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August 20, 2004

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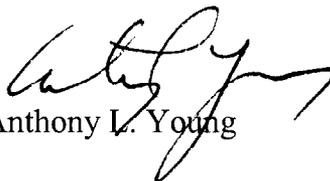
Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

Dear Sir/Madam:

Enclosed herewith for filing are an original and three copies of a Partial Withdrawal of Petition for Reconsideration and Petition for Stay of Action by the Chinese Herbal Products Committee of the American Herbal Products Association.

Thank you for your assistance.

Sincerely,


Anthony L. Young

Enclosures

1995N.0304

PSA 1

Docket No. 1995N-0304

**BEFORE THE
UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

**PARTIAL WITHDRAWAL OF
PETITION FOR RECONSIDERATION
AND
PETITION FOR STAY OF ACTION**

**BY THE
CHINESE HERBAL PRODUCTS COMMITTEE
OF THE
AMERICAN HERBAL PRODUCTS ASSOCIATION**

**Final Rule Declaring Dietary Supplements Containing Ephedrine
Alkaloids Adulterated**

August 20, 2004

Pursuant to 21 CFR § 10.33 ("Administrative reconsideration of action") and 21 CFR § 10.35 ("Administrative stay of action"), the undersigned Chinese Herbal Products Committee ("Committee") of the American Herbal Products Association ("AHPA") submitted on March 12, 2004 a petition to request a stay and reconsideration of the provisions of 21 CFR § 119.1 declaring dietary supplements containing ephedrine alkaloids to be adulterated which was made final in a Federal Register notice published February 11, 2004 (69 Fed. Reg. 6787).

The relief requested at that time was that the Food and Drug Administration ("FDA" or "Agency") reconsider the final rule to recognize that dietary supplements that contain ephedrine alkaloids do not present an unreasonable risk of illness or injury under conditions of use that include formulation as a traditional Asian herbal formula or as a traditional Ayurvedic herbal formula, and that are for dispensing by a licensed health care practitioner within a practitioner's scope of practice and in a manner consistent with traditional practice. Because the Agency erroneously stated that products that are traditional Asian herbal medicines are not marketed in the United States as dietary supplements, the petition also requested that FDA stay the final rule only insofar as it pertains to traditional herbal formulas, as described above, until the Agency has reconsidered the action based on readily available information regarding how traditional Asian or Ayurvedic herbal formulas are labeled and marketed as dietary supplements in this country.

In addition to the relief requested regarding the application of the final rule to traditional Asian or Ayurvedic herbal formulas dispensed by licensed health

care practitioners, it was requested that the Agency stay the final rule until after it has provided for notice and opportunity for comment on its decision to include pinellia (*Pinellia ternata*) and heart-leaf sida (*Sida cordifolia*) within the reach of the final rule.

The Committee has determined to withdraw those parts of its petition to reconsider the final rule in relation to use of ephedrine-containing traditional herbal formulas dispensed by licensed health care practitioners, except insofar as such practitioners use dietary supplements containing *Pinellia ternata* or *Sida cordifolia*. The Committee has also determined to continue to request a stay of FDA's position regarding *Pinellia ternata* and *Sida cordifolia* in dietary supplements, as implied in statements made in the preamble to the final rule. It is the Committee's continuing position that the Ephedra rulemaking, insofar as it purports to declare or imply that products containing *Pinellia ternata* and *Sida cordifolia* to be unlawful for use in dietary supplements, is arbitrary and capricious and contrary to law because there was no opportunity for notice and comment on this interpretation of the final rule.

A. Decision Involved

In the Federal Register of February 11, 2004, 69 Fed. Reg. 6787, the Agency published a final rule declaring dietary supplements containing ephedrine alkaloids to be adulterated. The effective date of that final rule is April 12, 2004. The Agency has previously announced, through the Commissioner of Food and Drugs, that it will take prompt regulatory action with respect to products that remain on the market after that date.

B. Action Requested

The AHPA Chinese Herbal Products Committee requests that the final rule on ephedrine-containing dietary supplements be stayed with respect to its application to the use of pinellia (*Pinellia ternata*) and heart-leaf sida (*Sida cordifolia*) in dietary supplements until the Agency has provided notice and opportunity for comment on its decision to include *Pinellia ternata* and *Sida cordifolia* within the reach of the final rule.

C. Statement of Grounds

In the preamble to the final rule FDA made several statements to the effect that the Agency considered the rule to be relevant to dietary supplements products that contain *Pinellia ternata* or *Sida cordifolia*. For example, the Agency stated:

This final rule applies to dietary supplements containing ephedrine alkaloids, including, but not limited to, those from the botanical species *Ephedra sinica* Stapf, *Ephedra equisetina* Bunge, *Ephedra intermedia* var. *tibetica* Stapf, *Ephedra distachya* L., ***Sida cordifolia* L. and *Pinellia ternata* (Thunb.) Makino** or their extracts (emphasis added). [69 Fed. Reg. 6793.]

