

Commentary – *Pharmacopeial Forum* 34(2) March-April 2008
Interim Revision Announcements to *USP 30-NF 25*
Revised June 30, 2008

Revision proposals published in *Pharmacopeial Forum* often elicit public comments that are forwarded to the appropriate Expert Committee for review and response. In accordance with the Rules and Procedures of the 2005-2010 Council of Experts, revision proposals can advance to official status with minor modifications, as needed, without requiring further public review. In such cases a summary of comments received and the appropriate Expert Committee's responses are published in the *Commentary* section of the USP website at the time the revision becomes official. For those proposals that require further revision and republication in *Pharmacopeial Forum*, a summary of the comments and the Expert Committee's responses will be included in the briefing that accompanies each article.

The *Commentary* section is not part of the official text of the monograph and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of the Expert Committee's response to public comments. If there is a difference between the contents of the *Commentary* section and the official monograph, the text of the official monograph prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the *Commentary* section, shall prevail.

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Pharmacopeial Forum 34(2)

Monograph(s)/Section(s): Black Cohosh, Black Cohosh Fluidextract, Black Cohosh Tablets, Powdered Black Cohosh, Powdered Black Cohosh Extract /Labeling

Expert Committee(s): Dietary Supplements - Information

No. of Commenters: 13

Background and Summary: A label caution statement was proposed for black cohosh family monographs in PF 33(5) [Sept. – Oct. 2007], pages 954-962. The USP Dietary Supplement Information Expert Committee (DSI-EC) reviewed the comments on the proposal, and decided to modify the wording of the proposed label statement to read as follows, to become official on April 1, 2008:

Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice.

Comment #1: One commenter asked whether USP has assigned to itself an inappropriate regulatory role by requiring cautionary labeling for all dietary supplement products containing USP listed black cohosh ingredients.

Response: The EC does not believe that USP has assigned itself an inappropriate regulatory role. The US Dietary Supplement Health and Education Act of 1994 (DSHEA) amendments to the Federal Food, Drug, & Cosmetic Act (FFD&C Act) stipulate that if a Dietary Supplement is 1) covered by the specifications (tests, procedures, and acceptance criteria of a monograph) of an official compendium, 2) is represented as conforming to the specifications of an official compendium, but 3) fails to so conform, then the supplement is considered to be misbranded within the meaning of the FFD&C Act [§ 403(s)(2)(D)]. Since USP and NF are both official compendia of the United States, this section of the Act affords legal recognition to USP–NF standards for dietary supplements, although compliance with compendial standards is voluntary and only enforceable if the dietary supplement is represented as conforming to those standards.

Comment #2: One comment stated that USP should not require labeling cautions for black cohosh-containing dietary supplements because FDA and FTC have not issued any regulation in this regard. Another comment expressed concern about the impact of the label caution requirement on the product market.

Response: In tune with the USP mission of “developing and disseminating quality standards and information”, the EC believes that the product label needs to define appropriate conditions of use (see DSHEA §402(f)(1)(A)). In setting these standards, USP is not limited to those particulars that have already been established by a governmental agency. Indeed, the USP already requires label statements for other dietary ingredients, such as Echinacea angustifolia, E. pallida, E. purpurea, licorice and St. John’s Wort. The DSI-EC also notes that the leading black cohosh product contains a label caution similar to the one proposed by the DSI-EC, and National Center for Complementary and Alternative Medicine at the National Institutes of Health also carries a caution for black cohosh in its fact sheet.

Comment #3: Several comments questioned the wording of the proposed label statement. While appreciating the Committee preference for the term Caution over Warning, the commenters expressed concern that a consumer may not see the distinction between the terms. Further, the commenters were concerned about the implied causal association between black cohosh and liver damage.

Response: Comment partially incorporated. The Committee proposed the term Caution instead of Warning because the potential harm from black cohosh products is not adjudged as probable or certain causality. Considering that 30 reports of liver damage were on record, over millions of doses used, the DSI-EC proposed to include the text that “In rare cases” black cohosh has been reported to affect the liver. In light of the concerns of the commenters, the DSI-EC has revised the wording of the proposed statement to delete the text stating: “Caution: In rare cases black cohosh has been reported to affect the liver.” Given the possibility of serious adverse events, the Committee retained the sentence “Discontinue use and consult a healthcare practitioner if you have a

liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice” to inform consumers and healthcare professionals to pay close attention and minimize potential risk. Since dietary supplements are commonly used without professional intervention, the DSI-EC believes that this label statement provides an effective means of alerting consumers.

