COMMENTS ON THE STIMULI ARTICLE BY USP TALK EXPERT PANEL #2, "MODERNIZATION OF ASBESTOS TESTING IN USP TALC – PART 2[A]"

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PREMISES

In 2010, the United States Pharmacopeia (USP) Excipient Experts Committee formed a Talc Expert Panel (EP#1) consisting of members representing talc suppliers, pharmaceutical manufacturers, regulatory and government agencies, academia, and instrument manufacturers. Their charge was to "update and modernize" the methodology for asbestos testing adopted by the USP Talc monograph. Five years later, in 2015 EP#1 submitted an endorsement report for the control of the "Absence of Asbestos in USP Talc" ensuing a Stimuli article (STIM#1) published in the Pharmacopeial Forum (Block et al, 2014). This, suggested that pass-fail tests in the revised USP Talc monograph should now omit the previously recommended infrared (IR) spectroscopy test in favour of X-ray diffraction (XRD) in combination with one or more microscopic evaluation, as polarized light microscopy (PLM), transmission electron microscopy (TEM), and scanning electron microscopy (SEM). The Talc Expert Panel (EP#1) acknowledged that the microscopic identification and characterization of asbestos/mineral fibers is critical in the determination of the presence/absence of asbestos, and recommended including possible sample preparation methods to improve the feasible limits of fibers detection – as indicated in section 5.4 *Additional Sample Preparation/Concentration Techniques* of Block et al. (2014) STIM#1.

In the following lustrum 2015-2020, a renewed Talc Expert Panel (EP#2) responded to the previous statements via a second Stimuli article: STIM#2 (Pier et al., 2017). This last, proposed a phased approach focusing on the so-called Phase 1 of analytical procedures, still lagging on the use of XRD and PLM, and launched a round robin exercise participated by 5 laboratories "to establish a detection limit for the test", foreseeing electron microscopy only on the far horizon. STIM#2 article just added recommendation to take "future actions" for the evaluation and application of TEM and SEM to detect fibers that may not be resolved by PLM and to change the test name from "Absence of Asbestos" to "Test for Asbestos".

A third Stimuli article (Rutstein et al., 2020) recently appeared on the results of Phase 1 revision and round robin, including recommendation for the Phase 2 revision that should "evaluate and select appropriate electron microscopy methods to further enhance the test for asbestos in talc".

Even to respond to the international Pharmacopeia agencies, requesting further discussion about the last Stimuli article, this contribution aims at clarifying that it is time to include definitely in the USP Talc monograph the electron microscopy (TEM in particular) techniques. These are actually the Best Available Techniques (BAT) for the identification of asbestos presence in talcum powder, and the only ones able to grant that commercial talc does not contain asbestos fibers above any currently achievable detection limits. [Maybe, one can quantify here the current detection limits achievable for different fiber types].

INTRODUCTION

Asbestos impurities are common in mineral deposits of talc, as both talc and asbestos rocks are made of hydrated magnesium silicates. Unfortunately, medical reports from regions where asbestos-contaminated talc was mined – e.g. in New York State (US), starting in the 1900s – demonstrated since the 1940s that asbestosis, excess lung cancer, and mesothelioma are associated with the miners exposure.

Concerns over the purity of talc as a raw material and potential asbestos presence in the related consumer products have been reported since the 1960s, when numerous cosmetic products tested positive for asbestos. In the 1970s, Selikoff's group at the Mount Sinai School of Medicine (NY)

