

Asbestos
Eli Lilly and Company

This submission is in reference to the Federal Register notice of September 28, 1973, proposing to establish certain criteria on the use of talc and asbestos filters in drug manufacturing operations.

As a major pharmaceutical manufacturer, we are concerned with the implications of this notice and are herewith submitting comments with respect to the merits of this proposal.

The format for our comments will follow the order of the proposed regulations in the reference notice.

We will be happy to supply any additional information or clarification that may be necessary.

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1. Reg. 121.101 Substances That Are Generally Recognized
As Safe

Since this revised regulation is pertinent to foods
and our submission is basically exclusive to drugs,
we have no comment.

2. Reg. 121.2006 Talc

The proposed method for determining asbestos fibers in talc is described under subparagraph (c). This method is subsequently referred to as the determinant for establishing acceptable talc which can be used as a component in drugs. Accordingly, we have the following comments on the proposed method.

We believe the proposed method to be inadequate as follows:

- a. The optical microscope has limits of resolution such that particles of asbestos as small as those described in at least one of the references would escape detection.
- b. The scanning procedure described is quite time consuming and requires the services of a highly skilled and patient technician.

A further elaboration of these points is as follows:

- a. The limit of resolution, that is the distance between two points that can just barely be made out as individuals, is given as:

$$r = 0.61 \lambda / NA$$

where r = resolution
 λ = wavelength of light used
NA = numerical aperture of objective

The analytical system as described calls for examination at 400x. This is best obtained with a 40x objective and a 10x ocular. The usual 40x objective has an NA of 0.65 or 0.85. Therefore, at best, using blue light, the optical system described would have a resolution of 0.35 μ m.

Reference 44 of the preliminary discussion shows an asbestos fiber only 0.05 μ in diameter found in the peritoneum of a rat. This fiber would not be seen by optical methods because it would be below the resolving power of the microscope.

- b. The method calls for a scan of an area 18 mm. square at a power of 400x. A 40x objective looks at a field of about 0.06 mm² at a time. In order to scan the whole area under the cover slip (18²/.06) 5400 fields would have to be examined. This would require an automated device. However, the procedure as written requires examining suspicious particles to determine their refraction index in order to distinguish asbestos from particles of talc that have split, are on edge, or have become rolled up

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2. Continued

- b. into cylinders. This last step automated instruments are not yet capable of.

Accordingly, the proposed method for examining talc seems to be quite inadequate. A method which might have utility in this regard is attached. This method "The Detection and Determination of Chrysotile in U.S.P. Talc" is soon to be published in the Journal of Pharmaceutical Sciences.

**The Detection and Determination
Of Chrysotile in USP Talc**

Harry A. Rose

Abstract ☐ A procedure for the determination of chrysotile in talc has been developed. It depends on the adsorption of a sulfonphthalein dye by chrysotile but not by talc. The final measurement is a spectrophotometric determination of the dye left in solution after the adsorption step.

The wide use of talc as a dusting powder and as a diluent in capsule contents has caused concern about possible impurities in the talc and especially the possible presence of asbestos. Cralley et al. (1) found asbestos in a number of cosmetic talcs. Merliss (2) implicated asbestos in talc as a cause of stomach cancer in Japan.

Talc is a hydrated magnesium silicate which may ideally be represented as $Mg_3(OH)_2Si_4O_{10}$. It may be contaminated with other minerals such as quartz, dolomite, chlorite, and the various forms of asbestos. Of the asbestos minerals, chrysotile is currently of most physiological concern. Chrysotile is also a hydrated magnesium silicate which may ideally be represented as $Mg_6(OH)_8Si_4O_{10}$. The structure of both minerals is apparently made up of sheets of silicon and oxygen atoms interspersed with sheets of magnesium and oxygen atoms, the difference being in the added magnesium and oxygen in the chrysotile structure.

USP XVIII (3) is rather vague about the chemistry of talc and apparently would admit a talc containing some chlorite. The concern is for rather gross impurities such as excesses of pH or water-soluble iron. Thus, a rather substantial contamination of the talc with chrysotile could occur, and unless the product became gritty, no cause for rejection would appear.

Several tests can be proposed to detect the chrysotile in talc, but each suffers from some difficulty, all relating to the very large ratio of talc to chrysotile which should be present. Obviously, a simple determination of magnesium, hoping to find the excess due to the chrysotile, would fail because of the natural variability of the talc itself. X-ray diffraction, which Rickards (4) has used very elegantly for measuring air pollution by chrysotile, becomes very uncertain at low percentages when much talc is present. Optical microscopic examination suffers because the particles approach the limit of resolution of the instrument.