Comment #4: One comment suggested that USP may not have adequately considered various ingredient forms of black cohosh in proposing the same caution statement for all the monographs.

Response: The review of the case reports by DSI-EC indicated usage of different forms of black cohosh – in whole or powder form (Levitsky et al 2005, Lynch et al 2006, MedWatch #84565), or various extracts (Whiting et al 2002, TGA #220336, Lontos et al 2003), or unknown formulations (Cohen et al 2004, CADRMP reports). These reports presented a prominent signal of likely hepatotoxicity from black cohosh products. While the common feature of all these reports is that the products are derived from black cohosh, the DSI-EC does not view the information to be sufficient to restrict the label statement requirement to only certain forms of black cohosh preparations.

Comment #5: One comment suggested that USP may not have adequately considered the dose, duration, and frequency of use in proposing the caution statement.

Response: The daily doses of black cohosh in the AERs ranged from 20 mg extract to the extract from 1500 mg of root. The Canadian black cohosh monograph cites the dose range for nontraditional uses as 40-200 mg dried root or rhizome per day, and for traditional uses at 300-3000 mg dried root or rhizome per day. Therefore, the toxicity reported in the AERs occurred within recommended dose ranges. Further, the reported duration of use before the adverse events ranged from 1 week (Whiting et al, 2002), to 2 weeks (Cohen et al, 2004), to 8 months (Lynch et al., 2006) or 2 years (TGA #216299).

Comment #6: Two commenters asked whether the Committee followed the Institute of Medicine (IOM) framework for evaluating the safety of dietary supplements.

Response: The DSI-EC used its Admission Criteria for dietary supplements in the USP-NF in 2002 (see Schiff PL, Jr., Srinivasan VS, Giancaspro GI, Roll DB, Salguero J, Sharaf MH. The development of USP botanical dietary supplement monographs, 1995-2005. *Journal of Natural Products*. 2006;69(3):464-472). The USP criteria do not differ significantly with the IOM framework. The USP safety criteria were presented to IOM for their consideration in the development of the IOM framework. The USP criteria require that USP conduct safety reviews for all dietary supplement ingredients for which USP-NF monographs are to be developed, and to monitor the signals of safety concern. Adverse event signals can prompt the DSI-EC to reevaluate safety and possibly reclassify the supplement’s safety. One element of the safety monitoring program is the ongoing review of the ingredient’s regulatory status in the United States and other countries. In this case, a change in the regulatory requirements in Australia, Canada and European Union signaled the need for a re-evaluation of the safety of black cohosh.

Comment #7: Several comments suggested that a safety review must be based on the totality of the available scientific, clinical and epidemiological evidence. The commenters asked whether the Committee analyzed any information related to the botanical and/or chemical analysis of products implicated in the adverse event reports AERs, pharmacological and toxicological experiments, human clinical trials, and epidemiological data, in conducting an appropriate risk assessment, to justify a caution statement on the potential hepatotoxic effect from black cohosh preparations. Another comment suggested that USP's safety determination inordinately emphasizes case reporting.

Response: The EC agrees that a comprehensive safety review requires analysis of all the pertinent information. As detailed in the USP Admission Criteria for consideration of selection and prioritization of dietary supplements proposed for placement in the USP-NF (PF 29 (1) [Jan.-Feb. 2003]), DSI-EC conducts extensive safety reviews of the selected dietary ingredients, analyzing information from human clinical case reports, adverse event reports (AERs), animal pharmacological and toxicological data, historical use, regulatory status, and global contemporaneous extent of use. The DSI-EC reviewed the safety of black cohosh and assigned a Class 1a safety rating in 2002 (meaning that no label caution is required). While that original safety review covered all the parameters just mentioned, the current proposal is the result of the DSI-EC periodic monitoring program. In the current review, clinical case reports and spontaneous AERs were analyzed. DSI-EC gives primacy to reports on human beings, in tune with Institute of Medicine (IOM, 2005) recommendations: "When available, concerns raised by human data are weighted more heavily than animal data, and are thus given higher priority. Concerns raised by either human or animal data are given greater weight than concerns raised by bioactivity of related substances or in vitro data, which are weighted equally." During the safety review the Committee also noted the limitations of the DS adverse event reporting systems. As observed in an FDA-commissioned study, the agency estimates that it receives less than 1% of all AERs associated with dietary supplements. The DSI-EC also acknowledges that clinical trials and postmarketing studies, under controlled conditions, are unlikely to demonstrate rare cases of adverse events. Accordingly, IOM states that "Absence of evidence of risk does not indicate that there is no risk." In accordance with USP's policy of continuous revision, the safety classification may be reviewed as new information becomes available. Reclassification of black cohosh as Class 1 would lead to removal of the label cautionary statement. New information may arise through the DSI-EC's constant monitoring of current reports concerning the safety of supplements or may be submitted to USP by interested parties. [The Committee also notes that an additional case report of liver damage related to black cohosh, leading to liver transplantation, was published in *Liver International* (2007 Sep; 27(7): 1017-8), and that a report of possible mechanism of liver damage by black cohosh was published in *Cell Mol Life Science* (2007 Oct 12).]

