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The Commissioner
Through: The Deputy Commissioner _____

Acting Director
Bureau of Drugs

Preliminary Report: "Special Survey on Asbestos Particles in Parenteral Drugs" - INFORMATION MEMORANDUM

PURPOSE

In our Information Memorandum to the Commissioner dated January 24, 1972, concern was expressed in the potential medical hazards posed by the presence of asbestos particles especially in parenteral drugs.

In order to obtain information to assess this potential, a Special Survey was instituted which entailed the inspection (with the collection of appropriate samples) of fourteen parenteral drug manufacturers. The objective of this study was to determine the extent of use of asbestos-containing filters and filter aids in the manufacture of drugs, and also to analyze samples for the presence of asbestos particles by appropriate methodologies, namely, light microscopy and electron microscopy.

TEXT OF INFORMATION

The Special Survey Program, dated July 16, 1972 was prepared by the Office of Compliance in collaboration with the Bureau Project Officer for Asbestos. It contained methodologies for both light and electron microscopy to be used by our New York Laboratory and Bureau of Biologics, respectively, since they possessed the facilities, capabilities and requisite expertise to carry them out.

The field inspection reports of the fourteen firms (Tab A) indicated the following usage of asbestos filters:

a. Seven firms do not use asbestos in any form.

b. Four firms use asbestos filters but the drugs are final filtered through membrane filters.

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One of these firms uses asbestos filters to filter its rinse water without final filtration.

c. Two firms only use asbestos filters for filtering their rinse water but without final filtration.

d. One firm uses asbestos filters in all its filtrations without final filtration.

The proposed methodology for Light Microscopy was modified (Tab B) by our N. Y. Laboratory analyst because of severe problems encountered in the filtration process and in the preparation of the membrane filter for observation of the different samples. They were examined at 400-500X using Nomarski-Interference, Phase Contrast and Polarized Light Microscopy. Seventeen samples collected in the Survey were subjected to the procedure and the results (Tab A) showed 11 positive for presence of asbestos, 1 questionable positive, 1 negative and 4 could not be satisfactorily completed because of preparation problems.

The proposed methodology for Electron Microscopy likewise was modified (Tab C) by our Bureau of Biologics analyst because of problems encountered in preparing and analyzing the samples. They were examined by Scanning and Transmission Electron Microscopy following preparation of samples either by ashing, filtration or centrifugation using asbestos-free reagents and clean room techniques; identification was based on morphology and in some cases by electron diffraction.

This phase of the analysis presented the extremely difficult problem of quantitation. The use of a computer is presently being utilized to surmount this difficulty. Since this study is still ongoing, the results can only be stated in qualitative terms.

The seventeen samples analyzed (Tab A) showed 12 positive and 5 have not been satisfactorily completed because of preparation problems.

J. Richard Crout, M.D.

Enclosures
Tab A - Preliminary Results of Special Survey
Tab B - Light Microscopy
Tab C - Transmission Electron Microscopy and Scanning Electron Microscopy

Prepared by: BD-140, ARCasola, S/9/73, X33418

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Preliminary Results of Special Survey - Asbestos Particles in Parenteral Drugs (CP 7323.11)

Below, in tabular form, is listed the pertinent information obtained from field inspections of fourteen firms with regard to the use of asbestos filters, and of analytical results by light and electron microscopy obtained on the seventeen samples procured from these firms by our inspectors.

It cannot be stressed strongly enough that each drug product, when subjected to the analytical procedures, presented its own individual problem(s) of preparation due to its distinctive chemical and physical properties and mode of preparation. Therefore, it may be necessary to utilize a different and possibly unique procedure, rather than a standard one, in order to render each sample amenable for analysis.

It should be noted that one firm (#10) was not manufacturing at the time of inspection. Thus, no sample was available for the study. Incidently it was the sole firm using asbestos filters in production without the use of a final membrane filter.

Two samples were obtained from three firms (# 1, 2, 3) in an attempt to correlate, to some extent, the effect on the asbestos content by the elimination, or reduction, in the use of asbestos filters in production.

No attempt has been made in this preliminary report to describe the fibers, found by light microscopy, according to size categories. This will be done in the final report.

