautionary statements failed to adequately warn of all the known material risks.**

CSPI examined the labels of 11 St. John's wort supplement products<sup>33</sup> and found that most labels failed to warn adequately of the known, material risks discussed above. When warning statements were present on labels, the degree of disclosure was often insufficient. Instead of disclosing specific, known risks, many labels make vague statements drawn from a handful of boilerplate warnings.

The warning statements on St. John's wort supplements range from the short, minimal, and uninformative (e.g., the general "Note" to consult your doctor from the brands Whole Foods (365) and Nature's Plus) to the unduly long and complicated (e.g., the New Chapter example, which uses the Latin species name of St. John's wort and ar-

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<sup>32</sup> See *Side Effects and Cautions* on the *Herbs at a Glance* webpage, available at <http://nccam.nih.gov/health/stjohnswort/ataglance.htm> (last visited Sept. 16, 2011).

<sup>33</sup> See attached Table.



cane medical terminology that buries the meaning of the warning). One brand<sup>34</sup> lacked any warning at all.

Further, the advice offered on various labels is inconsistent (e.g., Vitamin Shoppe plainly states that St. John's wort should not be used with antidepressants, while Solaray simply advises that those taking antidepressants<sup>35</sup> should "consult your physician"). Kira boldfaced and underlined its cautionary statement saying that "recent data suggest that . . . you should consult with your healthcare practitioner to avoid any interactions with St. John's Wort." However, Kira also placed the warning statement on the side panel of its box, making it difficult to find, and failed to use strong language (e.g., "do not use this product if . . ."). This kind of inconsistent content on warning labels is confusing to consumers and undermines the authority of accurate, reliable warning labels.

CSPI's survey of existing St. John's wort labels demonstrates that allowing manufacturers to provide warnings at their own discretion has failed to adequately protect consumers. From the information we have gathered, it appears that many manufacturers simply wish to protect themselves from product liability suits by placing boilerplate warnings on the label rather than actually alerting consumers to the known, material risks of drug interactions associated with the product.

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<sup>34</sup> Bluebonnet Herbals St. John's wort.

<sup>35</sup> This label refers to antidepressants as "MAO inhibitors." MAO Inhibitors were the first modern antidepressants. A.M. Cesura and A. Pletscher, *The New Generation of Monoamine Oxidase Inhibitors*, *Prog. Drug Res.* (1992);38:171-297.

## B. Statement of Legal Grounds

### 1. FDA has the authority to require warning statements on dietary supplement labels.

FDA has ample authority to require warning labels on food and dietary supplements. The strength of this authority derives from the fact that dietary supplements are deemed to be food for the purpose of the misbranding provisions of the Federal Food, Drug, and Cosmetic Act.<sup>36</sup> Under the Act, a food is “misbranded” if its labeling is “false or misleading in any particular.”<sup>37</sup> Both Congress and FDA have clarified that labeling is misleading if it “fails to reveal facts . . . material with respect to consequences which may result from the use of the article . . . .”<sup>38</sup> FDA has further clarified in its regulations that “[a]ffirmative disclosure of material facts . . . may be required” by regulation or court enforcement action.<sup>39</sup>

Additionally, in carrying out its mandate to prevent misbranding, FDA can require “special labeling” for food “where information is necessary to ensure that consumers are aware of special health risks associated with consumption of a particular product.”<sup>40</sup>

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<sup>36</sup> See FDCA § 201(ff), 21 U.S.C. § 321(ff) (“Except for the purposes of [food registry requirements and the definition of ‘drug’], a dietary supplement shall be deemed to be a food within the meaning of this Act.”).

<sup>37</sup> FDCA § 403(a), 21 U.S.C. § 343(a).

<sup>38</sup> Congress wrote this language in the Food, Drug & Cosmetic Act’s definitions section, FDCA § 201(n), 21 U.S.C. § 321(n). FDA used identical language in its regulation, “Failure to reveal material facts.” 21 C.F.R. § 1.21(a).

<sup>39</sup> 21 C.F.R. § 1.21(b).

<sup>40</sup> 61 Fed. Reg. 3117 (Jan. 30, 1996) (Final rule permitting use of Olestra saying that a label may be misleading if the label omits “certain material facts from the label or labeling of a food [that] causes the product to be misbranded within the meaning of 21 U.S.C. 343(a)(1) and 321(n).”).

Under the authority of these provisions, FDA can require affirmative disclosure of consequences that may result from the supplement's use on its label.<sup>41</sup> In other words, FDA has the authority to require a warning label about possible adverse effects of a supplement.

