VIA ELECTRONIC SUBMISSION

March 27, 2025

Food and Drug Administration
Dockets Management Staff
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2023-N-4225 for "Testing Methods for Detecting and Identifying Asbestos in Talc-Containing Cosmetic Products"; Request for Comments

Dear Sir/Madam,

On behalf of the United States Pharmacopeia (USP), I appreciate the opportunity to offer our comments to the Food and Drug Administration (FDA) on the proposed rule *Testing Methods for Detecting and Identifying Asbestos in Talc-Containing Cosmetic Products* ("Proposed Rule"). USP is a private, scientific, non-profit organization founded in 1820 with a mission to improve global health through public quality standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. We work to strengthen the supply chain so that the medicines people rely on for health are available when needed and work as intended.

USP provides three critical compendial standards for talc for pharmaceutical use, which could be appropriate for use in the referenced application discussed in the Proposed Rule. The USP Talc Monograph and the two General Chapters <901> and <1901> on detection of asbestos in talc address several of the limitations or shortcomings mentioned in the Proposed Rule. These revisions and improvements resulted from USP acting upon the 2010 FDA's Monograph Modernization Task Group letter to USP to consider revision to the USP Talc monograph's current tests for asbestos to ensure adequate specificity. USP created the Talc Methods Expert Panel under our Simple Excipients Expert Committee working to address the FDA letter.[1] A USP Talc monograph revision proposal and the proposals of two new General Chapters <901> *Detection of Asbestos in Pharmaceutical Talc* and <1901> *Theory and Practice of Asbestos Detection in Pharmaceutical Talc* were published in *Pharmacopeial Forum* (PF) 48(2) and became available on June 1, 2023 on the *USP-NF* online platform.[2,3,4] Chapters <901> and <1901> became official December 1, 2023, while the USP Talc monograph revisions are targeted to become official on December 1, 2025, to provide the time needed by manufacturers and users to make necessary changes.

USP respectfully offers the following comments on the Proposed Rule.

Section III.B. Need for the Regulation

[1] FDA letter in 2010 at US Pharmacopeial Convention (USP) website. https://www.usp.org/sites/default/files/usp/document/get-involved/monograph-modernization/2010-11-16-letter-from-fda-task-group.pdf. (Accessed on March 20, 2025)
[2] USP Talc monograph (revised), to be official on December 1, 2025
[3] USP General Chapter <901> *Detection of Asbestos in Pharmaceutical Talc*, official as of December 1, 2023.
[4] USP General Chapter <1901> *Theory and Practice of Asbestos Detection in Pharmaceutical Talc*, official as of December 1, 2023

USP-Rockville
12601 Twinbrook Parkway | Rockville, MD 20852-1790, USA
+1-301-881-0666 | usp.org

As part of the background, the Proposed Rule states, “In considering existing voluntary consensus standards or published methods for testing for asbestos in talc, we did not find any standardized testing method that laboratories can follow without modification to test for asbestos in talc-containing cosmetic products. Specifically, we found that the published standards and methods to test for asbestos in talc (*i.e.,* USP Talc monograph and CTFA method J4-1) have long-recognized shortcomings in specificity and sensitivity compared with electron microscopy-based methods (Refs. 17, 20, and 21).” As detailed below, recent revisions and improvements to the USP Talc monograph as well as new General Chapters <901> and <1901> may address some of the limitations or shortcomings mentioned in the Proposed Rule. Further, additional study will be beneficial to determining the scope of appropriate testing methods.

