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Modernization of Asbestos Testing in USP Talc[a]

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ABSTRACT In response to a request from the U.S. Food and Drug Administration through the FDA Monograph Modernization Task Group, the *USP Talc* monograph is being modernized to ensure that the tests for asbestos have adequate specificity. The USP Excipients Expert Committee of the Council of Experts approved the formation of a Talc Expert Panel, which is charged with modernizing the *USP Talc* monograph. This *Stimuli* article outlines the current thinking of the USP Talc Expert Panel and discusses several test procedures and measurement criteria that are under consideration. The Talc Expert Panel is considering these procedures and criteria for recommendation to the USP Excipients Expert Committee for control of *Absence of Asbestos* in USP *Talc.* This article concludes with a summary of the adverse health effects resulting from asbestos exposure, and a proposal for updating the *Definition* and *Labeling*sections of the *USP Talc* monograph. The USP Talc Expert Panel's recommendation for revision of the test for *Absence of Asbestos* will include omission of the infrared spectroscopy test and inclusion of a revised x-ray diffraction procedure, in combination with one or more microscopic evaluations (polarized-light microscopy, transmission electron microscopy, or scanning electron microscopy).

1. INTRODUCTION

As part of USP's initiative to update and improve its monographs for drug substances and products in the *U.S. Pharmacopeia* and *National Formulary* (*USP–NF*), USP is focusing on monographs recently identified as high priority by the U.S. Food and Drug Administration (FDA) through the FDA Monograph Modernization Task Group (MMTG). On November 16, 2010, the FDA MMTG sent a letter to USP indicating the desire to modernize the high-priority *USP Talc*monograph[f] (1). The request for revision was stated as follows: *“Labeling should be revised to match the statements that are provided in the Talc FCC monograph, thereby assuring that Talc is not sourced from mines that are known to contain asbestos. Also, USP should consider revising the current tests for asbestos to ensure adequate specificity.”*

The current *USP Talc* monograph contains a test for *Absence of Asbestos* that includes three procedures. Analysts are given the option to perform either *Procedure 1* or *Procedure 2,* which consist of infrared spectroscopy (*Identification Tests*–

General ⟨ 191 ⟩) and x-ray diffraction (*Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction (XRPD)* ⟨ 941 ⟩), respectively. If either test gives a positive result, then the third procedure, consisting of optical microscopy (*Optical Microscopy* ⟨ 776 ⟩) must be performed to confirm. The infrared spectroscopy (IR) and x-ray diffraction (XRD) methods, as currently written, can lead to false-negative results, which could allow talc samples with asbestos contamination to pass the *Absence of Asbestos* test in the *USP Talc* monograph. Even after applying the current USP microscopy method, the analyst cannot rule out the presence of hazardous fibers in a sample of talc. In addition, the lack of identification procedures in the optical microscopy section of the method could lead to false-positive results. This underscores the need to modernize the current monograph for two reasons: 1) both the IR and XRD methods have relatively high detection limits for asbestos, and 2) there is no known "safe" level of asbestos exposure.

In response to FDA's request to modernize the *USP Talc* monograph, the USP Excipients Expert Committee (EXC EC) formed a Talc Expert Panel (EP). The Talc EP consists of volunteer members from among talc suppliers, pharmaceutical manufacturers, regulatory and government agencies, academia, and instrument manufacturers. The charge of the EP is to update and modernize the methodology for testing that is described in the *USP Talc*monograph, thereby establishing a quality standard based upon well-defined specifications and analytical methods. This modernization will ensure that the production of talc meets an appropriate standard for the *Absence of Asbestos,* using currently available methods set below the feasible limits of detection.

This *Stimuli* article outlines the current thinking of the Talc EP and details its objectives and charge. The article then discusses several test procedures and measurement criteria under consideration by the Talc EP for recommendation to the EXC EC for the control of *Absence of Asbestos* in USP *Talc.* Section 2 discusses the derivation of talc and the formation and composition of talc deposits, whereas section 3 addresses the mineral chemistry and morphology of asbestos species potentially encountered in commercial talc deposits. Section 4 highlights the current USP test procedures for determination or analysis of asbestos in a talc matrix, while section 5 introduces methods under consideration for asbestos testing in USP*Talc.* Section 6 discusses the adverse health effects from asbestos exposure and outlines why asbestos contamination is a serious concern for USP *Talc,* thereby underscoring efforts to ensure that asbestos levels are below the feasible limit of detection when using current, state-of-the-art methodology. Finally, section 7 addresses labeling while section 8 includes the conclusions and summary.

2. TALC DERIVATION—OVERVIEW OF FORMATION AND COMPOSITION OF TALC DEPOSITS

Talc is a member of the phyllosilicate (sheet silicate) group of silicate minerals.[9] Talc's normative chemical formula is $Mg_3Si_4O_{10}(OH)_2$, with generally small amounts of substitution of other elements in more than trace amounts. These substitutions, which

include Fe for Mg, Al for Si, and F for OH, generally do not have a major effect on the mineral's desirable properties. Structurally, talc is composed of a layer of Mg-O-OH in octahedral coordination sandwiched between two layers of Si-O in tetrahedral coordination. The tetrahedral-octahedral-tetrahedral units (t-o-t) are linked together by relatively weak van der Waals bonds, which result in the characteristic friability or cleavage of talc layers (*Figure 1*).