The test described here will detect chrysotile contamination in talc but not the amphibole types of asbestos such as tremolite. The test depends on the adsorption of bromcresol purple by chrysotile and the lack of adsorption of that dye by talc. Other sulfonphthalein dyes of this series have similar behavior, however, bromcresol purple was selected because of its convenient range for change of color to the acid form.

EXPERIMENTAL

Reagents - The bromcresol purple used was obtained from Matheson, Coleman, and Bell and was used as received. A stock solution of this dye was made up by dissolving 0.15 gram in 250 ml. of 95% ethanol and diluting to 500 ml. with water.

The working solution was made by taking 20 ml. of the stock solution plus 40 ml. of 95% ethanol and diluting to 100 ml. with pH 4.2 acetate buffer. This working solution when diluted 10 ml. to 25 ml. with pH 4.2 acetate buffer should have an absorbance of .325 at 422 m μ .

The chrysotile was obtained from the Johns Manville Research Center and was used as received except for reduction in particle size to that of the talc being tested.

Procedure - Weigh three 0.2000 ± 0.0010 gram samples of the talc. To sample number two, add about 3 mg. of chrysotile and to sample number three about 6 mg. of chrysotile, both accurately weighed. To each sample add 10 ml. of 50% ethanol-water. Also, provide a 10-ml. sample of the 50% ethanol-water to serve as a blank. All samples and the blank are given an ultrasonic treatment¹ for two minutes at 70 watts of power. After the samples have cooled to room temperature, add 10 ml. of working dye solution to each sample and the blank. Mix and allow to stand for 30 minutes with occasional shaking. The samples and blank are then centrifuged followed by filtration through a .45 μ . millipore filter. A 10-ml. aliquot of each filtrate is diluted to 25 ml. with pH 4.2 acetate buffer.

¹Sonifier Cell Disrupter, Model W185D, from Heat Systems Ultrasonics, Inc. of Plainville, N.Y. The micro tip adapter was used.

The optical absorbance is then determined at 422 m μ . in a suitable spectrophotometer. The absorbance is then plotted against mg. of chrysotile added. (See Figure 1). By extrapolation to a baseline, the level of which is indicated by the blank, the chrysotile content of the talc may be determined.

RESULTS AND DISCUSSION

The assay design used here follows that used by Rickards (4) for an x-ray diffraction determination of chrysotile in air pollution studies. The design used here differs in that instead of a positive slope for additions of chrysotile (increased peak height), a negative slope is obtained (increased adsorption, hence lower amount of dye remaining). The advantage of using the design here is that in effect, an internal standard is being used which can compensate for variations in the dye used, and it makes unnecessary a fixed calibration curve.

The double separation step involving centrifugation and filtration was found to be needed because the finest talc and chrysotile particles could not be removed in reasonable time by centrifugation alone. On the other hand, attempted direct filtration rapidly resulted in a plugged filter before enough filtrate could be collected.

Figure 1 shows a typical determination on a talc which had been "spiked" with 0.5% chrysotile. The result

from the assay in Figure 1 would indicate 1.1 mg. chrysotile in a 200-mg. sample, or 0.55%.

Eli Lilly and Company has been fortunate in being able to obtain USP talc free of chrysotile so that tests for precision of the assay have all been done on "spiked" samples. A limited number of determinations on a sample containing 0.5% chrysotile have indicated a standard deviation of $\pm 0.06\%$.

Most of the work was carried out on a sample of chrysotile obtained from Johns Manville Research Center. In order to eliminate the possibility that a peculiarity of that sample was responsible for the dye adsorption, another sample was obtained from the Geology Department of Indiana University. This sample gave substantially the same adsorption behavior as the Johns Manville sample.

SUMMARY

A determination of chrysotile impurity in talc has been developed. The assay has been demonstrated to be useful at least at the level of 0.5% chrysotile. An internal standard method is used which eliminates the need for a standard calibration chart. The assay depends on the adsorptive property of the chrysotile for a sulfonphthalein dye.

