AMERICAN HERBAL PHARMACOPOEIA

To Whom It May Concern,

It recently came to our attention that one document was missing from the comments we submitted August 9 regarding GMPs. We understand the commenting period is over but we hope you will be so kind as to add this to the previously submitted comments of AHP. We are aware that an extension has been given for submission of additional economic impact information. We appreciate your consideration of this request.
Please insert this addendum into the AHP/ GMP comments binder section tab #3 Appendices at the beginning of (3) Monograph Comparison.

Sincerely,

Roy Upton, Executive Director

96N-0417 C247

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AMERICAN HERBAL PHARMACOPOEIA

Docket No. 96N-0417 August, 2003

Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements

Provided by: American Herbal Pharmacopoeia
P.O. Box 66809
Scotts Valley, CA 95067

Comparison of monographs of the American Herbal Pharmacopoeia (AHP), European Pharmacopoeia (EP), United States Pharmacopeia (USP), and World Health Organization (WHO): Valerian Root. To be inserted in comments submitted by the American Herbal pharmacopoeia

A comparison of the bodies of information contained in various pharmacopoeial sources should clearly demonstrate the need for recognition of the scientific validity of a broader number of sources of quality control information regarding botanicals. Typically pharmacopoeial monographs contain standards of identification and purity and testing methodologies. As previously noted, a broader body of information than typically occurs in either pharmacopoeial sources or AOAC is needed to assure the true quality of botanical products. Comparison of the monographs of AHP, EP, and USP should illustrate the importance of other bodies of information.

Valerian Root

Botanical Identification

Botanical identification is the primary form of identification for plant materials. There are numerous species of valerian that possess similar macroscopic and morphological characteristics and contain similar compounds that prevents proper identification if only typical pharmacopoeial tests are applied. Most in industry rely only upon chemical testing of a single marker compound, which again, does not establish identity. AHP and WHO monographs include botanical identification.

Adulterations

There are a number of species of valerian in international trade. Most are simply traded as "valerian" root and may include: *Valeriana edulis, V. sitchensis, V. jatamansi, V. wallichi, and V. coreana.* Most of these contain compounds identical to those found in *V. officinalis* the primarily accepted medicinal species of trade.

Handling
Proper handling of raw material is imperative for preservation of pharmacologically relevant compounds. In valerian, the essential oil, of which the pharmacologically relevant valerenic acid is a part, is contained in the hypodermis of the rhizome. Because of this, freshly harvested material must be handled with care to prevent damage to these cells and subsequent exposure of the essential oil to degradation.

Drying
The essential oil of valerian has been found to be most correlated with pharmacological activity. With valerian it is extremely important that it not be exposed to excess amounts of heat, including during the drying process. Drying crude material at temperatures under 40 ° C is required. This is stated in most pharmacopoeias. However, it is equally important to control temperatures during the milling process or significant degradation of volatile compounds will occur.

Characterization with Thin Layer Chromatography (TLC)
Most pharmacopoeias include TLC characterization in their monographs. However, because more emphasis is often placed on specific methods of analyses, such as HPLC, little interest is given to TLC and so often, the systems developed are not appropriate for the analytical endpoint. In the case of valerian, the volatile compounds are most desired. In choosing the most appropriate TLC method for the AHP monograph, the systems of both EP and USP were compared. That of EP was focused on valerenic acid. That of USP was focused on valepotriates. Valepotriates were previously believed to be correlated with pharmacological activity. However, this has since been refuted. Valepotriates degrade rapidly and are typically not found in commercial products after more than a few weeks. Therefore, analysis of valepotriates has little value for quality assurance of valerian raw materials or products.

Quantitation of Pharmacologically Relevant Constituents
Significant controversy surrounds the quantitative analysis of herbal products. The typical drug development model requires identification and isolation of an active compound. With crude botanical products, this model is of limited utility due to the fact that the activity of a large number of botanicals can not be correlated with a single compound. Therefore, analysis of a number of compounds or classes of compounds are much more reflective for quality assurance purposes.

Again, AHP compared the HPLC methods of both EP and USP. Both were based on an earlier method of Haensel and Schulz (1982) and is a method widely used in both Europe and the US. However, the means by which valerenic acid, a primary pharmacologically relevant compound, is quantified is different between the two. Recognizing that a number of compounds closely related to valerenic acid contribute to the total activity of valerian, the EP quantifies the sum of acetoxyvalerenic acid, hydroxyvalerenic acid, and valerenic acid as a valerenic acid value, whereas the USP only quantifies pure valerenic acid. The

USP approach is problematic from a number of perspectives. 1. Quantitation of valerenic acid alone is not reflective of a total extract of valerian which has been shown to be more effective than valerenic acid alone. 2. The majority of valerian extract manufacturers originate in Europe and therefore are required to follow the EP standards. 3. Products labeled according to calculations of EP versus USP will be disparate even though the products may be identical. 4. Because there is a perception among the consuming public that higher concentrations of a compound are "better" there is a disincentive for manufacturers to follow USP specifications for valerian. 5. Using disparate methods of calculation make it difficult to test products for regulatory purposes if it is unknown which methods were used. This is only known if the manufacturer claims compliance with a specific standard (e.g. Valerian Root AHP, Valerian Root EP, Valerian Root USP), or through formal regulatory action. AHP calculations allow for quantitation of valerenic acid alone or in conjunction with acetoxyvalerenic acid, hydroxyvalerenic acid, valerenic acid, valerenal, another compound with known pharmacological activity. We believe this underscores the need to have available appropriate means for quantifying compounds from different perspectives, depending upon the analytical endpoint. It also underscores the importance of disclosing what standard or method is being used.

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