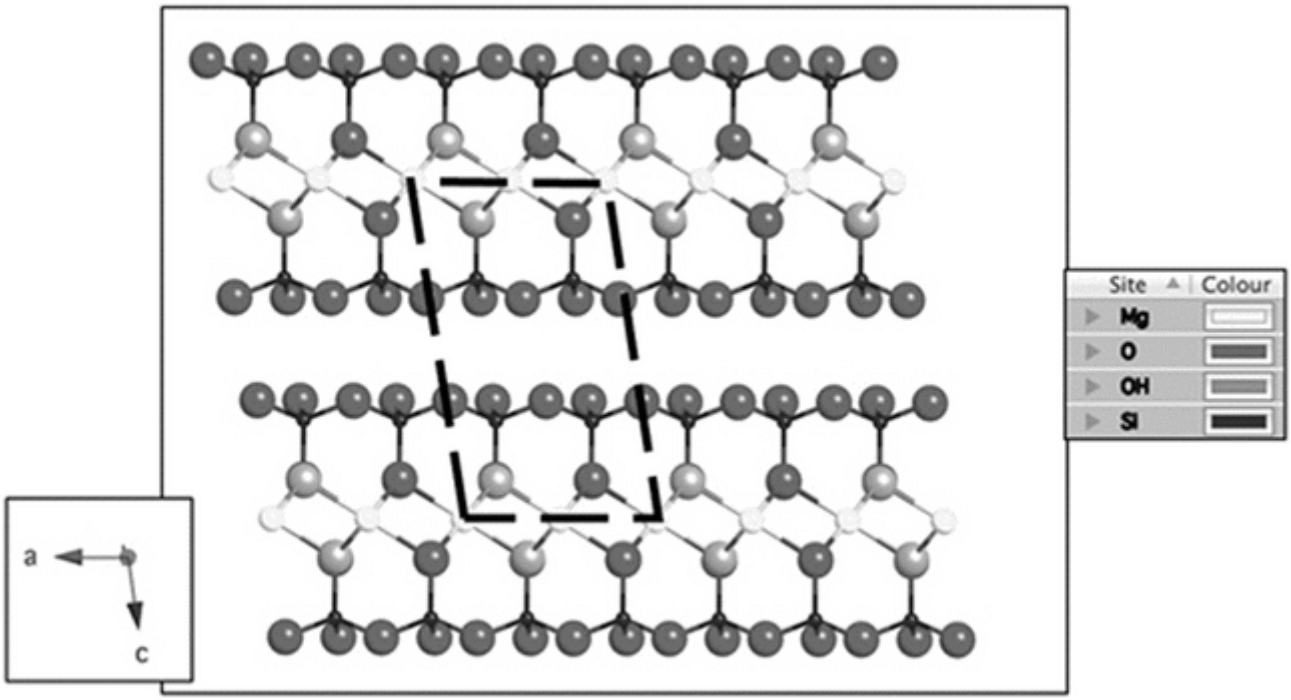

Figure 1. Crystal structure of Talc. The atoms are shown as small balls: magnesium (yellow), silicon (blue), and oxygen (red with orange for OH). Silicon, surrounded by four oxygen atoms, occupies the tetrahedral site while magnesium, surrounded by six oxygen atoms, occupies the octahedral sites of the unit cell. The unit cell (shown with the dashed black line) has dimensions of 5.3 × 9.2 × 9.5 Å. Created with CrystalMaker® version 8.7.

Talc can form when the requisite stoichiometric combination of elements is present in the initial rock (protolith) at sufficient temperature, pressure, and length of time. Talc can also form as an “up-temperature” (prograde) or “down-temperature” (retrograde) reaction product. The preservation of talc from elevated metamorphic conditions depends largely on cooling rates and the chemical flux of volatiles, especially water and carbon dioxide.

Macroscopic talc forms individual crystals and masses of crystals that separately and collectively have a “platy or plate-like” appearance (2). Talc “plates” can be relatively “small”—micrometers across—or relatively “large”—centimeters or more across (3) (*Figure 2*). Aggregates of the plates have been described as having a sample texture

that is micaceous or foliated. "Foliated" means that the flattened talc grains are largely oriented as sub-parallel plates.