RESULTS OF SPECIAL SURVEY

Firm	Use of Asbestos filter	Use of Membrane Filter (or Final Filter)	Sample Amount	Light Microscopy 400-800 X Fibers as chrysotile and/or amphibole	Electron Microscopy Presence of Asbestos Fibers
1	no	yes	a(1): 1 ml	3	Positive
			b(2): 1 ml	11	Positive
2	yes (only for rinse water)	yes	a(3): 1 ml	8	Positive
			b(4): 10 ml	9	Positive
3	yes	yes	a(5): 1 g.	preparation problem	preparation problem
			b(6): 1 g.		
4	yes	yes	1000 ml	7	Positive
5	no	yes	10 ml	7	Positive
6	no	yes	30 ml	preparation problem	preparation problem
7	yes (only for rinse water)	yes (not for rinse water)	a: 500 mg	0	preparation problem
			b: 500 mg	27	Positive
8	yes (not for rinse water)		1 g.	5	Positive

RESULTS OF SPECIAL SURVEY CONT'D

Firm	Use of Asbestos filter	Use of Membrane Filter (or Final Filter)	Sample Amount	Light Microscopy 400-500 X Fibers as chrysotile and/or amphibole	Electron Microscopy Presence of Asbestos Fibers
9	no	yes	40 g.	preparation problem	preparation problem
10	yes	no	no sample available	-	-
11	no	yes	1000 ml	1	Positive
12	no	yes	500 ml	25 (questionably positive, identity not assured)	Positive
13	yes	yes (not for rinse water)	30 ml	4	Positive
14	no	yes	1 ml	1	Positive

NOTES: (1) drug produced using asbestos filter before it was eliminated by firm'
(2) same drug produced using only final membrane filter
(3) & (4) these are different drugs produced by the firm
(5) & (6) same drug; respectively before and after partial elemination of asbestos filters in the manufacture

Light Microscopy:

Using clean room techniques a given amount of sample, as suspension or solution, is filtered onto a 0.22 micron millipore filter, 13 mm in diameter, in a Swinnex holder using vacuum. It is rinsed with 100 ml. of ultra-clean distilled water, followed by a rinse with 5 ml. ultra-clean isobutyl alcohol. Allow the filter to dry in holder using vacuum. Remove the filter and place it on a glass slide - cover the sample and allow it to dry for 1 hour at 100-150°C on a hot plate. Place the dried filter in a plastic petri dish for storage. To examine, mount the dried filter on a clean slide with a 1 to 1 solution of diethyl oxalate and dimethyl phthalate (refractive index 1.455 to 1.470). Cover with a pre-cleaned cover glass and examine in the light microscope using phase contrast, polarized light and Nomarski interference microscopy.

Transmission Electron Microscopy:

(A) A given amount of a sample is suspended in filtered distilled water (filter pore size 0.22 micron) to give 40 ml. It is centrifuged at 22,000 rpm for 1 hour in a number 25 rotor on a model L 1 Beckman centrifuge. The supernatant fluid is poured off and the pellet resuspended. The sample is centrifuged again for 1 hour at 22,000 rpm. The supernatant is poured off and the pellet suspended in 0.1 ml. of filtered distilled water. A five microliter drop of this preparation is placed on an electron microscope grid and examined at 20,000 magnification. Asbestos particles are identified by morphology and electron defraction.

(B) A given amount of a sample is pushed through a 0.22 micron membrane filter and rinsed with filtered distilled water, dried and ashed in a low temperature asher. The ash is resuspended in 0.1 ml. of filtered distilled water and dispersed using an ultrasonic generator or placed directly on the electron microscope grid and examined at 20,000 magnification.

Scanning Electron Microscopy:

A given amount of sample is pushed through a 0.22 micron membrane filter and rinsed with filtered distilled water. The filter is either coated with Gold-Palladium and examined in the Scanning Microscope, or ashed and the ash is examined in the Scanning Electron Microscope after being coated with Gold-Palladium. Energy Dispersive X-ray Analysis is done on fibers and a count of Magnesium and Silicon peaks is used to determine the presence of asbestos.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Dr. Armand Casola - Chairman, Asbestos Work Group, BD-54 DATE: July 10, 1973

THRU: Dr. Bennett L. Elisberg, Director, Division of Pathology, BoB

FROM : Mr. Philip McGrath, Director, Electron Microscopy Branch PPM. Division of Pathology, BoB