**2. FDA has previously used its authority to require warning statements for dietary supplements.**

FDA's authority to require specific warning statements is well-established through many prior actions where FDA required warning statements on labeling. FDA has previously used its broad "authority to promulgate regulations for the efficient enforcement of [the Federal Food, Drug, and Cosmetic Act]"<sup>42</sup> to require a warning label on dietary supplement products, specifically those containing iron.<sup>43</sup>

On January 15, 1997, FDA promulgated a final rule governing iron supplements,<sup>44</sup> and as a result, any iron-containing supplement currently must bear the following warning statement:

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.<sup>45</sup>

Significantly, during the comment period, FDA's authority to mandate this warning label apparently went unchallenged, though FDA did receive many comments directed to

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<sup>41</sup> Congress has also contemplated that dietary supplements would bear warnings. *See* FDCA § 403(s), 21 U.S.C. § 343(s) ("A dietary supplement shall not be deemed misbranded solely because its label or labeling contains directions or conditions of use or warnings.").

<sup>42</sup> FDCA § 701(a), 21 U.S.C. § 371(a). Use of this rulemaking authority is specifically contemplated by FDA's regulation on requiring affirmative disclosure. *See* 21 C.F.R. § 1.21(b)(1).

<sup>43</sup> 21 C.F.R. § 101.17(e); 21 C.F.R. § 310.518(a)(1).

<sup>44</sup> 62 Fed. Reg. 2218.

<sup>45</sup> 21 C.F.R. § 101.17(e).

the specific language of the proposed warning.<sup>46</sup> The fact that no one raised a reasonable challenge to FDA's legal authority to require warning statements indicates common acceptance of FDA's authority to act in this area.<sup>47</sup>

Many past regulations further establish the breadth of FDA's authority to require warning labels. For instance, for more than seven years, FDA required that foods containing olestra bear the warning statement:

THIS PRODUCT CONTAINS OLESTRA. Olestra may cause abdominal cramping and loose stools. Olestra inhibits absorption of some vitamins and other nutrients. Vitamins A, D, E, and K have been added.<sup>48</sup>

That example is particularly noteworthy because, although FDA did not believe that olestra posed a safety risk, the information was nonetheless considered material, and thus could be *required* in order to avoid misbranding, because "the agency believ[ed] that consumers should be provided with information to enable them to associate olestra with the GI symptoms that it may cause."<sup>49</sup> The warning CSPI suggests for St. John's wort is intended to provide consumers with information that would enable them to avoid far more serious medical consequences than loose stools.

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<sup>46</sup> See "II. Warning Statement for Iron-Containing Products," 62 Fed. Reg. 2218, 2218-27.

<sup>47</sup> By way of contrast, in the very same rulemaking, industry objected to FDA's authority to set packaging requirements. See "III. A. FDA's Legal Authority to Establish Packaging Requirements for Iron-Containing Products," 62 FR 2218, 2227-28. Ultimately this packaging requirement was successfully challenged in court. *Nutritional Health Alliance v. FDA*, 318 F.3d 92 (2d Cir. 2003). However, this judgment in no way affected the labeling requirement, which apparently never faced challenge and is still effective. See 68 Fed. Reg. 59714, 59714 (Oct. 17, 2003) (revocation of packaging requirement "does not affect the provisions of 21 C.F.R. § 101.17(e), which requires label warning statements on all iron-containing dietary supplements in solid oral dosage form . . .").

<sup>48</sup> 61 Fed. Reg. 3118, 3159-60 (Jan. 30, 1996), formerly codified at 21 C.F.R. § 172.867(e). FDA stated initially that this was an interim requirement (see 61 Fed. Reg. at 3160), and FDA later repealed this requirement in response to a petition from Procter & Gamble. 68 Fed. Reg. 46364 (Aug. 5, 2003).

<sup>49</sup> 61 Fed. Reg. at 3161.

FDA's required warning statement on high-protein products provides another clear example of the extent of FDA's labeling authority.<sup>50</sup> Although high-protein products are not inherently harmful, FDA required strong warning labels to alleviate the concern that these products might be used as part of dangerous weight-loss plans.<sup>51</sup> High-protein products that are represented for use in reducing weight must state:

WARNING: Very low calorie protein diets (below 400 Calories per day) may cause serious illness or death. Do Not Use for Weight Reduction in Such Diets Without Medical Supervision. Not for use by infants, children, or pregnant or nursing women.<sup>52</sup>

FDA's authority to require this particular warning statement was challenged and upheld in court.<sup>53</sup> The fact that FDA can require such a label is now cited for the broad proposition that any "increased risk to consumer safety constitutes a 'material change[,]'"<sup>54</sup> thus underscoring the FDA's authority to require a warning label on St. John's wort and other potentially harmful supplements.