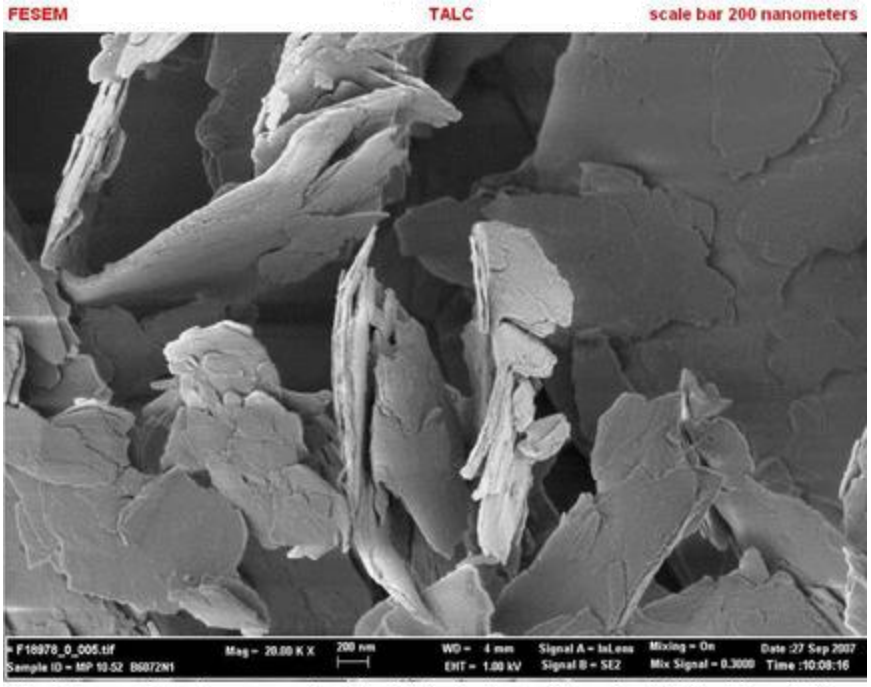

Figure 2. Scanning electron microscopy image of typical lamellar Talc.

The physical form of talc rock is related to the geologic source (protolith) and the geologic conditions during the formation of the deposit. Talc's platelet size determines its lamellarity. Highly lamellar talc (informally classified as macrocrystalline talc) has large, stacked platelets, whereas microcrystalline talc has small, randomly oriented platelets.

The lamellar aggregates are accumulations of individual crystals that are approximately equidimensional in the equatorial plane and relatively thinner perpendicular to that plane. Occasionally, talc will grow “faster” in the shortest atomic-length direction and produce a gross shape that is elongated lamellar, which is similar to a ribbon and is informally described as “ribbon talc”. When the growth in a single direction is extreme, the talc can develop a fibrous morphology.

Given the variability of pressure, temperature, and chemical flux in the geologic environment, it is not uncommon for talc to undergo alteration, via chemical and structural changes, to other minerals. Talc may even be found occasionally in a transitional state when a reaction is incomplete and frozen-in.

The four types of geologic environments most typical for talc formation are:

1. Large geographic-geologic areas (regionally) of prograde metamorphic sedimentary rocks [derived from either Mg-rich carbonates (dolomites) or shale (clay- and quartz-rich sediments)];

2. Magnesium-rich, silica-poor (ultramafic) rocks undergoing serpentinization (an alteration process that results in hydration and enrichment in silica) followed by chemical alteration arising from the influx of carbon dioxide-rich fluid;
3. Amphibole-bearing metamorphic rocks undergoing retrograde metamorphism;
4. A broad variety of protoliths undergoing local metamorphism because of elevated heating (contact metamorphic effects) (2, 4).

Talc ores are sometimes classified into two major groups based on the type of geologic environment: talc deposits with amphibole minerals as important components of the host rock, and talc deposits that are essentially "amphibole free." The majority of globally produced commercial talc is formed by the prograde sequence of sedimentary rocks (Type 1), or to a lesser extent, derivation from ultramafic igneous rocks (Type 2). *"Ultramafic is the most abundant deposit worldwide, but metasedimentary is by far the most widely exploited commercially and accounts for more than 70% of world production [of all talc, including pharmaceutical grade]"* (2).
For the remaining 25%–30%, industry experts have estimated that only a minor segment of all markets uses talc derived from amphibole-bearing metamorphic rock, and this has declined in recent years (5, 6) (*Figure 3*). Talc derived from host deposits with amphiboles is of primary concern because of the possible presence of amphibole and serpentine asbestos in the final product. Historically, tremolitic talc (Type 3) has not been used in the United States for pharmaceutical applications. *Figure 3* represents the current estimated world production of talc (5) divided into the four types.

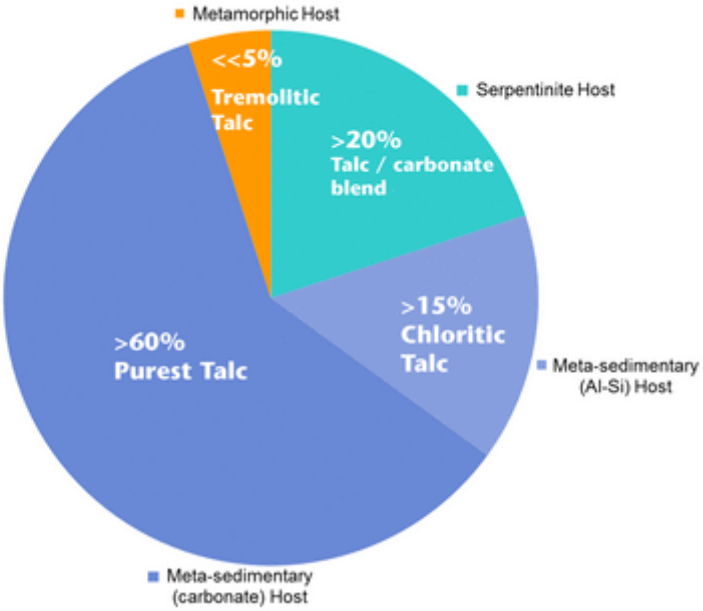

Figure 3. Current estimated world production of Talc.