REFERENCES

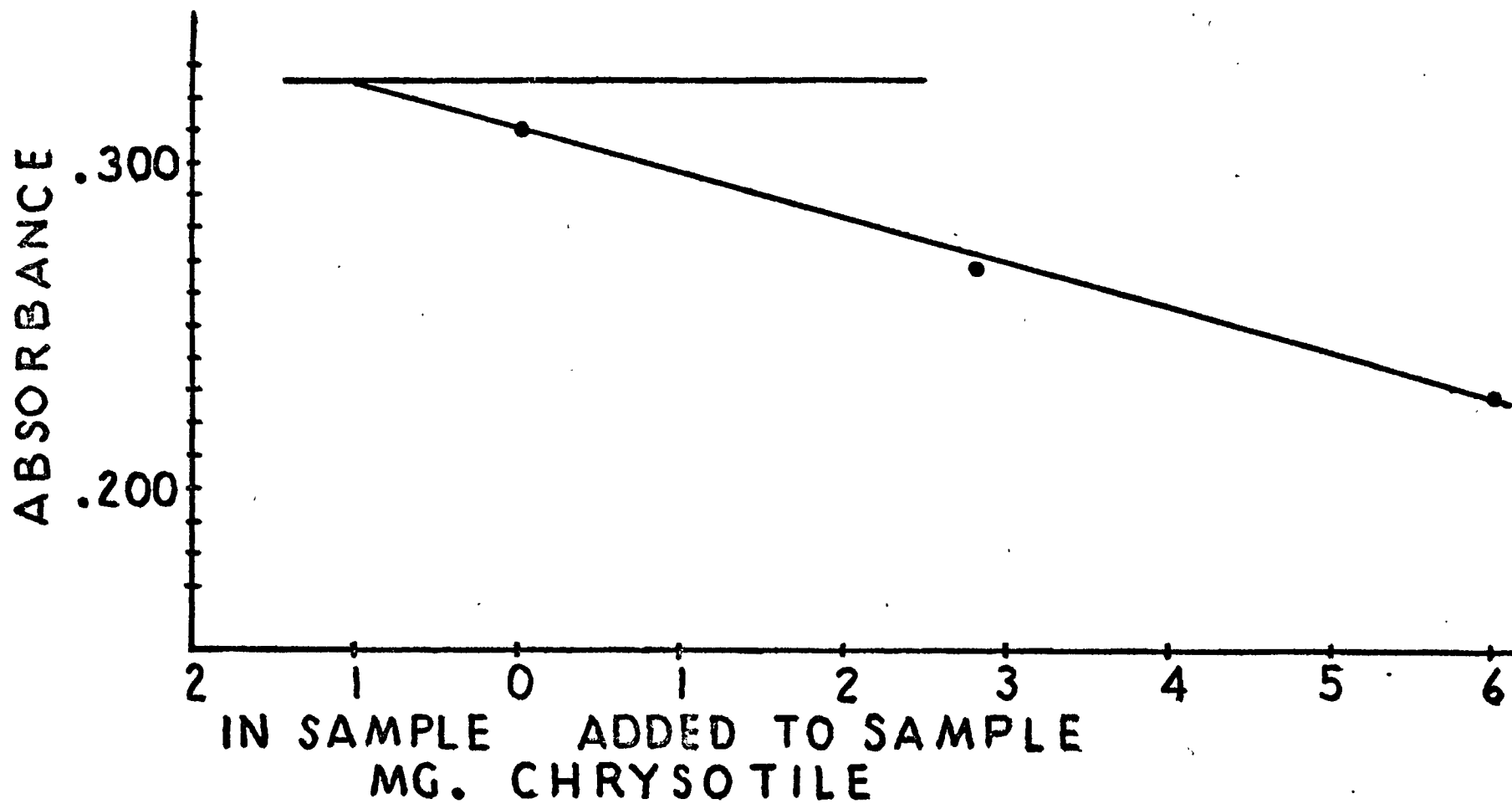
- (1) L. J. Cralley, M. M. Key, D. H. Groth, W. S. Lainhart,
and R. M. Ligo, Amer. Ind. Hyg. Ass. J., 29, 350-354
(1968).
- (2) R. R. Merliss, Science, 173, 1141-1142 (1971).
- (3) The United States Pharmacopeia, 18th Revision,
Mack Publishing Co., Easton, Pa., p. 708.
- (4) A. L. Rickards, Anal. Chem., 44, 1872-1873 (1972).

ACKNOWLEDGMENTS AND ADDRESS

The author wishes to thank the Johns Manville Research Center and Dr. John M. Hayes of Indiana University for providing the samples of chrysotile.

