



December 15, 2008

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RE: Comments to *Pharmacopeial Forum 33(6) Stimuli* article on proposed General Chapter on Inorganic Impurities: Heavy Metals

Dear Dr. Zaidi,

This letter is written in response to the *Pharmacopeial Forum 33(6) Stimuli* article on a proposed General Chapter on Inorganic Impurities: Heavy Metals. The American Herbal Products Association (AHPA) has responded to USP requests for comments in the past and appreciates the opportunity to do so again on matters of importance regarding botanical materials.

AHPA urges USP adoption of AHPA's recommended interim limits.

A working group of AHPA's Standards Committee established an interim guidance on heavy metal limits for orally consumed botanical containing finished products after extensive consultation with industry members and laboratories as well as review of established authoritative limits. The AHPA board has now adopted this interim guidance, which represent what the trade believes to be an appropriate balance between practicality, public health, and responsible manufacturing. AHPA has nearly completed a white paper on heavy metal analysis and limits that covers the justification for these limits. It will be provided to USP as a separate communication.

AHPA recommends that USP adopt AHPA's interim limits. Additionally AHPA appropriately differentiates between heavy metal species focusing on inorganic arsenic and methylmercury. USP should do the same. AHPA's recently established interim limits are shown below and can also be found at

<http://www.ahpa.org/Default.aspx?tabid=69&aId=490&zId=1>.

AHPA’s Interim Guidance on Heavy Metal Limits

The approval of guidance policies by the Board suggests that adherence to these guidelines will support responsible trade in herbal products and is in the best interest of consumers. Therefore, AHPA highly recommends members and industry follow the association’s guidelines in addition to its trade requirements.

AHPA adopted as interim guidance specifications under current good manufacturing practice for quantitative limits of certain heavy metals that may be present in herbal supplements:

AHPA Heavy Metal Interim Recommended Limits for Orally Consumed Botanical Containing Finished Products

	Arsenic (inorganic)	Cadmium	Lead	Methylmercury
Limit (µg/day)	10	4.1	10	2.0

The following limitations and conditions apply to this guidance:

- Heavy metal quantities should be determined at the amount of a supplement that would be consumed when used at the highest labeled dose; however, the above limits are only applicable to herbal supplements that are consumed in a total daily amount of 5 grams or less. If the highest labeled dose is over 5 grams, heavy metal limits should be established at appropriate levels under current good manufacturing practice.
- A product in compliance with this interim guidance may require a clear and reasonable warning to comply with Proposition 65’s listing of these elements as known to cause cancer or reproductive toxicity.

Manufacturers and marketers are encouraged to submit information to AHPA to identify specific herbal ingredients that may require a different limit on one or more of the elements identified in this guidance, or to disclose the portion of manufactured or marketed products that exceed any of the quantitative limits established here or that require reformulation or reductions in daily serving size in order to meet these limits.

AHPA recommends that the list of metal impurities for dietary supplements be composed only of inorganic arsenic, cadmium, lead, and methylmercury at this time.

The list of USP metal impurities is quite extensive and includes nutrient elements, for which limits should not be set for dietary supplement products, and numerous metals which occur at low levels in all foodstuffs and are not known to pose particular health hazards. For the purposes of establishing limits for botanical containing dietary supplements, the list should be pared down to inorganic arsenic, cadmium, lead, and methylmercury. Other impurities should be considered only if there is a reasonable belief that they may be a problem, in which case measures should be taken by industry as appropriate. These elements are considered to be the most significant toxic elements that should be monitored when analytical procedures are employed to measure metal impurities. Appropriate risk assessment/analysis should be conducted, as for any other contaminant, in order to determine specifications for these four and for any other elements, as appropriate, from USP’s table in the *Stimuli* article.

USP should make it clear that the listing of limits for metal impurities does not present an implied need to employ analytical testing.

At the bottom of page 1 and the top of page 2 of the *Stimuli* article it states: “Regardless of source, the control of these impurities may be certified by a vendor, but purchasers also must corroborate the absence of impurities before using these materials in a manufactured article.” AHPA does not support this position as written because it promotes mandatory testing even when a risk analysis/assessment would indicate no need for the establishment of heavy metal limits. To do so would create a manufacturing burden without providing any additional assurance of safety.

