



MOUNT SINAI SCHOOL OF MEDICINE
of The City University of New York

FIFTH AVENUE AND 100TH STREET • NEW YORK, N.Y. 10029



Department of Community Medicine

May 9, 1972

Mr. John Tuit
Columbia Filter Company, Inc.
199 Seventh Avenue
Hawthorne, New Jersey 07507

Dear Mr. Tuit:

I am sorry that you have not yet received an answer to your letter of March 15. I had asked some of our laboratory staff to answer your specific questions; something may have gone awry. I will bring this once more to their attention.

Pending their response, I will add several comments of my own. First, the chrysotile fibers do not have a strong negative charge; this was a transcription error and was corrected in the manuscript some time ago. They have a positive charge.

Second, we have no knowledge of the source of other foreign fibers and particles, which were present in the drugs tested. These have not been identified and, failing such identification, their properties have not been explored. I believe this subject is of some importance and agree with the suggestion I infer, that investigation of such particles is in order. It would be. I accept, too, that it would be useful to investigate chemical contamination from synthetic membrane filter media. As you know, this area is one in which some research is being done, primarily insofar as tubing or containers are concerned, with plasticizers and stabilizers the objects of such study. I don't know whether filter material is also under scrutiny. Do you know whether they are? I have reviewed the question of phthallates with colleagues working in the field and find that trace amounts are not unusual in blood samples taken in some areas, although the source and significance of these findings are unstudied. I can't agree that it is important to investigate whether asbestos in parenteral drugs can cause cancer in humans; *pari passu* with administration of parenterals so contaminated. It would seem prudent to avoid such drugs.

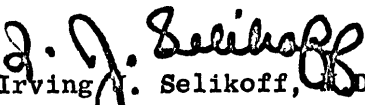
Mr. John Tuit

May 9, 1972

It is conceivable that asbestos filters could be used, because of their unique and valuable properties, provided further treatment of the filtrate would remove those fibrils that are added. This is a technical matter, however, and I am sure that you know much more about it than we do.

Finally, I don't believe that the paper claimed that we had evidence that asbestos contamination at levels mentioned constitute a threat to health. Indeed, I thought we made clear that cancers associated with asbestos in humans have so far been observed only in other circumstances, presumably at levels considerably higher than those associated with parenteral drug contamination. Indeed, we cannot even guarantee that the asbestos we have found in the particular drug samples tested by us came from asbestos filters in the production lines concerned; it is conceivable that contamination occurred at some point after filtration. However, we have ascertained that asbestos can be found in the filtrate of at least some production lines. We would be interested in such evidence as you might have that the filters made by your company do not shed fibers or fibrils to contaminate the filtrate.

Sincerely yours,


Irving J. Selikoff, M.D.
Professor

IJS:sa

cc: W.J. Nicholson, Ph.D.
C. Maggiore, Ph.D.

RECEIVED

MAR 17 1972

ERTEL ENG'N. CORP.

March 15, 1972

Irving J. Selikoff, M. D.
750 Broadway
Paterson, New Jersey

Dear Dr. Selikoff:

As manufacturers of asbestos-cellulose filter pads, we are interested in more details regarding your paper, "Asbestos in Parenteral Drugs."

The first item is your mention of the asbestos fibers, as used in the pharmaceutical industry, having a strong negative charge. Are you certain about this?

Further, we note that your preparation procedures were carried out with a laminar flow filtered air hood. Please advise us of the make and style unit employed, as well as the make and type of final filter used.

In your findings, you refer in passing to other foreign fibers and particles which were present in the drugs tested. To what do you attribute this, and what problems might they cause?

At this point, we do not believe that your paper presents conclusive proof that liquids may become contaminated with asbestos during filtration, or that such possible contamination at the levels mentioned constitute a threat to health.