3. MINERAL CHEMISTRY AND MORPHOLOGY OF ASBESTOS SPECIES POTENTIALLY ENCOUNTERED IN COMMERCIAL TALC DEPOSITS

A large number of accessory minerals may be found in talc deposits, depending on the formation conditions of the deposit. These minerals include but are not limited to dolomite, magnesite, calcite, and quartz, as well as a variety of micas, chlorites, feldspars, serpentines, and amphiboles. Of particular concern for this discussion are minerals which, under certain conditions, can occur in an asbestiform growth habit, and also the minerals that may interfere with detection of asbestos during analysis.
Chlorites, typically clinochlore and chamosite, have the general composition $[(Mg,Fe)_3(Si,Al)_4O_{10}(OH)_2 \cdot (Mg,Fe)_3(OH)_6]$ and are fairly common in some talc-rich rocks and ores. Chlorite group minerals are layered silicates (phyllosilicate) that are composed of “chemical sandwiches” similar to talc, but with an additional layer of Mg-Al-O inserted into the stacking sequence. Chlorites are highly variable in composition and structural complexity, and typically do not form fibrous morphologies. Asbestos is a commercial/industrial term applied to certain naturally occurring minerals when these minerals crystallize in the asbestiform habit (generally defined as minerals with the growth form similar to commercial forms of asbestos). The commercially desirable properties of asbestos include flexibility, tensile strength, and resistance to heat, electrical conductivity, and chemical corrosion.
Certain asbestiform minerals are regulated under the rubric asbestos in numerous federal and international regulations. These regulations are based primarily on the asbestos minerals that were used commercially, and most regulations and approved analytical methods specifically list those minerals because of early epidemiological studies linking commercial asbestos with disease. Historically, analytical methods used for identification of regulated asbestos rely on the commercial and physical properties of the minerals rather than properties that may be associated with the etiology of disease. The asbestos minerals typically listed in regulations and methods include chrysotile, a member of the sheet-silicate group, and five amphibole minerals of the chain-silicate group. These five are “amosite” (cummingtonite-grunerite asbestos), crocidolite (riebeckite asbestos), tremolite asbestos, actinolite asbestos, and anthophyllite asbestos. Historically, chrysotile has been the most commonly used asbestos in industry (approximately 90%). Chrysotile is still being mined in a few countries; however, most countries have banned the mining of all types of asbestos because of the demonstrated and perceived health risks of the material.
Although there is general agreement in the international community, it is important to note that there is no uniformly and universally accepted “group” of asbestos minerals, nor are there universally accepted definitions for asbestos and asbestos-related particles. A tabulation of definitions for asbestos, asbestiform, and other asbestos-related terminology used in this article can be found in Lowers and Meeker (2002), and ASTM D7712-11 (7, 8).

3.1 Serpentine

Serpentine is a subgroup of minerals with the composition $[(Mg, Fe)_3(Si_2O_5(OH)_4]$. Rocks containing serpentine minerals can contain serpentine asbestos (chrysotile) if formed under specific high-shear conditions. *“There are three principal forms of serpentine—*

lizardite, antigorite and chrysotile—all with approximate compositions of $Mg_3Si_2O_5(OH)_4$. The most abundant is lizardite and the least is chrysotile, but the latter is perhaps the best known...” (9)

Chrysotile is a layered silicate mineral with the nominal composition $Mg_3Si_2O_5(OH)_4$. The mineral generally forms as bundles of extremely thin fibers that can split into single units called fibrils. Chrysotile fibrils can measure as little as a few tens of nanometers in diameter, with lengths up to tens or hundreds of micrometers. These fibrils form as the mineral grows (growth habit) because of a slight atomic mismatch between alternating layers of SiO_4 tetrahedra and MgO octahedra. The atomic forces generated by this mismatch cause the layers to curve into a tight scroll during growth, thereby producing the individual fibrils.

3.2 Amphibole

The amphibole minerals have a double-chain structure composed of layers of rings of SiO_4tetrahedra held together by alternating chains of octahedral units and interlayer cations. Amphiboles have a general chemical formula of $A_{0\text{-}1}B_2C_5T_8O_{22}W_2$ where only the most common ions for each crystallographic site are as follows:

A = Na, K; B = Na, Ca; C = Mg, Fe, Al; T = Si, Al; W = OH, F, Cl

As suggested by the formula above, amphiboles can be extremely complex chemically, and more than 80 mineral names are currently designated, based on chemistry, by the International Mineralogical Association (IMA) (10, 11).

Amphiboles are fairly common rock-forming minerals and occur in a variety of growth habits depending on origin and conditions of formation. Single amphibole crystals are generally elongated along the *c* crystallographic direction and typically form in a prismatic (prism-like) habit. Amphiboles can also form as acicular (needle-like) crystals, and very rarely as asbestiform crystals. Amphibole asbestos fibrils can measure less than a hundred nanometers in diameter, with lengths up to tens or hundreds of micrometers. Amphibole asbestos has been mined commercially in the past, and two types, amosite and crocidolite, were widely used in a variety of commercial applications until the 1970s, when rising health concerns caused most countries to cease commercial production.

