HFD-30C

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

APR 14 1976

Mr. Joseph Stetler
President
Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

Dear Mr. Stetler:

This is in reply to your petition relating to the final regulation published in the Federal Register of March 14, 1975, entitled "Asbestos-Form Particles in Drugs for Parenteral Injection".

Your petition requested (1) withdrawing two subsections of the final regulation that you allege were not included as part of the original proposal, (2) rewording the subsection relating to subsequent use of a non-fiber releasing filter, and (3) delaying the effective date of the regulation.

Our response to your requested actions is as follows:

1. Definition of non-fiber-releasing filter to include non-glass fiber filters in § 211.40(j)(1).

Both your petition and a submission by Johns-Manville allege that the Commissioner issued the final regulations contrary to the rule making provisions of the Administrative Procedure Act in that the final regulations included a substantive provision not set forth in the proposed regulation. Specifically, you allege that although the proposed regulations did not make any reference to glass fiber filters, the final regulation prohibits their use in preparing drugs for injection into humans. As a result of the failure to mention glass fiber filters in the proposal, you allege that interested persons were precluded from presenting written data, views, and arguments concerning such filters.

It is our conclusion that, although the terms of the notice are broad enough to include glass filters, the lack of comments on the proposal with respect to the glass fiber filter issue indicates that the proposal may not have provided sufficient notice

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that the phrase "asbestos-containing or fiber-releasing filter" embraces glass fiber filters. Therefore, to eliminate the possibility of a legal challenge to the regulations on the grounds that the proposal was inadequate, an amendment to § 311.40(j)(1) will be published in the Federal Register to delete non-glass fiber filters from the definition of non fiber-releasing filter.

However, we maintain that the scientific data suggest that the presence of glass fibers in parenteral drugs is of sufficient public health concern to require agency action. Therefore, in the very near future we intend to propose an amendment to prohibit the use of glass fiber filters in the manufacture of parenteral drugs for human use.

2. Request for rewording of § 211.40(j)(2).

Your petition requests that § 211.40(j)(2) be amended to indicate that the use of asbestos-containing filter with subsequent use of a specific non-fiber releasing filter be routinely permissible. As published, the regulation permits the use of an asbestos containing filter with subsequent use of a specific non-fiber-releasing filter only upon submission of proof to FDA that the use of a non-fiber releasing filter alone will, or is likely to, compromise the safety and effectiveness of the drug product. Your petition states that a non-fiber-releasing filter will filter out any fibrous materials, thus meeting the agency's objective of eliminating fibers from the drug product. Therefore, since the agency's objective is met, you contend that it should not be necessary to demonstrate that the use of only a non-fiber-releasing filter will compromise the safety of efficacy of the drug.

We conclude that such a change would be unacceptable since the purpose of these regulations is to minimize to the greatest degree possible the amount of asbestos or asbestos-form fibers in parenteral drugs, thereby minimizing the possibility of deleterious effects. Although a non-fiber-releasing filter used after an asbestos-containing filter will substantially reduce the number of fibers in the product, one cannot be sure that it will remove all of this material. Therefore, the best means to eliminate asbestos contamination from parenteral drugs is by removal of the asbestos filters from the process whenever possible.

3. Filtration of wash-water (§ 211.55).

Your petition also contends that § 211.55 adds a new requirement that was not contained in the proposal. Specifically, your petition states that the specification that wash water used to clean

containers for parenteral drug products and their components must be filtered through a 0.22 micron filter (0.45 micron if the manufacturing conditions so dictate) was not in the proposal and therefore should be withdrawn or published as a proposed regulation. At issue is not the necessity for filtration of wash water, but the pore size of the non-fiber-releasing filter that will be required in water lines carrying water to be used for the final rinse of containers for parenteral drugs and their components. In addition to the allegation that the filter pore size was not included in the proposal, your petition states that the filter pore size specified is unreasonably small without the inclusion of an appropriate test method to determine the effect of filtration and that the large volumes of water involved in the cleansing and rinsing operations can pose many practical problems in terms of increased time involved and needless costs.