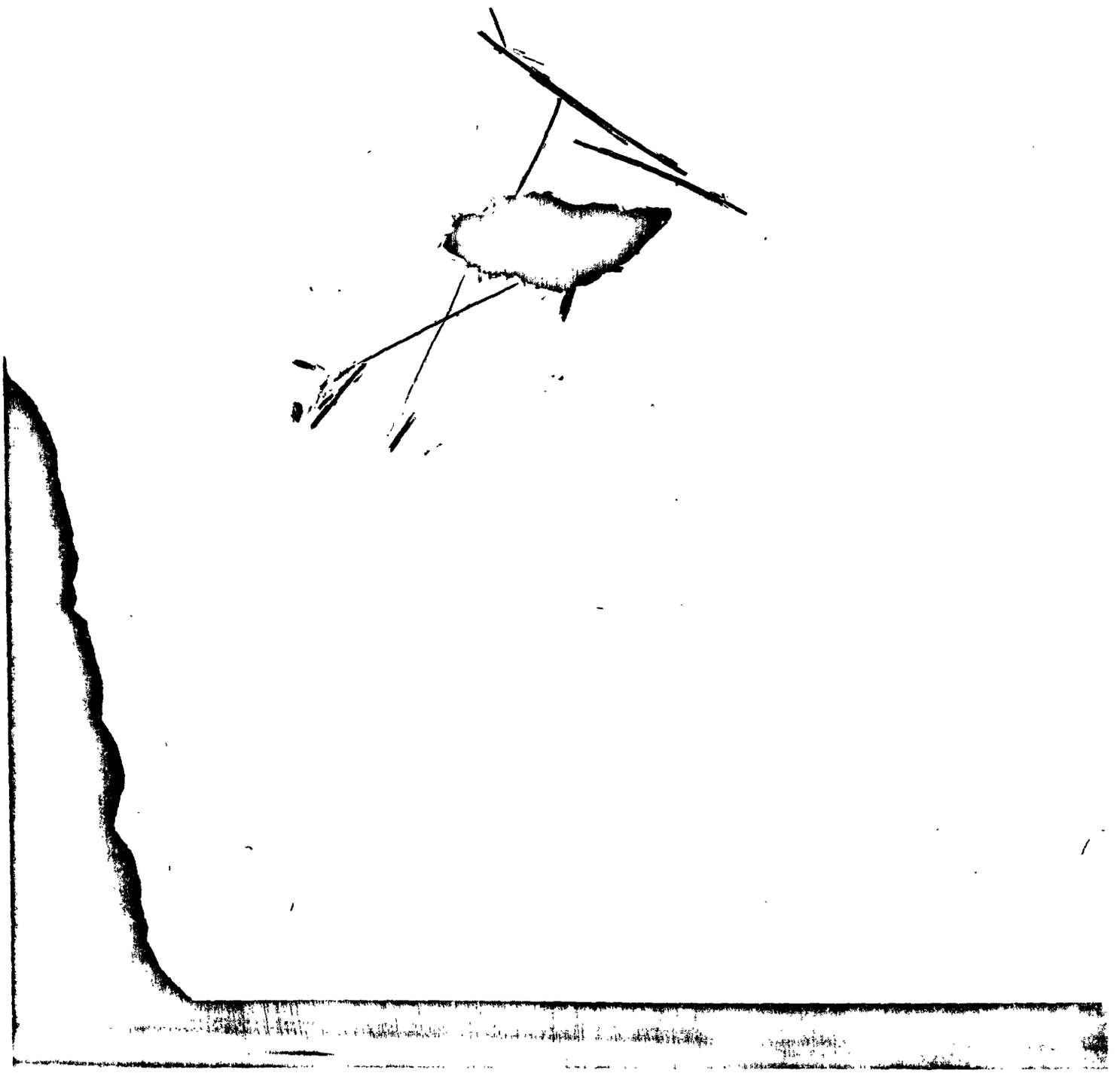
SUBJECT: Electron Microscopic Examination of a Suspension of 7RF02 Asbestos Before and After Filtration Through an Asbestos Filter Pad

One gram of 7RF02 asbestos from the Johns Manville Co. was suspended in 100 ml of distilled water. This suspension was filtered through a 6 cm. diameter sterilizing asbestos filter pad into a tibulated Erlenmeyer flask using laboratory vacuum with a negative pressure of approximately 20 to 25 inches of mercury. Carbon and formvar coated 300 mesh copper electron microscope grids were prepared by placing a 5 microliter drop of sample per grid and allowing it to dry in a closed petri dish. Five grids each were prepared from the sample before filtration and after filtration.

The five grids prepared from the asbestos suspension before filtration showed every grid square covered almost completely with asbestos fibers and fibrils. (Prints #1 and #2)

The five grids prepared from the filtrate show an occasional small clump of fibrils, one clump per every 30 grid squares counted. (Print #3) over 210 grid squares were surveyed at 20,000 magnification.

Filtration through an asbestos filter pad demonstrated the remarkable capacity of this device to reduce the amount of asbestos in a given sample. The few clumps of fibers seen may have come from the filter itself during filtration or have been a contaminant on the reverse surface of the filter. The filter was not washed before use but was used directly from the box without any treatment. Standard laboratory practice usually calls for wetting the filter by running 50 to 100 ml of water through the pad. The method we decided to employ called for the crudest laboratory procedure to test this device. I believe this demonstration illustrates the usefulness of this device when used as a depth filter in reducing the asbestos load of a sample.



Suspension 7FR02 after filtration
T.E.M.
Magnification 8,284

Suspension 7FR02 before filtration

Suspension 7FR02 before filtration
T.E.M.
Magnification 3.696

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