The Committee has reviewed the Agency's various Federal Register notices that constitute the history of the Agency's rulemaking on dietary supplements containing ephedrine alkaloids. The Committee finds no mention of *Pinellia ternata* in any such notice except in the publication of the final rule. Thus, the Agency has failed to give the Committee and other interested persons notice and the opportunity to comment on the inclusion of *Pinellia ternata* within the scope of the final rule. This failure contravenes the requirements of the

Administrative Procedure Act and the Agency's regulations implementing that Act. Accordingly, the final regulation, insofar as it purports to ban the sale of dietary supplements containing *Pinellia ternata* is unlawful.

The Committee notes that FDA identified *Sida cordifolia* in the proposed rule published on June 4, 1997 as follows:

§ 111.100 Dietary supplements that contain ephedrine alkaloids. The ephedrine alkaloids include ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine, and related alkaloids. These substances are chemical stimulants contained in particular botanical products, including those from the botanical species *Ephedra sinica* Stapf., *Ephedra equistestina* Bunge, *Ephedra intermedia* var., *tibetica* Stapf., *Ephedra distachya* L., and ***Sida cordifolia*** or their extracts (emphasis added). [62 Fed. Reg. 30717-30718.]

The Committee also notes, however, that FDA's June 4, 1997 proposed rule would have, among other things, placed maximum limits of 8 mg per single serving and 24 mg per day of total ephedrine alkaloids from any of the botanical sources cited in the proposed rule. The Agency did not at the time of the publication of the proposed rule provide any reference to data and information to substantiate that ephedrine alkaloids are found in *Sida cordifolia*. A reference subsequently identified in the final rule¹, however, provides information to quantify the amount of ephedrine in *Sida cordifolia* in the root of the plant at less than 10 ppm and characterize these as "minor components in the roots." This reference also states that the same ephedrine alkaloids found in the roots are also found in the stems and leaves, which represent the articles of commerce of this plant, and "constitute the major bases in the aerial parts." This implication of

¹ Ghosal, S., R. B. Chauhan, and R. Mehta, "Alkaloids of *Sida Cordifolia*," *Phytochemical Reports*, vol. 14, pp. 830-832, 1975.

a higher concentration of ephedrine alkaloids in the aerial parts of the plant is substantiated by other references² which quantify total ephedrine alkaloids in the aerial parts as 0.085 percent³. Based on this concentration, a product would need to contain over 9 grams per serving of *Sida cordifolia* aerial parts and would have to recommend daily consumption of over 28 grams of the herb in order to reach the maximum serving size and daily levels identified in the proposed rule. These serving amounts were not and are not relevant to dietary supplements containing *Sida cordifolia* as these amounts are far above standard servings and daily consumption levels that are normal for this herb. Accordingly, because commonly available herbal formulas containing *Sida cordifolia* would have been permitted to be marketed under the proposed rule, no comments were filed by AHPA or the Committee on this specific issue. The final rule, however, determined that no amount of *Sida cordifolia* will be allowed to be included in dietary supplements. It is not reasonable to assume that any marketer of *Sida cordifolia* could have known that the Agency's proposed rule, which would have imposed labeling restrictions on products containing this herb but would not have had the effect of completely prohibiting the legal marketing of dietary supplements containing this herb, would end in a final rule in which *Sida cordifolia* containing even *de minimis* amounts of ephedrine alkaloids would be declared to be adulterated. The effect of this is that FDA has failed to provide marketers with a reasonable opportunity for comment on a ban on dietary

² Ghosh, S. and A. Dutta, *J. Indian Chem. Soc.* 7:825, 1930, as cited in Chopra, R.N., *Indigenous Drugs of India*, pp. 409-411, 1982.

³ These references also quantify the ephedrine content of the seeds of *Sida cordifolia* at 0.3 percent.

supplements containing *Sida cordifolia*. This failure contravenes the requirements of the Administrative Procedure Act and the Agency's regulations implementing that Act. Accordingly, the final regulation, insofar as it purports to ban the sale of dietary supplements containing *Sida cordifolia* is unlawful.

If the Agency intends to ban these botanicals, *Pinellia ternata* and *Sida cordifolia*, from dietary supplements, it must correct the procedural failures identified here by issuing a new notice of proposed rulemaking and allowing opportunity for comment. That notice must, at a minimum, address the issue of whether these botanicals present an unreasonable risk of illness or injury by reason of the presence and concentration, if there be any, of ephedrine alkaloids in these botanicals, or for any other reason. In the event that only trace amounts or *de minimis* amounts of ephedrine alkaloids are believed to be or found to be present in these herbs, that notice must identify the information that is the basis for the Agency's conclusion that such trace amounts of ephedrine present an unreasonable risk of illness or injury under labeled or ordinary conditions of use.