Analytical Development Department, Eli Lilly and Company, Indianapolis, Indiana 46206.

Figure 1. Extrapolated graph of additions of chrysotile plotted against absorbance.



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3. Reg. 133.6 Components

Subparagraph (i) provides, in part, that any drug containing talc which does not meet the specifications of 121.2006(c) shall be deemed to be adulterated. It is stated that this will assure a purity of talc at least 99.9 percent free of amphibole types of asbestos fibers and at least 99.99 percent free of chrysotile asbestos fibers.

We believe that the imposition of such a restriction at this time is both unreasonable and premature as follows:

- a. The proposed method for determining asbestos in talc is inadequate as discussed above.
- b. The imposition of these limits on talc used in drugs is paradoxical when the ubiquitous nature of asbestos is acknowledged.
- c. An approach to the minimum feasible level of asbestos in talc has to be realistic in an awareness of the nature of talc and how it is mined and processed.
- d. There is no firm physiological evidence of the level at which asbestos in talc is hazardous.
- e. There is no sound evidence as to the upper or lower limits of particle sizes of asbestos which are harmful and therefore should be detected.

4. Reg. 133.8 Production and Control Procedures

Subparagraph (j) proposes to amend the Finished Pharmaceuticals: Manufacturing Practice regulations to provide essentially for the following with respect to the use of asbestos-containing filters in the manufacture of parenterals:

- a. Where possible a non-asbestos-containing or a non-fiber-releasing filter should be used.
- b. If an asbestos-containing filter is necessary, an additional non-asbestos containing or non-fiber-releasing filter shall be used to reduce the content of any asbestos-form particles in the drug.
- c. Use of an asbestos-containing filter without the follow-up use of a secondary non-asbestos filter is permissible only after a submission to the FDA of proof that the use of a secondary filter will, or is likely to, compromise the safety and effectiveness of the drug.

We find this proposed regulation to be constructive and reasonable. Accordingly, we do endorse the adoption of the provisions of proposed regulation 133.8 (j) when feasible.

We have reviewed our current production of parenterals and find that a good many of our filtering systems are or can be changed to be compatible with the provisions of the proposed regulation. However, in some cases it is not possible to estimate when changes can be instituted because of commercial availability of certain filters such as the Pall AB (absolute) filters which are asbestos-free. Studies on solvent-containing streams will be required with various filters to determine possible interaction, degradation and swelling of filters which could result in clogging or rupture.

In one product, Ampoules Parathyroid, it appears that an asbestos filter is necessary and the use of a secondary non-asbestos filter could adversely affect the effectiveness of the product. Under the provisions of this proposed regulation we would make the required submission to the FDA furnishing the necessary proof.

In proposed regulation 133.8(j), the provision to use a necessary asbestos-containing filter followed by non-asbestos filter is conditioned to evidence for reduction of any asbestos-form particles in the drug. Reference is made that the methodology for such a

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4. Continued

determination is available from the U. S. Government Printing Office. As you will note from the attached documents, we have been unsuccessful to date in procuring the reference document from either the U. S. Government Printing Office or the agency they referred us to. Accordingly, we petition the Administration to allow additional comments at a later date when such methodology is available.

Attachments

ELI LILLY AND COMPANY

INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 636-2211

October 9, 1973

Superintendent of Documents
U. S. Government Printing Office
Washington, D. C. 20402

Gentlemen:

Please send to me, at the above address, a copy of "Criteria for a Recommended Standard-Occupational Exposure to Asbestos," Report of Review Committee, National Institute for Occupational Safety and Health, Publication No. HSM 72-10267 (1972), as mentioned in the Federal Register, Vol. 38, No. 188 - Friday, September 28, 1973, p. 27080 (last paragraph).

Thank you for your attention in this matter.

Very truly yours,

ELI LILLY AND COMPANY



Paul M. Sanders, Head
Regulatory Requirements
M-772

A

PMS:AC

Health Services and Mental
Health Admin, HEW. Dept.
Bethesda, Md. 20014

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ELI LILLY AND COMPANY

INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 636-2211

November 7, 1973

Health Services and Mental
Health Administration
Health, Education, and Welfare
Department
Bethesda, Maryland 20014

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I wrote to Superintendent of Documents and was referred to your office (see attached). Thank you for your attention in this matter.

Very truly yours,

ELI LILLY AND COMPANY



Paul M. Sanders, Head
Regulatory Requirements
M-772

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Attachments: