

PALL CORPORATION



GLEN COVE, L. I., N. Y. 11542, U.S.A.
(516) 671-4000
TWX 510-223-0606
TELEX 126329
CABLE: PALLCO GLEN COVE

December 7, 1973

Food and Drug Administration
Hearing Clerk, Room 7-86
5600 Fishers Lane
Rockville, Maryland 20852

Subject: Proposed Regulation, Part 21, Par. 133.8, Fed.
Register Vol. 38 No. 188 - September 28, 1973

Gentlemen:

In response to the invitation for comments on the proposed regulation #21, Par. 133.8, we are enclosing a position paper and suggested change in wording of the proposed regulation. Our position paper is directed primarily toward clarifying the usage of the words "membrane filters", in order to avoid misinterpretation which would result in adverse effect on the sales of widely used non-asbestos-containing Pall Corporation* Ultipor^(R) Membranes.

To briefly summarize our position, we respectfully request the following changes in Par. 133.8(j):

- (1) First sentence: "Filters used in the manufacture of a parenteral drug or parenteral drug ingredient shall not exhibit particle or fiber migration from constituents of the filter medium. Filters should be sufficiently cleaned after manufacture or prior to use to assure a high degree of effluent cleanliness."
- (2) Second sentence: "No asbestos-containing or fiber-releasing filter.." to: "No asbestos-containing or media migration exhibiting filter..."

*As you may know, Pall Corporation with its present annual filter sales volume exceeding \$30,000,000, is a major supplier of fine filters to the pharmaceutical and related industries. The enclosed annual reports from 1972-73, the listing of Pall patents and the listings of selected pharmaceutical and food industries using Pall filters may be of interest in your evaluation of our comments.
(Appendix IV)

75P-0261

Engineered Products For The Control Of Fluids & Environments
REGIONAL CORPORATE OFFICES

U S A & Far East: Pall Corporation, Glen Cove, L.I., N. Y., U S A.
Europe & Middle East: Pall (U.K.) Ltd., Portsmouth, England

Latin America: Pall S.A. Mexico, D.F.
Canada: Pall (Canada) Ltd. Montreal, Canada

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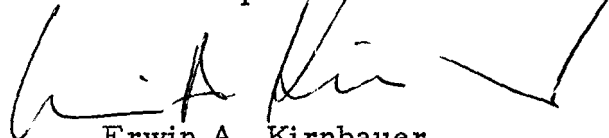
- (3) Third sentence: delete reference to "membrane filter"
- (4) Fifth sentence: change "...non-asbestos-containing membrane filter.." to "non-asbestos-containing filter"

The attached position paper explains in greater detail the background on which our comments are based.

Your consideration in this matter is greatly appreciated. Please let us know if you require any further information.

Sincerely yours,

Pall Corporation

A handwritten signature in black ink, appearing to read 'Erwin A. Kirnbauer', with a large checkmark to the right.

Erwin A. Kirnbauer
Corporate Consultant
Contamination

EAK:cm
enclosures

POSITION PAPER

DISCUSSION ON PALL CORPORATION
RECOMMENDED CHANGES TO PROPOSED
PARAGRAPH 133.8 OF CFR PART 21

It is our understanding that the intent of Par. 133.8 is to eliminate asbestos-containing-filters as a source of asbestos fibers in parenteral drugs or parenteral drug ingredients. Par. 133.8 as presently written also specifies that the filter used in the production of parenterals should not release fiber, citing a membrane filter as an example, and later specifying the use of a membrane filter as an asbestos fiber removal device to be used subsequent to an asbestos-containing filter under prescribed conditions.

We feel that further clarification of the term "non-fiber releasing" properties and of the usage of the word "membrane filter" is required to avoid possible misinterpretation, which could adversely affect Pall Corporation sales of the widely used Ultipor membranes. This clarification will also avoid specifying, by implication, cellulose ester membranes, which have their main application in the analytical field, and which in many cases are not optimal for bulk-volume sterile process applications.