In many cases, chrysotile is easy to define and identify because of its thin fibers, unique rolled sheet structure, and simple chemistry, but the same cannot be said of amphibole asbestos. The reasons for this include the extensive chemical substitution that can occur in amphiboles, and the fact that the IMA system of nomenclature is based on mineral chemistry. Mineral identification using the IMA nomenclature requires highly accurate chemical analyses, particularly where amphibole minerals are not close to pure end-member compositions (12, 13). For example, pure end-member tremolite has the composition $Ca_2Mg_5Si_8O_{22}(OH)_2$. If, however, fluids rich in sodium, potassium, and iron were present during formation, the resulting mineral might have a composition such as $(Na,K)_{0.4}(Na,Ca)_2(Mg,Fe)_5Si_8O_{22}(OH)_2$ due to chemical substitutions. The resulting mineral, although very similar to tremolite, would be classified by the IMA as winchite.

This example is significant because most current regulations list tremolite as regulated, but winchite is not even addressed, although the two minerals are associated with similar health risks (14–17).

In addition to chemistry, particle morphology is used to determine if a single amphibole particle or population of particles is asbestos. Again, the analytical methods rely on properties of commercial asbestos rather than properties directly tied to health effects. As stated above, amphiboles can form in a variety of morphologies ranging from prismatic to asbestiform.

4. CURRENT USP TEST PROCEDURES FOR DETERMINATION OR ANALYSIS OF ASBESTOS IN A TALC MATRIX

The current USP *Talc* analytical procedure for *Absence of Asbestos* utilizes either infrared spectroscopy (IR) or x-ray powder diffraction (XRD); the choice is left to the user. These initial screening methods are useful for evaluating the overall quality of the talc. Both the IR and XRD procedures, as written in the *USP Talc* monograph, are pass/fail tests that do not provide specific detection limits. If there is any indication in the test results that minerals which may have an asbestos component are present (a positive result), then the current USP method requires that the sample be examined using optical microscopy. Currently there are no standard reference materials available that can be used to document a laboratory's effectiveness in detecting asbestos in a talc matrix.

In addition, the pharmacopeial test procedures for determination or analysis of asbestos (IR, XRD, and optical microscopy) do not detect all particles thought to be hazardous, but only the subset of particles that are amenable to routine detection and quantification by the specific analytical test procedure being used. Because fibrous minerals in talc are contaminants rather than commercial materials added for their desirable properties, it is important to recognize that applying analytical methods developed for commercial asbestos may not be adequate in terms of sensitivity and specificity for determining the absence of asbestos in talc for use in pharmaceutical products (*Table 1*). In addition, other minerals (such as chlorite or kaolinite) can occur in talc; both cause interference in the detection of asbestos in talc. As with any analytical procedure, certified reference materials are necessary to properly calibrate the system.

Table 1. Current Methods for Asbestos Detection and Quantification in a Talc Matrix

Method	Description in current USP monograph	Advantages	Disadvantages
IR absorption spectroscopy	758 ± 1 cm^{-1}, may indicate the presence of tremolite or chlorite. If the absorption band remains after ignition of the substance at 850° for at least 30 min, this indicates the presence of tremolite. In the range 600 cm^{-1} to 650 cm^{-1}using scale expansion, any absorption band or	Instrumentation is typically available for companies that need to perform pharmaceutical testing.	Cannot distinguish asbestos from non-asbestos forms of the same mineral. The method is subject to interferences with other minerals.

Method	Description in current USP monograph	Advantages	Disadvantages
	shoulder may indicate the presence of serpentines.		Detection limit is unknown.
X-ray diffraction	The presence of amphiboles is detected by a diffraction peak at 10.5 ± 0.1° 2Θ, and the presence of serpentines is detected by diffraction peaks at 24.3 ± 0.1° 2Θ to 12.1 ± 0.1° 2Θ.	Important in fully characterizing mineral assemblage. Provides information about bulk purity. Can give information about the origin of the talc deposit and the associated risk. Can indicate if problematic levels of any phase are present.	Cannot distinguish asbestos from non-asbestos forms of the same mineral. Limit of detection may be too high for public health and regulatory purposes. Detection limit of serpentine is severely affected by presence of chlorite. May give false-negative result if used as a screening method.
Optical microscopy	The presence of suspect fibers is inferred from the occurrence of particles with length-to-width ratios in the range from 20:1 to 100:1, or higher for fibers longer than 5 µm.	Identification considers particle morphology.	Particles of milled material may be disaggregated and inconsistent with typical asbestos morphology. Particles of milled material may be below resolution limit. Due to lack of identification procedures, may give a false-positive result. Limit of detection may be too high for public health and regulatory purposes.

5. METHODS UNDER CONSIDERATION FOR ASBESTOS TESTING IN TALC

Talc analytical methods have been a subject of development by ASTM International (18). The Asbestos Analytical Committee (D22.07) has been working on a series of detailed procedures covering XRD, polarized-light microscopy (PLM), and transmission electron microscopy (TEM) analyses, specifically for pharmaceutical Talc. To date, drafts of all three procedures have been reviewed by the ASTM committee, although the TEM method has progressed the furthest. The Expert Panel is monitoring these methods and is working with ASTM, where appropriate, to further their development.