Comment #8: One comment suggested that USP has failed to qualify uncertainties in the cautionary labeling decision and to identify criteria that would reasonably lead to its removal. Several comments questioned the quality of black cohosh-associated hepatic adverse event reports, and indicated limitations such as lack of adequate documentation, as well as numerous confounding variables, viz., possibility of adulteration with Asian species, history of use of high levels of alcohol, the use of hepatotoxic prescription and nonprescription drugs, etc.

Response: DSI-EC has given consideration to the uncertainties of these cases. A careful review is now in press for the journal Menopause and expected to be published in July 2008. Case reports have been evaluated according to a causality assignment algorithm (Naranjo scale). The Naranjo scale provides a method to account for the confounders, such as alternative causality or concomitant use of other substances.

Comment #9: One comment questioned the qualifications of the members of the Committee, suggesting that the Committee lacks toxicologists and pharmacoepidemiologists with experience in the nuances related to botanical preparations, their use, relative safety, and adverse event potential.

Response: The Committee members have extensive experience in the area of dietary supplement safety and understand the nuances related to botanical preparations, their use, relative safety, and adverse event potential. The Committee membership includes a toxicologist. Two other members work closely with Poison Control Centers which monitor pharmaco-epidemiology as part of their functions.

Comment #10: Some comments suggested that the reports of liver damage by black cohosh-containing products might be similar to the background occurrence of idiopathic hepatotoxicity in general population.

Response: The Committee is aware that the estimates of the incidence of black cohosh-mediated liver damage vary. British MHRA estimated that in 2004 about 9 million treatment days were purchased in the United Kingdom. Thus MHRA estimates the rate of liver reactions is considered to be rare (occurring between 1 in 1000, to 1 in 10,000) to possibly very rare. Based on information from Australian TGA, Canadian NHPD estimated that the frequency of adverse reaction reports for black cohosh is fewer than 1 in 10 million daily doses. No definitive picture of the estimates is available for the United States. With this background, the Committee considers that the 30 adverse event reports constitute a sufficient signal to propose for a label statement to raise consumer awareness.

Comment #11: One commenter agreed with the need for the label caution but asked whether it is appropriate that only products that comply with USP standards (or other high quality standards) will bear this caution while other products of questionable quality (non-USP quality) will not bear the statement. Would potential consumers be more cautious about purchasing a good-quality (i.e., USP quality) material because it bears the warning statement? Would a potential consumer feel more secure in buying a product that is not labelled with a caution, although in reality the product may have a higher potential for presenting a problem?

Response: USP is exploring the feasibility and advisability of moving the cautionary statements to a general information chapter with character of recommendations instead of keeping them as standard requirements in the individual monographs. This approach may alleviate the issues raised by this commenter.

Comment #12: One commenter suggested continued monitoring of the safety of black cohosh, and suggested that USP enhance the monograph standards of identity, purity and composition of black cohosh to protect the public health.

Response: The commenter did not mention specifically how these standards could be improved. In accordance with USP's continuous revision policy (USP-NF Development Process: <http://www.usp.org/USPNF/devProcess/>), USP welcomes requests for revision with supporting data for enhancement of the quality monographs.

Monograph/Section(s): Irbesartan and Hydrochlorothiazide Tablets/Dissolution

Expert Committee(s): Biopharmaceutics

No. of Commenters: 0

Reason for Revision: The *Dissolution* test was revised to be consistent with the test conditions and requirements currently used in evaluating the approved marketed product. The *Medium* was changed from "0.01 N" to "0.1 N" hydrochloric acid and the volume of the medium was changed from "900" to "1000" mL. The *Time* was changed from "45" to "30" minutes and the Q value under *Tolerances* was changed from "75%" to "80%" (Q). The time specified in the *Tolerances* section was also changed from "45" to "30".

Monograph/Section(s): Oxandrolone Tablets/Dissolution

Expert Committee(s): Biopharmaceutics

No. of Commenters: 0

Reason for Revision: A "TEST 3" was added to *Dissolution* based on current approved marketed product conditions.