Have you investigated the alternatives? It would be interesting to investigate the possibility of absorption of chemical contamination, such as plasticizers, from the synthetic membrane filter media also widely used. This potential may exist, and is pointed out by the recent disclosure of a situation where IV solutions have been found to absorb plasticizers from their synthetic containers, with possible harmful results.

It appears that we are at a point where asbestos media is guilty of contamination of pharmaceuticals by inference and conjecture, rather than by proof. Rather than not knowing if

Irving J. Selikoff, M. D.

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March 15, 1972

asbestos in injectables can cause cancer in humans, which is your stated preference, I think that it is important to investigate the matter thoroughly to a definitive conclusion. To prefer ignorance in this matter detracts from the credibility of your work.

If asbestos media is truly a factor in contamination of pharmaceuticals, with resultant disease, we ~~could~~ be the staunchest advocate of the search for a superior substitute.

We look forward to receipt of your comments, and would welcome the opportunity to meet with you to discuss the matter in detail.

Very truly yours,

COLUMBIA FILTER CO., INC.

John Tuit,
President

JT/pn



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

June 27, 1972

We apologize for the delay in answering your letter of March 22, 1972. This delay had resulted from the new delegation of authority to the Division (copy enclosed) which requires proof of efficacy of all products. On May 31, 1972, a meeting was held at the Division in which experts in the field of allergy were present to study the matter of efficacy for allergenic products. No final decisions were made at that time. However, when current problems associated with the determination of efficacy are resolved, we will undertake a review of all allergenic products.

We have a few additional comments concerning your pending license application amendment for freeze-dried pollen extracts.

License Application

* Item 8 - Since it has been shown that asbestos particles can be carcinogenic, and that asbestos filters (Seitz, Ertel) adsorb considerable amounts of the active ingredients, we recommend that a millipore filter or similar type of filter be used for the sterilization of your allergenic extracts.

Item 10 - A stability study should be initiated using at least three lots of product from each allergen category (pollen, mold, dust, etc.). Moisture and vacuum determinations should be made every six months for the entire dating period. Such data should be submitted to the Division as collected.

Item 16 - Our test results on your submitted sample of American Elm Pollen Extract, #92-20-1F1 for residual moisture content was 1.26%. Please retest another final container of this lot and forward to us a copy of your results, along with another final container.

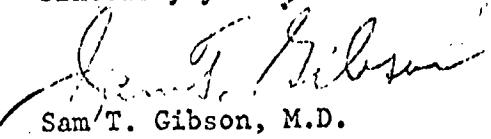
We are returning under separate cover, your labeling for freeze-dried pollen extracts with our comments.

Page 2

Our records do not indicate that we have received the information requested in our letter of February 29, 1972, regarding the manufacture of freeze-dried mold and house dust extracts.

In our letter of April 18, 1972, we accepted your method for carrying out the sterility test on final containers as described in your letter of March 16, 1972. The sterility test procedure has been subject to a new review. In order to establish the minimum acceptable level of sensitivity for the test, the minimum volume of final container material to be tested in each culture medium should be 1.0 ml. rather than 0.5 ml. Therefore, we recommend that your sterility test procedure be revised accordingly.

Sincerely yours,



Sam T. Gibson, M.D.

Assistant Director

Division of Biologics Standards

Enclosure



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

May 23, 1973

TO: All Licensed Manufacturers

SUBJECT: Asbestos-containing Filters

Asbestos contamination of parenteral drugs was reported recently by Nicholson et al. (Science 177:171, 1972). These findings come at a time when there is concern over the presence of asbestos in the environment because of the association of high exposure to asbestos with tumors in man.

Asbestos-containing filters are used in the manufacture of biologics, as well as other parenteral drugs, either for "in-process" filtration or for final filtration. We are asking each manufacturer to review the manufacturing procedures for each of the products for which your establishment is licensed, and to submit to the Bureau a list of those products for which the production includes the use of asbestos-containing filters for either "in-process" or final filtration. Preparation of water for glassware washing is considered an in-process step. In addition, the type of filter used for final filtration of each product should be provided. This information should be submitted within 90 days from the date of this memorandum.

