

STATE OF MICHIGAN



WILLIAM G. MILLIKEN, Governor

DEPARTMENT OF PUBLIC HEALTH

3500 NORTH LOGAN STREET, LANSING, MICHIGAN 48914

MAURICE S. REIZEN, M.D., Director

December 20, 1973

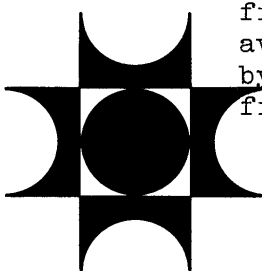
Hearing Clerk
Food and Drug Administration
Room 6-86
5600 Fishers Lane
Rockville, Md. 20852

Dear Sir:

Re: 21 CFR Part 133 Asbestos
Particles in Food and Drugs
Proposed Rulemaking -
Fed. Reg. 38 27076-27081
Sept. 28, 1973

The following comments are being provided in response to the notice of proposed rule-making, relating to the continued need to use asbestos-containing filters in the manufacture of certain biologic products in our establishment, under U.S. license #99.

In the MDPH we use asbestos-cellulose (Seitz-type) filter pads for both "inprocess" and final filtration of the following products: Diphtheria Toxoid, Tetanus Toxoid, Histoplasmin, Normal Serum Albumin (Human), Immune Serum Globulin (Human), Fibrinogen (Human), and Tetanus Immune Globulin (Human). The last four products listed are also passed through a fritted glass filter downstream from the Seitz-type filters. In a very recent development we now are able to provide Millipore membrane filtration of the serum albumin, after the albumin solution has been passed through asbestos-cellulose filter pads as a clarification step. Our last lot of albumin was passed through Seitz-type pads followed by an in-line millipore filter, comprised of a glass prefilter, 0.45 and 0.22 micron membranes. There was sufficient pressure to permit the in-line filtration with no slowdown in filtration rates; thus we feel that we can conform to the proposed new paragraph 133.8 (j), at least for this product. Noting the different filtration characteristics of Immune Serum Globulin (Human), we doubt that such a simple set up will work successfully, but we will have to gain further experience by trying alternative means to complete the filtration through a non-fiber-releasing filter. Clearly it is our experience with a number of these products (albumin, gamma globulin and fibrinogen in particular) that they cannot be passed through the presently available non-fiber-releasing filters until after they have been clarified by filtration through some of the tighter grades of asbestos-cellulose filter pads.



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As we all begin to look harder for solutions to the overall problem of the reduction of particulate matter in parenteral drugs (and the reduction of asbestos in particular) several major points seem to become quite clear. They are delineated below -

1. We subscribe to the position taken by B. Trasen * (Chem. Engr. Progress 64 64-68 (1968) Febr) that "before various methods to reduce or eliminate particulate contamination in pharmaceuticals are discussed, it is essential to have a workable procedure for determining the effectiveness of these methods."

We should somehow decide what the largest acceptable particle size is, in the final product, since total (absolute) eradication or absence of particles may be unprovable, even if asbestos-containing pads are eventually eliminated. There may be no valid solution to the problem by simply passing a liquid through a membrane filter rated at 0.22 microns pore size; indeed, it is our understanding that scientists at the Bureau of Biologics are studying asbestos contamination of a particle size that could pass through 0.22 micron membrane filters. We don't know on what basis or of what clinical significance they selected this criterion for particle size.

* In article entitled "Detection and Reduction of Particulate Matter in Pharmaceuticals"

2. We feel that it is very important to obtain precise information on exact practices used by different manufacturers in utilizing (or not utilizing directly) asbestos-cellulose sheets in their filtration work and relating this carefully to the specific problem that might or might not exist with regard to individual products from other manufacturers.

Our suggestion is to select one good, index-type of product (Normal Serum Albumin would be an ideal example) and obtain from each albumin manufacturer precisely what each one does to:

- a. Clarify and filter sterilize the product.
- b. Prepare and store water for parenteral products.
- c. Wash and sterilize final glass containers and stoppers.
- d. Filter products during filling operations.
- e. Provide wash and rinse water for vials and stoppers.
- f. Clean tubing and its policy on re-use.

Then the albumin products should be examined carefully by some of the presently available methods for the detection of particles, and, in particular, the types of asbestos which are present and their "true size".

3. We have not seen significant effort yet on the part of the filter industry to offer asbestos-free filtration devices for situations which apparently still require these depth-type (non-membrane) filters. This in itself points to the need for further time before prohibiting use of asbestos-containing pads. But, until

3. (continued)

a maximum acceptable particle size is defined, there will be limited success in achieving reduction in or the elimination of the use of asbestos-containing filters in certain filter operations.

In the nomenclature of filter types, the word "absolute" is not absolute; rather, it is a term which means that there is a definite largest particle that will pass through the filter (and that this particle size "rating" remains the same throughout the life of the filter - these types are the wire mesh screen filters and the membrane filters). A combination of a large depth-type filter with an "absolute" filter downstream of it, is generally the ideal system. This combination has solved many troublesome filtration problems. In summary the problem remaining today is to decide what particle size is acceptable and the nature of acceptable particles.

Thank you for this opportunity to comment on the proposed rule making.

Sincerely,



K. B. McCall, Ph.D., Assistant Chief
Division of Biologic Products
Bureau of Laboratories

KBM:be