TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION,
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER C--DRUGS

PART 133--DRUGS; CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURE, PROCESSING, PACKING, OR HOLDING

ASBESTOS-FORM PARTICLES IN DRUGS FOR PARENTERAL INJECTION

3/14/75
40 FR 11865

The Commissioner of Food and Drugs published in the FEDERAL REGISTER of September 28, 1973 (38 FR 27076), a notice proposing to restrict the utilization of asbestos filters in the manufacture of parenteral drugs and parenteral drug ingredients, and to prohibit the use of asbestos-containing talc as a food, or food or drug ingredient, or in food and drug packaging materials, within certain analytical restrictions. The notice provided for the filing of comments within 90 days.

Asbestos fibers are known to cause cancer when inhaled in large amounts. Also, asbestos and other fibers are considered likely to have a similar adverse effect if present in parenteral drugs, although this has not been proven. Because of this likelihood, this order provides that, whenever possible, asbestos-containing or other fiber-releasing filters not be used in the manufacture, processing or packaging of drugs intended for parenteral injection in humans. Also, it provides for measures to reduce the amount of fibers present in such products, where it is not possible to eliminate these filters in the production of a drug.

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The comments made in response to the September 28, 1973 proposal fall into two main categories. One concerns provisions to decrease the potential for ingestion of asbestos fibers. The other concerns provisions to decrease the potential for injection of asbestos fibers. A discussion of each category of comments, and the Commissioner's conclusions, are set forth below.

A. Comments on provisions dealing with ingestion potential of asbestos fibers:

1. The Commissioner proposed that any food, food packaging material, drug, drug ingredient or drug packaging material containing talc that is not free from asbestos fibers as determined by a particular analytical method should be deemed adulterated in violation of section 402(a)(1) of the Federal Food, Drug, and Cosmetic Act.

Nineteen comments related to the proposed analytical method for talc under § 121.2006 (21 CFR 121.2006). The comments were primarily from representatives of food, drug, and talc mining firms, but also included four consultant laboratories and two other federal agencies. Although it is apparent that most of these respondents did not actually use the designated method, and were, therefore, reflecting their general experience with optical crystallography or a personal preference for other analytical methods, none of the respondents supported the proposed method for compliance purposes. The predominant objections to the proposed method were that it is difficult to use, laborious, and not practical for its intended purpose. Several comments offered the opinion that only the most highly trained microscopists would be capable of using the method with any reasonable accuracy or precision. Members of one trade association collaboratively studied the method with 10 microscopists, each examining seven samples of talc. Four participants admittedly could not use the method to count the samples, and there was obvious inconsistency in the results reported by other microscopists.

A number of alternative methods for determining asbestos particles in talc were suggested by the respondents. Although optical microscopy using dispersion staining was the most frequently suggested method, others suggested x-ray diffraction, spectrophotometry, and several electron microscopy and microprobe techniques as preferred or supportive analytical methods. Many of the respondents additionally expressed their willingness to join a Food and Drug Administration analytical task force to evaluate applicable methodology.

Although the Commissioner cannot agree that the designated optical crystallographic method is unreliable when used by those experienced in the art, he recognizes that an effective compliance method must have greater utility and acceptance than indicated by the comments on the proposed method.

The Commissioner has, therefore, decided to delay any final regulation for talc until an acceptable method for determining the presence of asbestos particles can be developed for this substance. This area of research currently is being actively pursued by the Food and Drug Administration.

2. Several comments objected to the purity limitations for talc which were established by the proposed method. Many thought that requirements that talc be 99.9 percent amphibole-free and 99.99 percent chrysotile-free unreasonable, while others insisted that any limitation was unreasonable unless it could be demonstrated to reflect known hazard levels by ingestion. While one respondent calculated that 20,000 amphibole and 3,500 chrysotile fibers (of 5 micrometers x 1.7 micrometers size) should be permitted before any talc sample exceeded the established limits, another respondent observed that individual asbestos particles often vary in size a million-fold, thus making it difficult to relate particle counts to the percentage of asbestos contamination in talc.

Although the decision of the Commissioner to delay any final regulation on talc has rendered these comments moot, the Commissioner wishes to respond to these comments to clarify his position on possible future talc regulations.

As indicated in the proposal, the Commissioner recognizes that the evidence concerning the possible hazard from ingestion of asbestos particles is contradictory and inconclusive. The method was therefore not proposed in order to indicate any known hazard from asbestos, but was intended to establish a good manufacturing practice limitation for the use of talc in food and drugs until an assessment of the hazard, if any, of ingested asbestos can be determined.

The particle limitation accompanying the proposed method represents the best assessment by the Food and Drug Administration of the probability of occurrence of such particles in natural talc deposits, the ability of the method to detect such particles, and the need to assign a limit to define the absence of asbestos. The Food and Drug Administration has also examined numerous talc samples of undefined grade in the past 2 years, using the proposed methodology, and finds that approximately two-thirds of such samples are within these limitations. The Commissioner therefore concludes that the proposed particle limitations would not impose an unreasonable burden on manufacturers of talc if these limitations are ultimately adopted.

The Food and Drug Administration has been aware of the possible extreme variation in asbestos particle size that may occur in natural deposits of talc. Eliminating particles less than 5 micrometers long or with less than a 3-to-1 length-to-width ratio considerably narrows the range of permissible particles counted by the proposed method. Considering the variation in particle size that may yet be possible, however, a typical particle of 300 cubic micrometers, weighing approximately 1 nanogram

(Ref. 1) was used to assure a purity of talc at least 99.9 percent free of amphibole types of asbestos fibers and at least 99.99 percent free of chrysotile asbestos fibers.