USP Talc Monograph revisions and new General Chapters

The revised USP Talc monograph (targeted to become official on December 1, 2025) references the new method in USP General Chapter (USP GC) <901> - polarized light microscopy (PLM) method, which is a standardized test method and a significant improvement over the existing optical microscopy method in the current official USP Talc monograph. It also includes specific improvements in the CTFA J4-1 PLM method for talc, and for ELAP 198.6, and ISO 22262-1 when these methods are used for the analysis of talc. The new USP PLM method includes a technique that concentrates PLM-sized asbestos particles, improving detectability (no other standard method has this protocol). PLM-sized asbestos particles were shown to be present at all spiking levels from 0.1% to 0.0001% (1000 – 1ppm) via round-robin study published in the USP Stimuli article appearing in PF 46(5) [Sep.-Oct 2020].[5] Although some labs saw asbestos (even chrysotile) at levels lower than the method detection limit of 100 ppm, the reason for non-detection was not due to the size of the particles but by the scarcity of asbestos at these low concentrations.

A method detection limit of 0.01% (100 ppm) for this PLM method was experimentally established in the round robin study by consistent detection between 5 labs for 5 mg of sample analyzed. This is significantly lower than detection limits estimated by other methods. No other method has *empirically derived* detection limits. Asbestos was also detected at 0.001% and 0.0001% levels by some labs, indicating that lower sensitivities can be achieved, and that the test is limited only by the amount of material analyzed and adequate sampling. The total amount of material prepared on the microscope slide is scanned in its entirety, improving sensitivity over point-counting techniques recommended by other methods. Within resolution limits, the total amount of material analyzed (5 mg) is *50,000 times greater* for the new USP PLM method than the amount analyzed (0.1 µg) for transmission electron microscopy (TEM).

In the new USP PLM test, the total weight prepared on the microscope slide is accurately determined; therefore, a weight-based (or even fibers/gram) result can be achieved allowing comparison between methods. No other standard method has this protocol. The new USP PLM test includes 84 images of asbestos *in talc* demonstrating the appearance of both asbestos and talc by dispersion staining, thus reducing chances of misidentification between the two. The new USP PLM test also includes a useful reference to ISO 22262-1, Annex D, for images of 100% asbestos. The new USP GC <901> also includes the test method, X-ray diffraction (XRD) that provides a qualitative result. XRD can confirm the presence of other minerals or inorganic materials used as ingredients which could be sources of impurities. XRD can also establish upper limits of reported concentrations of asbestos estimated by microscopy methods.

Clarifications on USP Test for Asbestos

[5] USP stimuli article: Modernization of Asbestos Testing in USP Talc – Part 2, PF 46(5) [Sep-Oct 2020].

USP wishes to clarify that many of the recognized shortcomings have been resolved with the new Test for Asbestos in the revised USP Talc monograph and general chapters <901> and <1901>. Many limitations of older methods (i.e., the previous USP Talc monograph Absence of Asbestos tests and CTFA J4-1) have been resolved with the new Test for Asbestos by requiring PLM as a mandatory step and by the approach of concentrating and analyzing particles likely to be seen using PLM. Reference 21 in the Proposed Rule is a USP Stimuli article published in PF 40(4) [Jul.-Aug. 2014][6] that discusses significant shortcomings of all existing methods including those associated with XRD, PLM, Scanning Electron Microscope (SEM), and TEM. Therefore, USP does not recommend any single method as being better than others. Instead, USP recommends having a systematic review of experimentally validated methods, such as those obtained through round robin studies. In the Proposed Rule, sensitivity estimates of TEM are based on theoretical assumptions of particle size and the current use of TEM in air or water methods, where larger particles are not present. Analyzing only smaller particles by TEM has not been shown to be the best approach for bulk mineral powders. TEM dust methods were designed to look at asbestos in settled dust, i.e. settled airborne particulate, not bulk talc powder.