reported finding asbestos in talc products using earlier electron microscopy methods in widely publicized reports (Langer et al., 1972; Rohl et al. 1976). In the US, the Food and Drug Administration (FDA) started holding meetings with the talc industry since 1970s to regulate asbestos content. However, at that time the advance of asbestos testing methods was still in progress and earlier arrangements between FDA and industry trade associations led to indicate as standards analytical methods whose use is insufficiently sensitive to proclaim talc asbestos-free.
In 1976, the cosmetics industry in the US implemented voluntary asbestos testing of talc raw materials using the *Cosmetic, Toiletry, and Fragrance Association* method (CTFA J4-1, 1976). Talc suppliers to the pharmaceutical industry still use such a method employing XRD and Optical Microscopy (OM) to certify that talc meets the USP's requirement for "Absence of Asbestos".
Although huge improvements for asbestos tests by electron microscopy were attained in the ensuing decades (see e.g. Blount et al., 1990; Blount et al., 1990), to date both USP and CTFA methods rely on the use of XRD or IR spectroscopy, followed by PLM just in the case that results are positive for amphibole or serpentine minerals in talc. The CTFA J4-1 and USP methods remain the standard ones, despite their long-recognized shortcomings in specificity and sensitivity compared with electron microscopy-based analysis.
After repeated litigations that documented how mesothelioma and ovarian cancer can be associated to the regular use of talc products, almost six years ago, the US Pharmacopeia Expert Panel EP#2 began meetings to discuss the responses to the first Stimuli article written in 2014 by the first Expert Panel.

COMMENTS ON THE CURRENT USP ANALYTICAL PROCEDURES

Currently, there are no standard reference materials available to document laboratory's reliability in detecting asbestos in a talc matrix. Nevertheless, this is not a problem to identify the BAT to check asbestos presence in talc. Certified reference materials are necessary to calibrate the capability of measurement in quantifying the measurand, but for pass/fail tests of asbestos in commercials, there is no need to define exactly the found amount before phasing them out of the market. In fact, in most European national legislations no asbestos content at all is allowable: i.e. the Maximum Available Concentration (MAC) of asbestos is zero, which means that the detection level of 0.01 % (100 ppm, see Tab. I in Rutstein et al., 2020) claimed by all the laboratories participating in the round robin exercise of USP EP Phase 1 proposal, using XRD and PLM, is not satisfactory.
The USP procedure for "Absence of Asbestos" yet addresses to either infrared spectroscopy (IR) or X-ray powder diffraction (XRD), indifferently. These initial screening methods are useful for evaluating the overall quality of the talc. However, both the IR and XRD procedures, as reported in the *USP Talc* monograph, are pass/fail tests that do not provide specific detection limits and only if test outcomes indicate that the mineral may have an asbestos component (i.e. a positive result), then *USP* requires that the sample be examined using optical microscopy.
In addition, the USP procedures addressed for the 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 test. Because fibrous minerals in talc are contaminants rather than added for 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.
That is why we consider analytically uncomplete and unfit for identifying the presence of asbestos the statements actually maintained by the USP Talc monograph.

MOVING FORWARD TO ELECTRON MICROSCOPY

Recent reports from testing of cosmetic products indicate that because of shortcomings in sensitivity, currently adopted methodology, including PLM, sometimes fails to detect finely sized particles of asbestos and similar minerals even when they are present in talc. Moreover, modern laboratories with expertise in asbestos testing, when asked to test talc-containing consumer products, routinely perform

electron microscopy and do not rely solely on PLM. These findings provided support to recommendations from many scientific experts that transmission electron microscopy (TEM) should be used for asbestos testing of talc even if the findings of PLM are negative. See, for example, Rohl and Langer (1974), Millette (2015), Block et al. (2014). Notably, in 2018 the US FDA *Interagency Working Group on Asbestos in Consumer Products* (IWGACP, 2018) strongly recommended using TEM with EDS and selected area electron diffraction (SAED) analyses to reliably detect and identify chrysotile and asbestiform, and non-asbestiform amphibole minerals.

Italian scientists of ISS (the Italian *National Healthcare Institute*) published a report research on asbestos in Italy from 1980-2012 (Donelli et al., 2012), in which several pages (pp. 30-34) are devoted to talc. They highlighted that the best available test for asbestos presence was already reported in the IX Italian Pharmacopeia (Farmacopea Italiana, 1985) stating "For the quali-quantitative analysis of fibers, the use of Analytical Electron Microscopy is recommended" (p. 1638, note 1); see also Paoletti et al. (1984). I.e. the Italian Pharmacopeia in 1985 specified analytical electron microscopy for analyzing talc for asbestos contamination, yet the European Pharmacopeia in 2008 returned to less powerful methods of analysis. The authors of the above-mentioned ISS report repeatedly tried to warn the regulatory authorities in Italy and Europe, requiring more serious testing of Talcs for asbestos presence. This has not yet changed until the last 2020 edition of the European Pharmacopeia.