It is our conclusion that the proposal contains sufficient information to permit specification, in the final regulation, of the pore size of filters used to prepare water for cleaning and rinsing containers for parenteral drugs and their components. Therefore, we reject your request to withdraw this requirement. Your petition did not object to the pore size requirement for filtering drugs but only to that requirement as it pertains to the wash water. To require a filter with a pore size of 0.22 micron (0.45 micron if the manufacturing conditions so dictate) for parenteral drugs but to allow a filter of greater pore size to be used for the wash water would defeat the purpose of the regulation. If a filter of larger pore size than that used for the product were permitted, the filtered product could be free of fibers but the rinsed container could have fibers in it of a size that can pass through the filter used as a result of the known inherent fiber contamination of water. As a result, when the product comes into contact with the rinsed surfaces of such a container, the drug product could become contaminated. Such a result would clearly be contrary to the stated intent of the proposed regulation, i.e., to minimize the possibility of deleterious effects resulting from injecting asbestos fibers into man. Even when asbestos filters are not used by a manufacturer, asbestos particles have been found in parenteral drugs.

We recognize that the specific pore size to be used in filtering parenteral drugs, as well as to be used in filtering the wash water, was not mentioned in the proposal. The obvious and logical intent was that the same size filter should be used for both. The proposal did, however, contain the requirement that if an asbestos filter was required in preparing the product, "an additional non-asbestos-containing or non-fiber-releasing filter such as membrane

filter shall subsequently be used to reduce the content of any asbestos-form particles in the drug or drug ingredient. Evidence for reduction shall be based on the use of the methods described in 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)." Two comments objected to this proposed requirement of proof of reduction of asbestos fibers for the reason that the test was inadequate quantitatively to demonstrate reduction and is immensely difficult to perform. In issuing the final regulation, the Commissioner agreed that better methodologies for these analyses were needed. He therefore omitted proof of reduction from the final regulation and substituted the requirement for use of a filter of 0.22 micron pore size (0.45 micron if the manufacturing conditions so dictate) which is what was meant by a membrane filter in the proposal.

That the wording of a final regulation differs from the proposed regulation is not sufficient reason to require that the former be published as a new proposal. The important issue is whether the proposal adequately put interested persons on notice as to the intent of the regulation. In this instance the proposed regulation clearly gave notice that all reasonable attempts to exclude asbestos fibers from parenteral drug products would be required. It was also obvious that filters with comparable pore size would be necessary to preclude asbestos fibers from finding their way into the final drug product.

4. Delay of Effective Date of Regulation.

Your petition indicates that many parenteral products, especially biological products, have historically been filtered through asbestos filters or cannot be filtered through known non-fiber-releasing filters. Therefore, you allege that the requirements placed on manufacturers to prove that the use of non-asbestos-containing membrane filters will compromise the safety or potency of their products, before the use of asbestos filters is sanctioned, is unreasonable and would require considerable time and expense. Moreover, it is asserted, that FDA has not indicated what type of evidence will be considered proof that the use of a non-fiber-releasing filter will be likely to compromise the safety or effectiveness of a drug. Therefore, until such criteria have been defined, you request a delay in the effective date of the regulations. Specifically, you request that § 211.40(j)(3) be amended to read as follows:

> "Substitution for a fiber-releasing filter shall be achieved 180 days after FDA has established the criteria necessary to prove that use of a non-fiber-releasing filter will be likely to compromise the safety or effectiveness of a drug."

Having reconsidered the issue of what constitutes proof of a compromise of the safety or effectiveness of a drug, we reaffirm the statement in paragraph B.3. of the preamble to the March 14, 1975 publication to the effect that the responsibility remains with the manufacturer to demonstrate that the replacement of asbestos filters or the utilization of a final non-fiber-releasing, non-asbestos-containing filter decreases product quality, effectiveness or safety. Presumably each manufacturer knows the characteristics of his product. Based on that knowledge, and the knowledge of how the product is manufactured, the manufacturer is in the best position to determine how his product will be adversely affected by not using an asbestos filter and can pattern his evidence accordingly. The data necessary for one type of product could conceivably be quite different than that needed for another product. As pointed out by your petition, the use of asbestos filters with viral biological products may be to absorb undesirable components in tissue culture vaccines. Further, you also state that asbestos filters are used with viscous blood products, such as Normal Human Serum Albumin, because they cannot be filtered through membranes at temperatures required to prevent possible development of pyrogens. Obviously, data demonstrating a compromise of the safety or effectiveness of tissue culture vaccines will be quite different from data demonstrating a similar compromise for viscous blood products and is best elicited by the manufacture in each case.

As a result of a comment on the proposal, the final regulations provided for an 18-month period to allow for compliance. We consider this sufficient time for a manufacturer to either submit the necessary data or develop any new processes.

Sincerely yours,

Sam D. Fine
Associate Commissioner
for Compliance