In order to clearly state our position on this, the following detailed discussion is offered:

1. Regarding Fiber Releasing Properties of Filters:

We feel that the specific intent of this proposed requirement is to prohibit the use of asbestos filters with the latent intent of elimination of filters which add contamination, i. e., particles or fibers

to the filtered product. There are two reasons for a filter exhibiting this condition:

- (a) Filter medium migration, i. e. , continuous release of fibers or particles constituting a part of the filter medium, due to inadequate or no bonding of the filter matrix. This can occur under both steady state or under pulsating flow conditions.
- (b) "Built-in" contamination. This consists of particulate and fibrous debris picked up during manufacturing. These can be particularly harmful if they are located downstream of the filtering element. To reduce this type of contamination it is necessary to manufacture the filter under contamination controlled environmental conditions and to clean the filter after manufacture until the desired level is reached. This cleaning operation can be readily accomplished if the filter material lends itself to high velocity flushing with water or other fluids, a manufacturing step which can not be used on cellulose ester membranes, since it would remove the plasticizer on which these membranes depend for their mechanical integrity.

Manufacturing of cartridge type high area elements under clean conditions, without flushing after completion, will result in moderate to high levels of built in contamination. This is the case because cellulose ester membranes, like most other types of filters, being inherently mechanically weak, require a downstream fibrous support, as well as means for providing flow passages for the filtered fluid.

Depending upon whether the medium is pleated, wrapped around a simple cylinder core or spirally wrapped around a core, one or more fibrous layers may be used. It is difficult - and indeed most people familiar with this art would say impossible - to guarantee that these layers will not release fibers or particulates, and for this reason the ability to apply a high velocity flush is extremely important. Flush cleaning of cellulose ester membrane cartridges after manufacture can not be readily accomplished due to removal of the plasticizer.

Ultipor AB Filters can be readily flush cleaned after manufacture until the desired cleanliness level is reached, and this is our normal manufacturing process. The enclosed Pall Corporation Bulletin AB-800 (Table 2) shows typical particle count levels of various cartridges tested in 1972. Although the data are of limited nature, they show clearly the difference between "media-migration" and "built-in contamination." For example, filters type Q, R, S, and T show high initial fiber and particle counts, and they continue to show high fiber and particle counts after the initial 20 liter effluents, and therefore they exhibit media migration. The other types of filters show relatively low initial effluent counts and even lower (substantially zero) counts after the first 20 liter effluent.

The initial count of these low count filters is due to "built-in contaminant" which can be reduced by cleaning the filter cartridge after manufacture to a degree of effluent cleanliness as outlined in APPENDIX II. Review of the data from a filter material con-

struction point of view shows that the cleanliness levels of the non-migrating varieties of filters tested is not a function of the filter material composition and low levels are not restricted to cellulose ester membranes only.

For example, comparing specimen V, W, and Pall 0.2 micrometer filters shows cleanliness levels of the same order of magnitude, with the Pall 0.2 micrometer units somewhat cleaner than the cellulose ester membrane cartridges. Therefore, the word "non-fiber releasing" is not to be equated with "membrane filter" (as implied in the proposed regulation) but should be related to the degree of effluent cleanliness levels which can be achieved in non-migrating type filters. Based on the above discussion, we strongly recommend the word "fiber releasing" in the proposed regulation be changed to "particle or fiber migration", similar to the proposed wording in APPENDIX I.

2. Regarding usage of the word "Membrane-Filter":

It is commonly accepted by many, if not most filter users that the designation "membrane filter" refers specifically to cellulose ester filters, and to most of these, it means "Millipore filter." As an example, see Dr. S. Turco's paper*, which defines membrane filter as being "chemical compositions of cellulose esters." Many other literature citations with similar connotation can be made. In considerable part, this acceptance stems from the wide use of Millipore membranes in laboratory procedures.

*TURCO, S. J. et al, Comparison of Final Filtration Devices, Bulletin of the Parenteral Drug Association, Sept., Oct., 1973, Vol. 27, No. 5, page 209.

