

CUTTER LABORATORIES

December 27, 1973

Hearing Clerk
Food and Drug Administration
Room 6-86
5600 Fisher's Lane
Rockville, Maryland 20852

RE: 38 F.R. 27076 September 28, 1973
Asbestos Particles in Food and Drugs

Sir:

We submit in quintuplicate comments on the referenced proposal.

Recent publications, including the Federal Register notice itself have spurred many drug manufacturers to investigate the possibilities of eliminating asbestos filters from their processes. The investigation of non-asbestos filters seeks to prove that the substitute filter will do the filtering job needed and that in so doing, it will not have an undesirable effect on the product. Such investigations take time. Once an alternate filtering substance is found suitable, it and its related equipment must be ordered. With the intense interest in non-asbestos filter materials, there is often a significant lead time to acquire the equipment and filter material from suppliers. We feel that final regulations should allow a lead time of 12 months or more before becoming effective if all drug manufacturers are to be able to convert to non-asbestos filters in time.

In addition, final regulations should take into account the fact that asbestos filtration may be vital to certain production processes and that final filtration by membrane filters may have untoward effects on the product. For example, during the manufacture of plasma products by the cold ethanol processes developed by E. J. Cohn and collaborators, filtration procedures are employed at various process points to serve two objectives:

1. To render alcoholic supernatants from continuous flow centrifugation free of precipitated protein which was not totally removed by centrifugation.
2. To obtain solutions of plasma protein products which are bacteriologically sterile and suitable for parenteral administration.

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Filtration media containing asbestos in varying amounts have been successfully used for some 30 years in these applications and continue to be so used today. However, newer advances in filtration technology have permitted during the past several years the introduction of membrane filters of absolute porosity. These have been applied and found particularly effective for sterilizing the more recently developed plasma products such as Factor IX Complex (Human) and anti-hemophilic Factor (Human).

Long years of experience have amply demonstrated that filtration of protein solutions through asbestos containing media results in effects additional to particulate matter removal. Asbestos is a well known adsorbent of proteinaceous substances and as such is instrumental in removing trace contaminants from protein fractions. Some of the substances adsorbed can be described as well as the consequences of their removal. However, because of the complexity and heterogeneity of plasma protein fractions, it must be assumed that non-identified constituents are also adsorbed by asbestos, the effects of which are non-predictable in the final product.

As is well known in the field, the Cohn cold ethanol procedure for plasma fractionation does not result in pure final products. Traces of many plasma components can be found in all therapeutic materials so produced. One particularly troublesome impurity is the proteolytic activity which is often contained in fraction II products, the immune serum globulins. This presence can lead to proteolytic cleavage of the immune globulin molecule which seriously compromises the efficacy of the product. Experience has taught that filtration through asbestos during the fractionation of immune globulins and of the final bulk solutions to prepare sterile products, results in significant adsorption of proteolytic activity. Removal of this activity is essential to the quality of the product and no methods are now known short of revamping the entire fractionation process to effect its removal without using asbestos.

Similarly it is well known that components of the complex kallikrein system occur in fraction IV and V products. The consequences of their presence is not fully understood but it is known that there is an intricate interaction of activators, inhibitors and kinins and that we have empirically produced products which have accommodated to their presence. Eliminating asbestos filtrations would be expected to upset this fragile equilibrium leading to products which might elicit potentially new and/or different clinical effects.

These examples are but two which illustrate the precarious nature of plasma fractionation processes and the possible effect of a seemingly simple change as removing asbestos filtration.

Preliminary experiments in our laboratories have demonstrated the feasibility of employing non-asbestos containing membrane filters as final sterilizing filters. Therefore, we can support the proposal that asbestos filters will be permitted if necessary, providing an additional non-asbestos containing filter shall subsequently be used to reduce the content of any asbestos-form particles. We submit that the total elimination of asbestos filters would seriously jeopardize the ability to manufacture human plasma protein products.

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Since the feasibility of utilizing membrane filters on a manufacturing scale for all plasma proteins has not been proven, time for technical development is required. We suggest a period of at least eighteen months will be necessary to acquire the necessary equipment and carry out the development effort needed to adopt membrane filters as final filters.

Respectfully submitted,

CUTTER LABORATORIES, INC.

By _____
Edward A. Cutter
Secretary and Corporate Counsel
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