Your comments on the use of asbestos-containing filters in the manufacture of your products and the problems associated with the use of other types of filters for final filtration are requested.

Harry M. Meyer, Jr., M.D.
Director
Bureau of Biologics



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

January 26, 1973

This replies to your letter of January 16, 1973 concerning the use of asbestos filters in the food industry.

The Food and Drug Administration is currently investigating the use of asbestos filters in the food industry. We have recently had a meeting with several firms from the food industry and representative of the asbestos manufacturing firms to discuss the problem of asbestos, including the technological aspects of the use of any types or forms of asbestos in food processing applications.

It is our view that food should be free of asbestos form particles such as Tremolite or Chrysolite. Food manufacturers should assure themselves that the final consumer product is free of asbestos. Manufacturers of asbestos filters should take what ever steps are necessary to insure that use of these filters will not result in contamination of food with asbestos form particles.

Sincerely yours,

Pat T. Adamo
Assistant to the Director
Division of Regulatory Guidance
Office of Compliance
Bureau of Foods

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FEB 8 1973



INDUSTRY CIRCULAR

DEPARTMENT OF
THE TREASURY

Bureau of Alcohol, Tobacco and Firearms

Washington, D.C. 20224

Number 72-31

Date: October 18, 1972

FOREIGN SUBSTANCES IN BOTTLED ALCOHOLIC BEVERAGES

Proprietors of distilled spirits plants,
bonded wine cellars, breweries,
taxpaid wine bottling houses,
and others concerned:

We are becoming increasingly concerned about the reported finding of foreign substances in bottled alcoholic beverages. Among the materials found have been asbestos and cellulose fibers and glass. Because we know of your interest in having your products meet consumer protection standards, we are issuing this circular to make you aware of this problem, and to suggest that you evaluate your operations and take every precaution to see that your products, when shipped for sale, are free of foreign substances, some of which may be hazardous.

In the future, we shall make it a practice to keep you informed of pending investigatory studies concerning the effects of human ingestion of various materials. As you know, studies of this type frequently result in a declaration of probable hazard to health, with a resultant banning of use. We, of course, must enforce such bans at any of the plants regulated by this Bureau. Any questions you may have on this subject should be forwarded to the Director, Bureau of Alcohol, Tobacco and Firearms, Attention: Regulatory Enforcement.

Rex D. Davis

Rex D. Davis
Director

precipitation

Section 3.3. Pages 41/42 from Sterilisation - Desinfektion - Konservierung - Chemotherapie by Dr. K.H. Wallbeusser (Frankfurt/M. - Hochst) and Professor Dr. H. Schmidt (Wabern b. Bern)

WITHOUT COMMENTARY

3.3. The Removal of Pyrogens by Filtration.

Pyrogens are, in the main, constituents of the cell walls of bacteria, of which something towards 90% are bound to the cells. They can only be detected by animal experiments (see page 491). At temperatures over 200°C they are destroyed in approximately 30 minutes.

A pre-condition of their separation by filtration is the removal of all bacterial cells including those that have been killed by heat. Further, steps must be taken with injection solutions that are sensitive to microbial infection to prevent bacterial reproduction and combined therewith, accumulation of pyrogens. The strongest pyrogen formers are the gram-negative bacteria, *Pseudomonas* types, *E. coli* and so on although gram-positive bacteria and viruses can also play a part.

Although the "genuine" pyrogens can induce temperature increases within 30 minutes in animal experiments, the virus pyrogens lag behind somewhat and only show a significant fever effect after 1 - 2 hours. (The standard for control - lipopolysaccharide Pyrexal prepared by the Abbott Company causes in rabbits when used in a concentration of 0.25 mg/ml of substance in 0.5 ml of distilled water a temperature rise of 0.8 - 1.5°C within 30 minutes.)