Pall products are not so widely recognized because their principal area of use has been in plant scale applications.

As you may know, Pall Corporation is a major international supplier of 0.2 micrometer sterilizing filters and of coarser filters, which employ the patented non-asbestos-containing Ultipor inorganic fiber membrane, corrugated into high area filter element cartridges. The Ultipor membrane has pore size distribution similar to and somewhat narrower than cellulose ester membranes, with better maximum pore size control as shown in the attached paper by Dr. Pall (presented at the Parenteral Drug Association National Meeting of November 2, 1973.) The Ultipor membranes are non-migrating (non-fiber releasing) and are manufactured under clean conditions. Among their advantages over cellulose ester membranes, they can be "in-situ" steam sterilized, exhibit longer life and higher structural strength, and have wider solvent compatibility. They are well suited for sterile process filtration to remove bacteria and asbestos particles* from liquids and gases in pharmaceutical application, and are particularly useful for filtration of parenteral drugs and parenteral drug ingredients. Material used in construction of these filters are listed at the FDA under DMF 2063.

*Note: Preliminary tests at Pall Corporation laboratories show that the 0.2 μ m absolute and 3.0 μ m absolute Ultipor membranes quantitatively remove asbestos fibers (obtained from standard asbestos filters used for pyrogen removal) in the microscopic range, when using phase contrast microscopy per NIOSH publication No. HSM 72-10267. Further studies on coarser grades of similar membranes are presently being conducted. Asbestos removal efficiency tests have also been conducted by using SEM & XREDAS systems for analysis. A discussion of these methods and data obtained to date are summarized in APPENDIX III.

Because a large proportion of potential users accept the word "membrane filter" to denote a cellulose ester, we feel that the basic intent of the proposed regulation will be misunderstood by many filter users, who will interpret the regulation as proposed to mean that cellulose ester membranes are preferred over Ultipor membranes, or sintered porcelain filter candles. This, we believe, is certainly not the intent of this regulation. We are further concerned that user interpretation of this proposed regulation (without the modifications, per APPENDIX I) will result in undue hardship, production delays, and higher costs to those customers who have found it advantageous to use Ultipor membranes, some of whom will erroneously conclude from the present phrasing of the proposed regulation that they are required to use cellulose ester membranes. This also would result in an adverse effect on Pall Corporation sales of asbestos free Ultipor membrane cartridges, which we and many of our customers feel is a superior product and which certainly satisfy the intent of the proposed regulation to achieve asbestos-free and clean parenteral and parenteral drug ingredients by the most practical means.

Therefore, we respectfully request that the word "membrane" in the proposed regulation be replaced with "non particle or non-fiber migrating filter medium", similar to the proposed wording in APPENDIX I of this document.

APPENDIX I

PROPOSED WORDING

USE OF ASBESTOS-CONTAINING FILTERS

Filters used in the manufacture of a parenteral drug or parenteral drug ingredient shall not exhibit particle or fiber migration from constituents of the filter medium. Filters shall be sufficiently cleaned after manufacture or prior to use to assure a high degree of effluent cleanliness. No asbestos-containing or media migration exhibiting filter may be used in the manufacture of a parenteral drug or parenteral drug ingredient unless it is not possible to manufacture that drug or drug ingredient without the use of such a filter. If use of such a filter is required, an additional non-asbestos containing filter which does not exhibit particle or fiber migration 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). Use of an asbestos containing filter without subsequent use of the additional non-asbestos containing

filter is permissible only upon submission of proof to the Food and Drug Administration that use of a non-asbestos-containing filter will, is likely to compromise the safety or effectiveness of the drug.

Interested persons may, on or before December 27, 1973, file with the Hearing Clerk, Food and Drug Administration, Rm. 7-86, 5600 Fishers Lane, Rockville, Md. 20852, written comments (preferably in quintuplicate) regarding the petition and the Commissioner's proposal. Comments may be accompanied by a memorandum or brief in support thereof. The petition, background information referred to in this proposal, and comments received may be seen in the above office during working hours, Monday through Friday.