5.1 X-ray Diffraction

XRD is used for qualitative determination (identification) and quantitative determination (weight percent) of crystalline substances. The three-dimensional structure of crystalline substances generates elastic x-ray scattering called diffraction, and satisfies the Bragg Equation:

$$n\lambda = 2d\sin\theta$$

where n is an integer called the order of the reflection; lambda (λ) is the wavelength of the characteristic line of the tube anode material, typically Cu Kα; d is the interplanar spacing of given crystal planes of a crystal; and theta (θ) is the x-ray incidence angle (Bragg angle) under a given instrument geometry. The Bragg equation represents an inverse relationship where low theta (θ) values would have a corresponding high d-spacing (usually expressed in Angstroms) and vice versa. When using XRD, consideration should be given to the differences in the particle size distribution, crystallinity, and interferences, among others. Matrix-matching of the standard and test materials and their preparations are important criteria to meet in order to achieve precise and accurate results. XRD provides an important initial screening of the talc product for ancillary mineral phases, especially for those of total amphibole and total serpentine. Amphibole and serpentine minerals are typically non-asbestiform, but they can exist more rarely as an asbestiform variety. However, XRD does not delineate the non-asbestiform and asbestiform varieties of amphibole or serpentine; therefore, XRD should be combined with one or more microscopic techniques. For total amphibole, conventional XRD provides a qualitative non-detect at < 0.5% in talc. XRD performed with extended count times can achieve lower detection limits such as < 0.1%. For serpentine, XRD provides qualitative and quantitative detection limits that will vary because of interference from the chlorite group minerals; here, detection limits could be as low as 0.1% or as high as 2%.

5.2 Polarized Light Microscopy

Polarized-light microscopy (PLM) is used to identify a substance based on its optical properties. The fibers in talc product that satisfy pre-defined criteria for optical properties including refractive index, sign of elongation, and extinction angle, as well as dimensions and morphology, will be identified as asbestos based on specific regulatory methods. PLM can be used for quantitation of asbestos, often using a “point-count”

method (19). The detection limit can be improved by increasing the number of points counted. Accurate PLM quantitation depends on resolution and identification of asbestos and non-asbestos particles. The fibers with particle sizes below the wavelength of illumination cannot be resolved by PLM. The unresolved fibers are not counted, which may lead to false-negative results. For this reason, amphibole and serpentine detected by XRD may be unresolved by PLM.

5.3 Electron Microscopy

Electron microscopy, including transmission electron microscopy (TEM) and scanning electron microscopy (SEM), overcomes the resolution limitations of PLM and has the ability to detect extremely small asbestos fibers. The minimum fiber width that can be routinely characterized by TEM is on the order of 0.03 µm (19, 20), corresponding to the typical width of single chrysotile fibrils. TEM is the only method that can accomplish this, although the modern field emission SEM can approach this capability. TEM and SEM provide elemental composition data through energy dispersive x-ray spectroscopy (EDS), an important component of the identification of the mineral. TEM also provides information on crystalline structure through selected area electron diffraction (SAED), and recent developments using electron back-scattered diffraction (EBSD) may enable analysts to derive similar crystallographic information with SEM (21). In a recent review of the draft National Institute for Occupational Safety and Health (NIOSH) roadmap for asbestos research, the Institute of Medicine of the National Academies stated: *"The need to develop new [analytical] methods based on electron microbeam techniques is critical and should not be limited by existing regulatory constraints or existing policy."* (14, 15) A comparison of the methods described above, outlining their advantages and disadvantages, is presented in *Table 2*.

Table 2. New Microscopy Methods Under Consideration

Method	Description	Advantages	Disadvantages
Polarizing light microscopy	The presence of asbestos is confirmed by the occurrence of particles with asbestos morphology and their identification as an asbestos mineral based on optical properties/dispersion staining.	Identification is based on morphology and phase determination, which can be conclusive. Particles characterized by PLM are in the size range where they are easily distinguished as asbestos, compared with non-asbestos.	Normal quantitation limit may be too high for public health and regulatory purposes, if concentration techniques are not used. Particles of milled material (< 5 µm) may be below resolution limit.

Method	Description	Advantages	Disadvantages
		Good method for larger-size products typical of personal care talc products.	
Scanning electron microscopy (SEM)	The presence of asbestos is confirmed by the occurrence of particles with asbestos morphology that are identified as an asbestos mineral by EDS elemental analysis.	A larger sample size (µg range) is analyzed, relative to TEM. Identification is based on morphology and elemental analysis. Resolution is better than with PLM. Capable of disclosing surface morphology.	Fibrils of chrysotile may be below the resolution limit of older microscopes. Because it is a presumed identification based on chemistry and morphology alone, the test may give a false-positive result. Structural information methods are currently in development. Interferences include talc/anthophyllite, etc.
Transmission electron microscopy (TEM)	The presence of asbestos is confirmed by the occurrence of particles with asbestos morphology that are identified as an asbestos mineral by EDS elemental analysis and electron diffraction.	Identification is based on morphology, elemental analysis, and electron diffraction (structural information). May be the only method with resolution high enough to routinely detect fibrils of chrysotile.	May be prohibitive for quality control due to protracted prep/analysis time, high cost, irreproducibility, and small sample size (ng range). May miss the larger fibers associated with amphibole asbestos (false negative).

5.4 Additional Sample Preparation/Concentration Techniques

Detection of asbestos in talc by the instrumental methods outlined above can be enhanced through the concentration of asbestos particles or separation of asbestos from obscuring or confounding particles. Several sample preparation techniques are being evaluated; each targets a specific type of particle to analyze. These techniques are: 1) air elutriation, for the purpose of evaluating the fraction of particles that may become airborne; 2) aqueous elutriation, also for evaluating particles that may become airborne; and 3) wet sieving, which effectively concentrates asbestos in the larger, more easily characterized size fraction and lowers the overall detection limit of the methods.