Not only has FDA required warning statements on the labels of foods and dietary supplements that are only dangerous when misused (e.g., low-protein weight-loss products and iron supplements), but it has also required warning statements on foods containing olestra, a food additive for which the potential risks are much less severe than the consequences resulting from adverse drug interactions with St. John's wort.<sup>55</sup> The precedents in this area clearly support FDA's authority to require disclosure of

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<sup>50</sup> 21 C.F.R. § 101.17(d)(1).

<sup>51</sup> *Id.*

<sup>52</sup> *Id.*

<sup>53</sup> See *Council for Responsible Nutrition v. Goyan*, Food Drug Cosm. L. Rep. (CCH) ¶ 38,057Z (D.D.C. 1980).

<sup>54</sup> See *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 178 n.8 (D.D.C. 2000).

<sup>55</sup> 62 Fed. Reg. 30678, 30692 (Jun. 4, 1997).

known potential adverse effects from the ingestion of particular dietary supplements, especially those as severe as the drug interactions described in this petition.

**3. Requiring warning statements based on NCCAM research is in accordance with FDA policy and has a firm scientific basis.**

With respect to warning labels, FDA has repeatedly stated that its policy is to require “warning label statements to ensure that consumers are alerted to the potential health hazards associated with use of the product.”<sup>56</sup> By relying on cautionary statements issued by NCCAM—the program at NIH with special expertise in the field of dietary supplements and other alternative medicines—FDA would be leveraging NCCAM’s resources to further public health.

Furthermore, coordination with NCCAM’s research is consistent with Congress’s command that FDA “shall implement programs and policies that will foster collaboration between . . . the National Institutes of Health [of which NCCAM is part] . . . to enhance the scientific and technical expertise available to [FDA] . . .”<sup>57</sup> FDA can and should utilize the expertise accumulated by NCCAM to determine appropriate warning labels for dietary supplements. By engaging in “interagency collaboration,”<sup>58</sup> FDA could use existing research as the foundation on which to establish warning labels for dietary supplements, now and in the future, without the need to conduct expensive, independent research on safety.

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<sup>56</sup> *Id.* See also 58 Fed. Reg. 2850, 2872 (Jan. 6, 1993) (“The agency affirms its tentative position and does not intend to require warning statements except in specific instances where there is scientifically based evidence of a potential health hazard.”).

<sup>57</sup> FDCA § 903(c), 21 U.S.C. § 393(c).

<sup>58</sup> *Id.*

### **III. Conclusion and request for action**

The severe risks associated with the simultaneous use of certain drugs and St. John's wort have the potential to affect a great and growing number of consumers. Most labels currently on the market do not warn of the variety of adverse interactions described in this petition. When warnings are present, they are often difficult to find, and even then the effectiveness of the warning is diminished by different statements on other brands of St. John's wort. FDA should step in and use its authority to require standardized, accurate, labels, both to protect consumers and to ensure that no one manufacturer gains an unfair advantage in the marketplace by failing to disclose risks.

It took thousands of adverse event reports about supplements containing ephedra for the FDA to issue warning letters and disseminate information to the public regarding the ill effects of consuming ephedra.<sup>59</sup> The adverse implications of St. John's wort are equally deserving of FDA's ability to undertake preventative measures.

### **IV. Environmental Impact**

Labeling requirements, such as that proposed by CSPI, are granted a categorical exclusion from the need to prepare an environmental assessment (EA) or an environmental impact statement (EIS) if there will be no increase in the existing level of use of the product.<sup>60</sup> These labeling requirements for St. John's wort cannot be reasonably anticipated to lead to an increase in consumption of St. John's wort. Therefore, the categorical exclusion applies, and no EA or EIS need be performed for this proposed action.

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<sup>59</sup> 21 C.F.R. § 119.1; *NVE, Inc. v. Dep't of Health and Human Serv.*, 436 F.3d 182 (3d Cir. 2006).

<sup>60</sup> 21 C.F.R. § 25.30(k).

## V. Economic Impact

Pursuant to 21 C.F.R. § 10.30, information on economic impact will be submitted only if requested by the Commissioner following review of this petition.

## VI. Certification

The undersigned certifies that, to the best of his knowledge and belief, this petition includes (1) all information and views on which the petition relies and (2) any representative data and information known to the petitioner that are unfavorable to the petition.