PLM-sized particles are present in ground talc due to the presence of the entire particle size distribution for all phases, including coarse and fine particles (unlike naturally size-selected air samples, which contain only finer airborne-sized particles). If present in ground talc, enhancement of asbestos is expected in the coarser size fraction due to its resistance to grinding. Differential grinding effects are especially pronounced for mixtures containing asbestos (high tensile strength) and talc (soft and easy to grind). The presence of concentrated coarser asbestos particles offsets concerns that individual fibrils are not resolved by PLM. In fact, PLM-sized particles are present even for ultra-fine talc (demonstrated by a real-world milled talc sample with a median particle size of 1.5 µm). Coarse asbestos particles are more likely to show identifiable asbestiform morphology, allowing reliable discrimination between asbestos and non-asbestos types of the same mineral (confirmed in the USP PLM round robin study). While chrysotile by TEM is readily identifiable due to both its unique morphology and electron diffraction pattern, the finer or TEM-sized particles of amphibole are less likely to provide this information, especially where only a few particles are observed. Further, the use of < 5.0µm length particles make this even more difficult, the unique dimensionality of amphibole asbestos fibers more recognizable in the >5.0µm length particle sizes. The approach of analyzing PLM-sized particles was shown to be as effective for chrysotile as it was for amphibole asbestos in the USP round robin study. This was an unexpected result, further demonstrating the utility of experimental study to derive method-based detection limits by empirical data.

Section V.C. What test methods must you use? (Proposed § 730.3(c))

FDA proposes requiring manufacturers of talc-containing cosmetic products to test for asbestos using PLM (with dispersion staining) and TEM with energy dispersive spectroscopy (EDS) and selected area electron diffraction (SAED). FDA evaluated the USP test 'Absence of Asbestos' in the current USP Talc monograph as part of its considerations in the Proposed Rule, and notes that in the briefing to the new General Chapter <901>, USP proposed that a third talc expert panel be convened to develop an electron microscopy test method to complement the PLM method, that "promises to improve the sensitivity and specificity of the protocol for asbestos even further." As mentioned, updates to the USP Talc Absence of Asbestos test at FDA's request have been proposed to improve specificity and are supported by USP GC <901> and <1901>.

[6] USP stimuli article: Modernization of Asbestos Testing in USP Talc, PF 40(4) [Jul-Aug 2014].

Further study should be conducted to determine the most appropriate testing methods

USP suggests FDA to consider sensitivity and specificity determined from experimental study before indicating electron microscopy has improved sensitivity and specificity over the revised USP Test for Asbestos targeted to become official in December 2025. It has not been experimentally demonstrated that the approach of analyzing coarser particles in a ground bulk mineral powder by PLM is inferior to analyzing the finer particles by TEM. A recent publication by Sanchez et al. 2023 shows that PLM analysis was more sensitive to the detection of amphibole relative to conventional TEM analysis of a bulk material comparable to the FDA proposed rule requirements.[7] The most significant parameter in improving sensitivity is the amount of material analyzed (5 mg by the USP PLM test compared to 0.1 µg by TEM in the Proposed Rule). Since PLM-sized asbestos particles have been shown to be present at all spiked concentrations in the USP round robin study, the USP PLM method is shown to be appropriate for ground bulk mineral powders.

Although USP proposed a third expert panel to evaluate electron microscopy as part of its systematic review with experimental validation, no guarantees were made regarding improved sensitivity and specificity of TEM. The sensitivity of TEM is yet to be experimentally proven and the theoretical sensitivity will be discussed later in the comments. Notably, the specificity issues exist for TEM that are different than those of PLM. These include but are not limited to the following: 1) the interference between talc (the matrix) and anthophyllite asbestos (an analyte that could have similar chemistry and may produce ambiguous diffraction patterns), and 2) the inferior ability of TEM to distinguish asbestos from non-asbestos particles of the same amphibole mineral. This is even more pronounced using the counting criteria in the Proposed Rule. These issues, if not resolved, could increase the likelihood of false positives. Sensitivity and specificity issues relative to detection and identification have not yet been fully resolved for TEM but will be evaluated during the second-phase round robin study planned by the current USP Talc Expert Panel.

As in the PLM round robin study, spiked standards of chrysotile, tremolite asbestos, and tremolite (non-asbestos) are planned at levels from 0.1% (1000 ppm) to 0.0001% (1 ppm) to empirically determine the method detection level for TEM. In addition, spikes of anthophyllite asbestos and anthophyllite (non-asbestos) will be added to evaluate the specificity issue. After experimental studies take place, the utility of methods will be adequately compared and method-based detection limits, not theoretical detection limits, will be established.