Thus, it is not surprising that in 2010, FDA asked the USP to consider revising the current tests for asbestos in talc to ensure adequate specificity. Neither it is surprising that in 2014 the USP talc expert panel recommended an update of the USP Talc monograph requiring an electron microscopy method for the measurement of asbestos in talc (Woodcock, 2010; Block et al. 2014).

DISCUSSION

Nowadays, expert laboratories do not apply a single approach analysis using only one instrumental technique and skilled technicians know also that sampling is an issue, as from a few mg samples one should decide the absence or not of asbestos in tons of materials. That is why asbestos analysis on the available samples ought to be carried out through a complete analytical procedure starting maybe from stereo light microscopy, than using XRD, MOCF, MOLP, SEM with EDAX, and so on until reasonable certainty is attained of the negative response. Certainly, each further step is applied only if asbestos fibres are not found in the previous ones. However, there is no reason to cut the analytical sequence before the last step is applied, neither certified laboratories in both industry and control agencies can neglect any of the available passages until TEM analysis.

IWGACP strongly recommends using TEM with energy dispersive X-ray spectroscopy (EDS) and selected area electron diffraction (SAED) analyses to reliably detect and identify chrysotile and asbestiform and non-asbestiform amphibole minerals, including EMPs whose narrowest width is <200 nm (the limit of resolution for light microscopy). SEM might be useful as a complementary method but has significant shortcomings for identification of chrysotile and visualization of the narrowest particles in the population that can only be overcome by using TEM.

The first stimuli paper stated: "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".

According to the same paper: "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".

At the light of the previous observations, it is questionable that the USP Expert Panel #2, instead of immediately providing corrections to the *Talc Monograph* indicating Electron Microscopy as a mandatory technique, organized an academic exercise completing a round robin using pure commercial asbestos to spike talc samples. In this way, they stated that certain asbestos concentrations on a weight-to-weight ratio are measurable with known accuracy and precision, but giving no further answers to the focus point: that any quantities of dangerous fibres contained in talc are detectable at the level of the BAT. In addition, it is noticeable that no real talc samples known to contain asbestos fibers were included as measurand in the round robin to check the methods suitability to identify even fine amounts of fibers.
The difficulty of procuring such instruments as Transmission Electron Microscopy with microprobe for X-ray analysis of talc samples cannot be considered as a restriction not to implement the technique, as this is the only road to achieve affordable, reliable and uncontestable analytical results. In a recent review of the *Roadmap for asbestos research* provided by the National Institute for Occupational Safety and Health (NIOSH), 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" (NIOSH, 2011).

CONCLUSIONS

Unfortunately, industry specifications ambiguously state that cosmetic-grade talc must contain "no detectable" fibrous asbestos minerals, thus shifting the health protection dispute on the technical side, which strongly relies on the affordability of the analytical methodologies addressed to fulfill the tests. Most of the issues raised by asbestos analysis in talc for healthcare protection have already been tackled in details, although sometime controversially (see e.g. ANSES 2012; Fiume et al. 2015; Moline et al., 2020). Nevertheless, it is apparent that USP should head in the right direction by creating new legislation using electron microscopy to help regulate talc-containing cosmetics, also used for children.
As far as SEM is considered, it is used by many laboratories. Recently, a study of talc-containing cosmetics (Donahue, 2018), tested six samples from various brands using SEM and determined that three of them have the potential of being contaminated with asbestos. The outcomes of this study evidence the superior analytical effectiveness of any electron microscopy with respect to the current USP standards, and brings into question the regulations regarding talc in cosmetics.
SEM too present pitfalls as 1) it cannot verify crystallinity by diffraction, and 2) it tends to miss the finer fibers. Use of TEM in addition to PLM, would rapidly resolve the issues of sensitivity that cause reporting of false negatives.

We cannot conclude our comments without observing how most scientists on the USP Expert Talc Panels were representatives for the talc companies, while health representatives and advocates of public control agencies were under-represented. Among the 18 authors of the third Stimuli article (Rutstein et al., 2020), nine (50 %) declared conflicts of interest.

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