Sincerely,

Michael F. Jacobson, Ph.D.  
Executive Director  
Stephen Gardner  
Litigation Director

Erika Knudsen  
Litigation Project Paralegal

By:



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Stephen Gardner

Attachment: Chart, **Current Statements on St. John's Wort Products**



## CHART

### Current Statements on St. John's Wort Products

Product	Cautions on Label
Solaray St. John's Wort	<b>WARNING:</b> If you are pregnant, lactating or taking a prescription MAO inhibitor, consult your physician before using this product. Due to the potential photosensitizing properties of St. John's Wort, avoid prolonged exposure to the sun.
Vitamin Shoppe Standardized Herbs St. John's Wort Extract .3% Hypericin	<b>WARNING:</b> Do not use St. John's Wort if you are pregnant, nursing or taking anti-depressants, HIV protease inhibitors (such as Indinavir) or drugs to prevent organ transplant rejection (such as Cyclosporine). Consult your physician before use if you are taking oral contraceptives, anticoagulant medication (such as Warfarin), selective serotonin reuptake inhibitors, or any other medication. Limit exposure to sun and other sources of ultraviolet light. Stop use and ask a doctor if you develop a rash.
Nature's Plus Herbal Active St. John's Wort Extended Release	<b>Note:</b> If you are pregnant or nursing, consult your healthcare professional before using any herbal product.
365 St. John's Wort (Whole Foods brand)	<b>Note:</b> Individuals who are taking any prescriptions or are pregnant or lactating, consult your healthcare practitioner before using this product. <b>Keep out of reach of children.</b> Store in a cool, dry place
Gaia Herbs St. John's Wort	Not to be used during pregnancy or lactation. If you have a medical condition or take pharmaceutical drugs, please consult with your doctor before using this product. Avoid excessive exposure to UV radiation (e.g. sunlight, tanning) when using this product. Keep away from children. Use only as directed on label. Safety sealed for your protection. Keep bottle capped at all times and store in a cool dry place. Natural separation may occur. This does not affect product quality.

<p>Sundown Naturals St. John's Wort 300 mg Standardized Extract</p>	<p><b>WARNING:</b> Not intended for use by pregnant or nursing women. If you are taking any medications, consult your doctor before use. Discontinue use and consult your doctors if any adverse reactions occur. Not intended for use by persons under the age of 18.</p>
<p>Nature's Bounty Standardized Extract Double Strength St. John's Wort 300 mg .3% Hypericin Capsules</p>	<p><b>WARNING:</b> Not intended for use by pregnant or nursing women. If you are taking any medications, consult your doctor before use. Discontinue use and consult your doctor if any adverse reactions occur. Not intended for persons under the age of 18. Keep out of reach of children. Store in a cool, dry place. Do not use if seal under cap is broken or missing.</p>
<p>Kira St. John's Wort</p>	<p><b>Cautions:</b> If you are pregnant or nursing, consult a healthcare practitioner before using this product. Do not give to children under the age of 12 unless directed by a physician. <b>Recent data suggest that if you are taking <u>any drug product</u>, and in particular a blood-thinner or anti-organ rejection medicine or HIV/AIDS medicine, you should consult with your healthcare practitioner to avoid any interactions with St. John's Wort. St. John's Wort, and certain other food/herbal products, may affect Cytochrome P-450 enzyme activity within the body, a normal metabolic pathway that is also affected by certain drug products.</b> When taking this product, use caution in exposure to excessive sunlight.</p>
<p>Whole Foods Standardized St. John's Wort</p>	<p><b>Note:</b> Individuals who are taking any prescription medication or are pregnant or lactating, consult your health care practitioner before using this product. <b>Keep out of reach of children.</b> Store in a cool, dry place.</p>
<p>Bluebonnet Herbals St. John's Wort Extract</p>	<p>No warning</p>

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**Caution:** As with any dietary or herbal supplement, you should advise your health care practitioner of the use of this product. If you are taking a prescription medicine, check with a health care professional before using. St. John's Wort is not recommended for children, or for women who are nursing, pregnant, or considering pregnancy. Although phototoxicity in humans is rare, fair-skinned individuals should avoid excessive exposure to sunlight when using St. John's Wort (*Hypericum perforatum*). May potentiate pharmaceutical MAO-inhibitors. Use of *Hypericum perforatum* with pharmaceutical antiretrovirals such as protease inhibitors, non-nuclease reverse transcriptase inhibitors, and other drugs that are similarly metabolized (such as birth control pills, digoxin, cyclosporine, blood thinners, chemotherapy drugs, asthma medications, or drugs relating to the treatment of HIV) is not recommended and should be done only under direct supervision of one's physician. Other potential side effects may include gastrointestinal symptoms, dizziness, tiredness, and mild allergic reactions (skin rash).