FDA also notes that despite “demonstrated improvements” in sensitivity and specificity, the capability for detection and identification of asbestos in talc used to manufacture cosmetic products using the XRD and PLM techniques described in <901> and <1901> remains limited. Until experimental evaluation takes place, USP asks FDA to reconsider theoretical analytical sensitivities before concluding the USP PLM “Test for Asbestos” remains limited in comparison to electron microscopy. Techniques described in chapters <901> and <1901> include improvements in the PLM technique to those of existing methods, and the method equivalency, superiority, or inferiority has yet to be determined compared to TEM. Theoretical calculations indicate that the new USP PLM method should be more sensitive than TEM, not less, which is 200 fibers per gram (F/g) by USP PLM method compared to 10^7 F/g for TEM method stated in the proposed rule.

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[7] Sanchez, MS., McGrath-Koerner, M., McNamee, BD. “Characterization of elongate mineral particles including talc, amphiboles, and biopyriboles observed in mineral derived powders: Comparisons of analysis of the same talcum powder samples by two laboratories” Environmental Research, Volume 230, 1 August 2023, 114791

Although this implies that the USP PLM test is orders of magnitude more sensitive than TEM for fiber counts, this approach does not take into account the uncertainties inherent to the instrumentation, particle population sizes, chrysotile compared to amphibole asbestos, and sample preparation effects. The USP Talc Expert Panel will be determining a method detection limit for electron microscopy in its ongoing work to account for these uncertainties. Simply, specific method detection limits for TEM versus PLM still need to be determined. Method detection limits involve statistical confidence in results, which depend on factors such as reproducibility and consistent detection (especially problematic with asbestos because analytes occur as discrete particles in the bulk mineral matrix). Reproducibility issues acknowledged in the Proposed Rule may be due to this rather than lack of standardized methods, as it is observed even when the same TEM method is followed. Because there are some shortcomings of TEM regarding both sensitivity and specificity, without experimental validation, its advantage over the revised USP PLM "Test for Asbestos" method remains undetermined.

Proposal to use the limit of detection corresponding to detection of a single asbestos fiber as the basis for a positive sample

FDA is also seeking comments regarding a proposed requirement on how FDA determines whether a sample is positive. FDA notes in the Proposed Rule that it has used the limit of quantification as the basis for determining that a sample is positive, however, they are now proposing that the limit of detection corresponding to detection of a single asbestos fiber as the basis for a positive sample.

USP notes that this proposal diverges from the current generally accepted TEM fiber counting procedures promulgated in certain United States laws and regulations, as well as in some international standard methods, including those used by the FDA's referenced 200 samples, which use the Poisson distribution statistical test to set the baseline for detection limits based on a defined count above background. Further, a more targeted justification for the use of detection limits based on counts with parameters determined by experimentation is set forth in detail in ASTM D6620-19.

USP also notes that there may be challenges to reproducibility of a single asbestos fiber limit, including those caused by laboratory contamination, especially for laboratories that routinely handle asbestos standard reference materials and perform testing on asbestos-containing building materials, and/or environmental presence of background fibers from multiple potential sources. Also, extrapolations of potential results require statistical validation based on empirical data, which is currently insufficient. Therefore, the USP Talc Expert Panel intends to determine an empirically based and method specific detection limit through ongoing round robin studies of SEM and TEM based on known spiked concentrations. We'd welcome the participation of the Agency in these round robin studies.

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Thank you for the opportunity to comment. We look forward to continuing to work with FDA and industry on testing methods for asbestos in talc. For more information, please contact Hilary Daniel, Senior Regulatory Affairs Policy Manager, at hilary.daniel@usp.org.

Sincerely,

Jaap Venema, Ph.D.
Chief Science Officer and Chair, Council of Experts