5.4.1 FLUIDIZED BED ASBESTOS SEGREGATOR

The fluidized bed asbestos segregator (FBAS) is a sample preparation instrument that utilizes air elutriation to separate particles on the basis of aerodynamic diameter, which correlates positively with particle size and inversely with particle density. Asbestos structures (fibers, fiber bundles, and fibers/bundles in matrices) are collected on a filter which can then be analyzed by TEM or other appropriate microscopic techniques. The performance of the FBAS preparation method was recently evaluated by the U.S. EPA using a variety of performance-evaluation (PE) standards that spanned different matrix materials (soil and vermiculite) and different types of asbestos (chrysotile and amphibole). Results for these PE standards show that there is an approximately linear relationship between the concentration of asbestos in the PE standard (as mass percent) and the mean concentration estimated by the TEM analysis following preparation by FBAS, expressed as asbestos structures captured on the filter per gram of test material (s/g). Method detection limits achieved in these studies ranged from 0.002% to 0.005% by weight, which is approximately 100 times lower than the detection limits that are usually achieved using other analytical methods for asbestos in soil and other solid media.

The FBAS unit is compact, fitting into a standard laboratory fume hood, and components of the unit are relatively easy to decontaminate or are disposable. The FBAS unit construction and operation costs are relatively low, and sample throughput is high (up to 20 samples per day). Current research using the FBAS unit is ongoing, and an interlaboratory validation study is in progress (15). Although the FBAS method has not yet been applied to the evaluation of asbestos contamination in a talc matrix, this approach appears to have promise as a fairly inexpensive and highly sensitive method for the identification of low levels of asbestos in talc (22).

5.4.2 AQUEOUS ELUTRIATION

This elutriation technique uses water rather than air to separate particles (23, 24). A sample is suspended in a funnel of water which is constantly flushed with water coming in from the bottom. The flow rate is controlled to flush out of the top of the funnel only particles smaller than a pre-determined aerodynamic diameter. This portion is filtered and prepared for TEM analysis. The use of water removes any undesirable electrostatic interactions that can occur in air samples. Method detection limits vary based on the duration of elutriation and the differences in the aerodynamic diameters of the target particles and matrix particles, as is the case for FBAS.

5.4.3 WET SIEVING TECHNIQUE

The technique of wet sieving a milled talc product capitalizes on the natural characteristics of asbestos (i.e., flexibility and durability, which make it resistant to grinding). After milling, the sieve acts to concentrate any asbestos present by removing the easier-to-grind matrix material (i.e., talc with a softness of 1 on the Mohs Scale of Hardness). Although the size fraction analyzed is not that which includes the finest

particles, this technique is an easy and cost-effective way to indicate whether or not asbestos is present. Studies have shown that even in the finest micronized talc (median particle size of 1 μm) asbestos was easily detected by conventional microscopy techniques. The effect of concentration also lowers the detection limit, for example samples with 100–500 ppm asbestos—confirmed by TEM—were effectively detected by PLM (25). In addition, asbestos particles in the larger-size fraction are more likely to maintain the unique characteristics of asbestos, which facilitates an unambiguous identification. An inexpensive, standard 325- to 400-mesh laboratory sieve is used with standard laboratory procedures to achieve these results.

6. ADVERSE HEALTH EFFECTS FROM ASBESTOS EXPOSURE

Health effects associated with workplace asbestos fiber exposures were clearly identified in the early part of the twentieth century and continue to be further elucidated through research and ongoing health studies. The major non-cancer health effects associated with airborne asbestos exposure increase with increasing levels of exposure and include pleural effusions, pleural fibrosis [both circumscribed disease (plaques) and diffuse disease], and interstitial fibrosis (also known as “asbestosis”). The observable onset of these conditions, which can occur in combination, usually takes more than 20 years from initial exposure (latency period) and can progress in severity from asymptomatic to disabling and fatal, despite cessation of exposure years earlier (26). The risk for asbestos-related malignancies also rises with increasing levels of exposure. Among these malignancies, lung cancer is the most common. However, the types of lung cancer observed with asbestos exposure are similar to those seen with cigarette smoking, and often may not be identified as asbestos-related given the high prevalence of smoking exposures. It should be noted that the risk for lung cancer is greatly increased by the combination of asbestos and smoking exposures. Mesothelioma is a very rare cancer of the pleura (outer lining) of the lungs and abdomen (peritoneum) that is predominantly caused by asbestos exposure; it is not related to smoking and usually occurs 20–40 years after the initial exposure. According to the Centers for Disease Control and Prevention, the annual U.S. death rate due to mesothelioma is about 14 per million people for those over 25 years of age (27). The risk for mesothelioma increases with greater asbestos exposure, however, there are numerous cases of seemingly inconsequential, low-dose paraoccupational and environmental asbestos exposures that are associated with this malignancy. Per the International Agency for Research on Cancers (IARC), there is sufficient evidence in humans that all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) cause mesothelioma and cancer of the lung, larynx, and ovary. Positive associations also have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum (19, 28).