Pinellia ternata is a much more broadly used botanical ingredient in traditional Asian herbal products than is *Sida cordifolia*. Members of the Committee have also informed AHPA that *Pinellia ternata* is also much more broadly used than ephedra in traditional herbal products. Nevertheless, Committee members were surprised to learn, based on the statements made in the final rule and the reference provided by FDA in publishing that rule⁴, that *Pinellia ternata* is purportedly a source of ephedrine at a concentration less than

⁴ Oshio, H., M. Tsukai, and T. Matsuoka. "Isolation of *l*-Ephedrine From 'Pinelliae Tuber'," *Chemical and Pharmaceutical Bulletin* (Tokyo), vol. 26, pp. 2096-2097, 1978.

20 ppm (parts per million), as these firms were not aware that *Pinellia ternata* had been reported to contain ephedrine alkaloids.

The Committee's members have therefore caused samples of raw material *Pinellia ternata* and products containing *Pinellia ternata* to be tested for the presence of ephedrine alkaloids and have done so using GC-MS analytical methods⁵. In no case have any of these companies found any amount of ephedrine alkaloids in any sample of *Pinellia ternata* or product containing *Pinellia ternata*.

It is the Committee's understanding that the Agency has also analyzed samples of *Pinellia ternata* and/or products containing *Pinellia ternata*. AHPA does not know what analytical method was used by the Agency for these analyses. As the Agency is aware, however, AOAC International, under a specific contract with FDA and the Office of Dietary Supplements at NIH, has worked to develop an analytical method for determination of ephedrine alkaloids in botanical ingredients and botanical products. This method has now been adopted as a first action official method, "Determination of Ephedra Alkaloids in Dietary Supplements, Botanicals, and Nutraceuticals, HPLC-UV," and was published in the January/February 2004 issue of the *Journal of AOAC International*.

Federal regulations establish that it is FDA's policy, where a method of analysis is not prescribed in a regulation, to utilize AOAC's official methods of

⁵ Most companies submitted their samples to an analytical lab that performed analysis for detection, identification and quantification of any of the six ephedrine alkaloids using GC-MS (NIST database). The lowest calibration standard, other than a blank, for this analysis was 1 ppm. The quality control checks had a 90-98 percent recovery. Two internal standards, 2-fluorobiphenyl and p-terphenyl-d4, which eluded before and after the ephedrine alkaloids, were used.

analysis in its enforcement programs. 21 CFR § 2.19. As FDA has stated that the final rule applies to all dietary supplements containing ephedrine alkaloids, including those from *Pinellia ternata*, the Agency's interest in the presence of ephedrine alkaloids in this species is necessarily an enforcement issue. Therefore, and also given FDA's active role in contracting AOAC to develop this new method, the Committee assumes that FDA has utilized this method in its analysis of *Pinellia ternata*, even though the above cited method has at this time only been adopted as a first action official method.

Nevertheless, if the Agency has used methods other than the above identified AOAC method for analysis for the presence of ephedrine alkaloids in *Pinellia ternata* raw material and products, the Committee hereby requests a copy of the method used ("In the absence of an AOAC method, the Commissioner will furnish a copy of the particular method, or a reference to the published method, that the Food and Drug Administration will use in its enforcement program." 21 CFR § 2.19), as well as an explanation as to the rationale that supported a decision to use any other method of analysis than that published by AOAC.

4. Conclusion

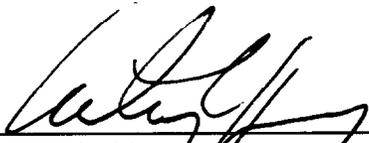
On the basis of the foregoing, the Committee requests that the Agency stay the final rule regarding ephedrine alkaloids insofar as it applies to pinellia (*Pinellia ternata*) and heart-leaf sida (*Sida cordifolia*) in dietary supplements until the Agency has provided notice and opportunity for comment on its decision to include these species within the reach of the final rule.

In addition, the Committee requests that FDA inform AHPA of the analytical method or methods it has used in its analysis of *Pinellia ternata* raw material and product samples, as well as an explanation of its determination to use an analytical method that differs from the above identified AOAC method, if, in fact, an alternate method has been used, and that the Agency also provide AHPA with a copy of the method of analysis that the Agency has used and intends to use to identify the presence of ephedrine alkaloids in botanicals.

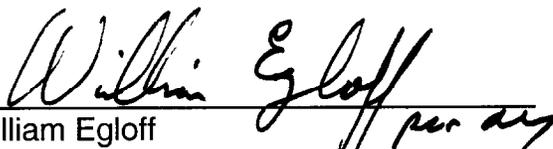
Respectfully submitted,



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