

PHARMACEUTICAL MANUFACTURERS

Association
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September 11, 1975

Alexander M. Schmidt, M.D.
Commissioner, Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Schmidt:

Pursuant to the provisions of the Administrative Procedure Act (5 USC 553 e) the Pharmaceutical Manufacturers Association petitions the Food and Drug Administration to amend the final regulation relating to "Asbestos-Form Particles in Drugs for Parenteral Injection" by (1) withdrawing two subsections of the final regulation that 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 reasons for the requested action are set forth below.

Withdrawal of Those Subsections not Originally Proposed for Comment

The regulation in question, pertaining to asbestos form particles in parenteral drugs, was finalized on March 14, 1975 (40 FR 11869). This final regulation contains two essential new concepts (subsections 133.8 (j) (1) and 133.9) that were not included in the original proposal of September 28, 1973 (38 FR 27076).

Subsection 133.8 (j) (1)

This subsection substantially expands the definition of a non-fiber releasing filter from the original proposal by including non-glass fiber filters in the definition. This change effectively prohibits the continued use of glass filters in filtration systems for parenteral drugs, unless it can be shown that it is not possible to manufacture the drug product without the use of such a filter.

When the regulation was first proposed, many manufacturers substituted glass fiber filters for asbestos filters because they were the only available substitute, and manufacturers were quite understandably under the impression that glass filters would be acceptable. Nowhere in the proposed regulation was there any mention of glass filters as being considered "fiber releasing" or presenting a potential hazard.

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Also, we are unaware of any scientific data that indicates that the use of glass filters in the manufacture of parenteral drugs results in any adverse effects in humans. Unless there is a reasonable scientific basis for such a prohibition, we urge that subsection 133.8 (j) (1) be withdrawn and the use of glass fiber filters be permitted in filtration systems for parenteral drugs.

In the alternative, the FDA should re-publish for comment that aspect of the regulation pertaining to the use of glass fiber filters. The minimum requirements of subsection 553 (c) of the Administrative Procedure Act mandates an opportunity for comment on such administrative rule making.

Subsection 133.9

This subsection adds a new requirement not contained in the original proposal to the effect that wash water used to clean drug components and containers for parenteral drug products must be filtered through a 0.22-0.45 micron filter.

We believe that the specification for filter size is unreasonably narrow 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.

In our judgment, Subsection 133.9 should be withdrawn or at the very least it should be re-published for comment since it was not part of the original proposal. Such re-publication, as indicated earlier, is mandated under the Administrative Procedure Act.

Rewording of Subsection 133.8 (j) (2)

This subsection requires that "use of an asbestos containing filter with or without subsequent use of a specific non-fiber releasing filter is permissible only upon submission of proof to FDA that the use of a non-fiber releasing filter will or is likely to compromise the safety or effectiveness of the drug product."

Subsequent use of a non-fiber releasing filter will filter out any fibrous materials and therefore should be satisfactory compliance with FDA's desire to eliminate fibrous materials. Such use of a non-fiber releasing filter should eliminate the need for submitting proof to the FDA that its use will compromise the safety or efficacy of the drug. To accommodate this view we urge that 133.8 (j) (2) be amended by deleting the words "with or" in the second sentence of the subsection. This way a manufacturer using a subsequent non-fiber releasing filter would be in compliance with the regulation.

Delay of the Effective Date of the Regulation

There are numerous products, particularly biologicals, which cannot be filtered through known non-fiber releasing filters (membranes). Asbestos-containing

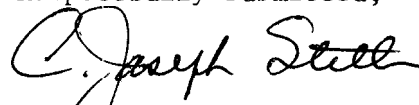
filters have been used in the manufacture of biological products for many years. The advantages of such use include basis effectiveness as filters as well as reported depyrogenizing effects and absorption of undesirable components including active viral particles in the manufacture of tissue culture vaccines. Products such as Immune Serum Globulin (Human), Tetanus Immune Globulin (Human) and Normal Serum Albumin (Human) cannot be filtered through membranes at temperatures required to prevent possible development of pyrogens. Subsection 133.8 (j) of the regulation prohibits the use of an asbestos-containing filter unless the manufacturer proves that the use of a non-asbestos-containing membrane filter would compromise the safety or effectiveness of the drug. In the case of many biologicals, a new requirement that the manufacturer prove that the use of non-asbestos-containing membrane filters will compromise the safety or potency of these products is unreasonable and would require considerable time and expense.

FDA in a recent letter (see enclosure A) acknowledged the problems associated with biologics. However, the agency has not indicated the type of evidence which will be considered as proof that use of a non-fiber releasing filter will be likely to compromise the safety or effectiveness of a drug. We therefore, urge a delay in the compliance date until such time as FDA is able to define the criteria a manufacturer must meet to continue the use of fiber releasing products. Therefore, subsection 133.8 (j) (3) should 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.

We urge that this petition be favorably considered. Should you require further information we will be happy to supply it.

Respectfully submitted,


C. JOSEPH STETLER
President

Enclosure



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
BETHESDA, MARYLAND 20014

August 6, 1975

Alan Gray, Ph.D.
Merck, Sharp & Dohme,
Division of Merck & Co., Inc.
West Point, PA 19486

Dear Dr. Gray:

As Dr. Gibson discussed with you in Philadelphia in June we have been reviewing your thoughtful letter of May 28, 1975. It is evident from the response to our survey of April 25, 1975, that much progress has been made but also that there are definite indications asbestos filters cannot be eliminated entirely from biologics manufacture at this time.

After further discussion with the Commissioner we will communicate again with all interested manufacturers about what will be considered as proof that use of a non-fiber releasing filter will be likely to compromise the safety or effectiveness of a drug. We would be interested in the position of plasma derivative manufacturers on such proof.

Sincerely yours,

Paul Parkman
for Harry M. Meyer, Jr., M.D.
Director
Bureau of Biologics

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DIRECTOR OF BIOLOGICS