According to Siegart and collaborators (S.-B. Ges. Ford. gen. Materialien. (Hamburg) 83, 1/2; 84, 1 (1961/62), 255) there are significant differences between bacterial and virus pyrogens. Whereas the former can be separated from the cell wall (soluble) and are only destroyed after heating for a longer time (30 minutes) at 200°C, the latter cannot be separated from the virus particles, they are more readily inactivated by heating and can be neutralised by anti-bodies. The bacterial pyrogens are not volatile in steam but, nevertheless, substances are carried over on distillation which do result in a fever reaction, although only after several hours. It is probable that the products carried over are bacterial breakdown products such as amines and other nitrogenous compounds.

The removal of the pyrogens bound to the bacterial cells or fragments thereof can be effected by filtration through a membrane filter (maximum pore size 250 m micron) (Schmidt, B., V. Blass; Z. Hyg. 142 (1955/56), 183, 298), or Seitz filter sheets (Wilke, H., H.E. Voss: Arzneimittelforsch. 4 (1954), 8; K.D. Rudat; Zbl. Bakt., I.Abt. Orig. 164 (1955), 370). The removal of the "free" partly soluble pyrogens is far more difficult. These can only be eliminated by means of adsorptive action filters and, when necessary, by repeated filtration processes. The loading limit (the available adsorptive surface) is, according to Wilke and Voss for 1000 cm² filter surface (EKS) some 2000m², the composition (and particularly the protein content) of the solution to be processed and the pyrogen content all play significant roles. If the loading limit is exceeded then the pyrogens will pass through. In any case proving experiments should be used to clarify the corresponding relationships. In general it can be said that with watery solutions which do not contain too much high molecular weight substances all pyrogens (up to 1 mg/l) will be removed in the course of the sterilising filtration. Colloids (serum, proteins etc.), high viscosity solutions (plasma substitute) as well as surface active agents substances (Saponins, preservation additives etc.) hinder quite significantly the pyrogen adsorption process. With surface active substances the small amounts of pyrogens remaining in the filter sheets after manufacture can even be eluted out. These small amounts of pyrogens can normally be disregarded owing to the high adsorptive action of the filter sheets. The best safety measure is, in any case, to use the greatest possible filtering surface and this should always be done, especially with infusion solutions.

Dextran solutions (molecular weight approximately 50,000) can be satisfactorily depyrogenised through EKS sheets at a loading of 500 litres per square metre. Albumen hydrolysates are more difficult and whereas hydrolysates prepared by acid hydrolysis can be adequately depyrogenised by double filtration through EKS², this is not adequate for the high molecular weight products obtained by the enzymatic splitting of albumen. A pretreatment with ion exchange resins (e.g. Amberlite of Roehm & Haas) is of assistance. In this case the EKS filter sheet is covered with a 5/10 cm thick layer of the ion exchange resin.

According to Kuntcher, H., W. Fahrig, the soluble pyrogens in concentration ranging from 10 to 100 $\times$ 100/ml can be adequately removed by filtration through a single sheet (Seitz-EK) of 100 cm² surface and a volume of 25 litres.

According to a recent report from the Seitz-Munko a 10% gammaglobulin solution a prefiltration through five sheets 40 x 40cm Grade AKS4 (these sheets which are some 5 mm thick contain in addition to cellulose and asbestos fibres as the basic structure a high content of very fine activated carbon to increase the filtration effect and to prevent the washing through of the activated carbon carry on the outlet side a suitable filter paper that will hold it up) and a finishing sterilisation with 15 EKS sheets proved satisfactory.

Investigations of Kienholz, M. (Arzneimittel-Forsch. 14 (1964), 1259) have shown that 1 m² of Seitz EKS sheet is adequate to depyrogenise approximately 90 m³ water with a pyrogen content of some 500 mg from added E. coli-Lipopolysaccharide.

GO/MD

5.12.1973.