Although the relationship between airborne asbestos exposure and respiratory disease is clear, associations between ingestion of asbestos fibers and gastrointestinal (GI) cancers, or other cancers due to translocation of fibers from the pulmonary or gastrointestinal tract, is more difficult to assess. Studies in humans and animal models

have provided differing evidence for ingestion-related GI cancers, which were estimated to be elevated by the EPA and the National Academy of Sciences (29).

There are currently no established safe levels of asbestos exposure. This underscores the efforts of the Talc EP to identify strategies and methods for reducing the potential for asbestos contamination of talc to the lowest feasible levels. More effective analytical approaches are needed to achieve much lower levels of detection than those traditionally used to evaluate asbestos contamination of bulk materials. The existing methods are not necessarily adequate for assessing the potential health risks of these materials. Research by the U.S. EPA and others has shown that disturbance of matrices (e.g., soil, vermiculite insulation) containing asbestos concentrations identified by the lower detection limits of PLM—well below 1% asbestos by weight, the limit historically used by the U.S. EPA to define an Asbestos Containing Material)—can generate potentially hazardous exposures (30–32). This issue, while not currently evaluated, may be particularly relevant for the talc used in powders and cosmetics.

Current standards and recommendations have generally focused on controlling asbestos mineral fiber exposures (chrysotile, crocidolite, amosite, anthophyllite asbestos, tremolite asbestos, and actinolite asbestos) by using optical microscopy methods and counting all fibers with specified aspect ratios (e.g., 3:1 or greater) and fiber lengths (e.g., > 5 µm). However, the specified dimensional criteria (length and aspect ratio) used for the quantification of asbestos may not be optimal for protecting exposed individuals, as these criteria are not based solely on health concerns (15). Animal studies and epidemiologic studies have found that various forms of asbestos, or certain dimensional characteristics of fiber exposures, were associated with different responses of the respiratory tract and different potency for disease such as mesothelioma (15, 28). Generally, the accepted physiochemical properties of asbestos fibers that are related to pathogenicity include 1) fiber dimensions (i.e., length, width, aspect ratio), 2) surface chemistry, 3) surface area, and 4) biopersistence. Although the latter three properties are not reflected in the current analytical methods for identification of asbestos (15, 28, 33), efforts are underway to better understand the inter-relationships of these physiochemical properties in association with observed health effects. For example, researchers from the U.S. EPA and other federal agencies have recently shown that the role of surface area, as well as other factors, is important in understanding the toxicity of asbestos and other hazardous elongate mineral particles (33). Also, exposures to certain nonregulated minerals such as fibrous forms of winchite, richterite, and antigorite are of concern. Recent studies have found that such exposures are associated with increased risks of mesothelioma and other asbestos-related diseases (15, 16, 34, 35).

The USP Talc Expert Panel agrees that exposure risks can and should be mitigated by revising USP methods, which will then allow for much lower detection limits for asbestos, and if warranted, other mineral fibers. The Panel is not proposing to identify and exclude all mineral fibers under this standard, but these methods appear capable of identifying other fibers that appear to be hazardous.

7. LABELING

FDA's November 2010 letter included the following requests: *“Labeling should be revised to match the statements that are provided in the Talc FCC monograph, thereby assuring that Talc is not sourced from mines that are known to contain asbestos. Also, USP should consider revising the current tests for asbestos to ensure adequate specificity.”*

However, the existing FCC description (36) is informational, qualitative, and not easily defined. Further, the FCC monograph does not include a labeling statement or any methodology for asbestos detection.

It is the conclusion of the Talc Expert Panel that mine suitability as a source of talc is not subject to USP quality standards. Rather, it is the responsibility of the talc supplier to supply a product that is asbestos free and can meet the USP compendial standards. Based on the above, the panel recommends updating statements in the definition and/or labeling sections to indicate that talc containing (detectable) asbestos is not pharmaceutical grade.

8. CONCLUSIONS AND SUMMARY

Proposed updates to the current official harmonized *USP Talc* monograph's test for the*Absence of Asbestos* will incorporate current analysis protocol:

- Pass-fail must include microscopy follow-up to XRD.
- Definitive microscopic identification and characterization of asbestos/mineral fibers is critical in the determination of the presence/absence of asbestos.

XRD or IR analysis provides for the detection of total amphibole or total serpentine. Failure to detect amphibole or serpentine by XRD or IR does not provide adequate assurance regarding the absence of asbestos contamination.

The USP Talc Expert Panel's recommendation for revision of the test for *Absence of Asbestos*will include omission of the IR spectroscopy test and inclusion of a revised XRD procedure in combination with one or more microscopic evaluations (PLM, TEM, or SEM).

The panel also recommends including additional sample preparation/concentration methods to improve the feasible limits of detection as indicated (see section 5.4).

These recommendations for method revision and labeling will help to ensure that talc does not contain asbestos or other hazardous mineral fiber contamination such as winchite or richterite as determined by current state-of-the-art procedures. The analytical approach recommended by this Expert Panel, consistent with the industry norm at present, should continue to ensure that current supplies of talc are of the highest quality, in accordance with current best practice procedures.

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[f] In accordance with *USP General Notices and Requirements, section 2.20, Official Articles,* the USP *Talc* article is capitalized.

[g] Geologists define a mineral as a naturally occurring, homogeneous solid, inorganically formed, with a definite chemical composition and an ordered and periodic atomic arrangement.