Manufacturers already bear the burden of making sure their products are safe under current Good Manufacturing Practice (cGMP) as codified under Title 21 CFR Part 111. Specifically, § 111.70(b)(3) states that limits must be established “on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement.” Therefore AHPA recommends that USP’s statement be modified accordingly and be changed to “Regardless of source, the control of these impurities may be certified by a vendor, but purchasers also must corroborate that contaminants likely or certain to contaminate the product be within established recommended limits before using these materials in a manufactured article.” USP has provided no justification that additional testing is required, or that initial testing is needed to provide safety assurance that would not otherwise be already handled under cGMP

As is the case for foods, the establishment of generally applicable limits of contamination does not necessarily place a testing burden on manufacturers. The setting of specification limits for heavy metals should be risk based, which does not confer a testing requirement unless the risk is likely to be present. Also, if testing is done by one supplier subsequent testing by other suppliers and manufacturers down the supply chain is not necessary so long as the results on a certificate of analysis are properly qualified under § 111.75(3)(2)(ii) of Title 21 CFR. USP should clarify this in their proposed general chapter. Also, in situations where individual monographs are developed to include metal impurity recommended limits, the specific metals to be tested should be identified.

USP should establish an interim period of implementation and use their metal impurities project team to evaluate potential issues with the recommended limits.

Where practicality issues are known to exist (for example, lead) there should be a review of the recommended limits over an interim period. At the IOM-USP workshop, Dr. Kabelitz of Phytolab presented data showing that a 10 mg/kg lead limit would place three

herbal commodities outside the 90th percentile in delivering over 10µg/day if used in amounts over one gram. USP should review this and other data in order to identify individual botanicals for further study with specific metals testing. AHPA is willing to share preliminary data from industry values and encourages USP to employ their metal impurities project team for this work.

USP should replace the concentration column with calculation examples.

The concentration column of allowable metal impurities should be deleted and replaced with an example of a calculation of how to convert ppm (or other concentration based units) into a delivered dose in µg/day. This is needed because retail product manufacturers must work in concert with ingredient suppliers to ensure that specifications for the final retail product are met. USP should propose a standardized methodology for converting a product concentration into actual intake so that appropriate comparisons can be made. AHPA suggests that USP only present metal impurity limits for delivered doses.

AHPA supports performance based methods of analysis and requests a clarification.

AHPA supports the adoption of performance based methods of analysis of heavy metals as USP has done in the *Stimuli* article. Clarification may be in order however for the section *System Suitability* subsection *Recovery* on page 3. It could appear that a separate monitor solution is indicated for each individual sample in which case each sample would have to be run twice - once without a matrix spike and once with a spike. AHPA believes that USP intended analysis of the monitor solution as a one time validation for the sample preparation of a test article but that subsequent testing of each test article of the same material prepared in the same way would then be exempted from this requirement save for the routine quality acceptance criteria required during each routine batch analysis. AHPA requests clarification on this matter.

Limits are not a license to levels lower than achievable under cGMP.

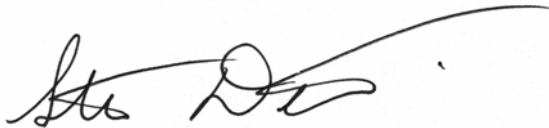
Unless indicated otherwise it is assumed that heavy metal limits are intended as guidance for manufacturing products to be consumed by adults. It is understood that the use of the terminology “under current good manufacturing practice (cGMP)” means that actual product heavy metal limits are to be kept as low as reasonably possible. Establishing recommended maximum limits does not give license for companies to permit higher levels than the lowest reasonably obtainable amount under cGMP. They do however establish maximum recommended manufacturing heavy metal levels so that any product found to

exceed the recommendations during the implementation of cGMP can be thoroughly investigated as to the reasons why and how the heavy metal burden may be reduced. It is understood that USP's proposed elements limits, like those of AHPA, do not permit a higher limit than achievable under cGMP. AHPA recommends that USP adopt language to clarify this position in the proposed general chapter.

Respectfully submitted,



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