3. Three comments from industrial firms objected to the proposed analytical requirements for talc used in the manufacture of paper and paperboard in § 121.101(h) (21 CFR 121.101(h)). All of these comments contended that asbestos, in asbestos-containing talc, does not migrate to packaged food when talc is used for this purpose. One of these comments contained results of recently conducted studies which were intended to prove this contention.

After a thorough review of submitted comments, and examination and evaluation of additional requested studies, the Commissioner concludes that this comment has demonstrated the validity of this contention in a manner consistent with available methodology. In the conducted studies, the comment has demonstrated that dry packaged and shipped salt contains less than 0.01 part per billion asbestos when in direct and continuous contact with uncoated paper containing up to 6 percent tremolitic asbestos. Although detection was limited by the bulk of ash recovered from other products, such as fresh wrapped and frozen meat, dry packaged macaroni, dried milk, rice, and corn flakes, the comment has also demonstrated that these products contain less than 10 parts per billion asbestos under test and market conditions. The analytical details of these studies are on file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

The Commissioner concludes that the above reported salt study represents a practical upper limit of migration of asbestos from food-contact paper and paperboard. This conclusion is based upon consideration of the extreme abrasive nature of salt as compared to other dry foods, and the unusually high tremolitic asbestos content of the test paper (6 percent) as compared to reported levels of use (0.02-0.4 percent) in food-contact paper and paperboard.

The Commissioner therefore concludes that the comment has demonstrated that the asbestos content of talc used in the manufacture of food- or drug-contact paper and paperboard does not represent a potential contaminant of packaged food or drugs, as assessed by currently available methodology. Accordingly, the Commissioner is withdrawing the analytical limitations proposed for talc in § 121.101(h), unless new methodology or toxicological assessment requires further evaluation of this question.

4. The Commissioner stated in the proposal that it had been decided not to promulgate a proposed regulation governing the utilization of asbestos filters in the processing of food and beverages. One comment stated that this was inconsistent with the Commissioner's proposed regulation on the asbestos content of food-grade talc, and that attempts to limit asbestos ingestion should apply uniformly to all sources. Another comment stated that the Commissioner's decision not to regulate the use of asbestos filters in food, beverage and nonparenteral drug preparations was based on the unproven notion that the amounts of asbestos which are contributed to man's overall exposure by these substances are small. The comment contended that evidence is lacking to show that the

ingestion of small amounts of asbestos is safe and that the responsibilities of the Food and Drug Administration for promulgation of regulations to lessen the total human exposure to asbestos were not mitigated by the fact that all human exposure to asbestos cannot be regulated by the agency.

The Commissioner agrees that uniform and consistent regulations should be adopted on an industry-wide basis. In this instance, the lack of available reproducible methodology for determining asbestos-form fibers in beverages and other foods led the Commissioner to propose the regulation of talc before handling other related matters. In any event, the comment has now become moot since the Commissioner has decided to delay a final ruling on talc as a direct food or drug ingredient.

The Commissioner also concludes that neither the available data on the addition of fibers to foods and nonparenteral drugs by use of asbestos filters nor the data on the asbestos content of municipal water are sufficiently reliable to permit promulgation of regulatory controls at this time. Evidence indicates a wide variation of asbestos fiber contamination in the water supply of the cities of the United States, with some reports that the waters of the San Francisco, CA, and the Duluth, MN, areas are among the highest in asbestos content. However, the lack of consistency of test methods and their applications leads to questions concerning these data. A recent epidemiological study of cancer mortality in Duluth over the last 14 years (Ref. 2) has concluded that, up to this time, no carcinogenic effect could be demonstrated from ingestion of the municipal waters. Some reports have been received

claiming little or no asbestos addition to the aforementioned products by the use of filters (Ref. 3). Other reports from Canada, which indicate some increases in the asbestos content of beverages (Ref. 4 and 5) over background water, show that the final levels are comparable to the background levels in areas of the United States. Therefore, the Commissioner has decided to delay the promulgation of any regulation on the prohibition of use of asbestos filters for the preparation of foods and non-parenteral drugs until more reliable data can be obtained on the background concentrations of asbestos in drinking water and the role of asbestos filters in regard to the addition of fibers to ingestible products.

5. Many comments endorsed or condemned the proposals, or parts of them, with respect to water, food, and beverage contamination. Although most of these comments did not supply any additional data or information, a current asbestos feeding study by J. M. G. Davis (Ref. 6) and a 1967 study by G. M. Bonser and D. B. Clayton (Ref. 7) were cited as further evidence of no harm from ingested asbestos. Other comments cited the 1972 conclusion of the Advisory Committee on Asbestos Cancers (Ref. 8) that there was no evidence of an increased risk of cancer from asbestos fibers in water, beverages, and food, or in fluids used for the administration of drugs, and one comment cited a recent study by Kleinfeld, Messite, and Zaki (Ref. 9) which reports no increase of gastrointestinal and peritoneal cancer among talc workers exposed to talc dusts for a minimum of 15 years.

From analysis of the foregoing comments received concerning the limitation of asbestos in talc, from thorough re-review of the scientific evidence available concerning the adequacy of the available methodology to determine the amount of asbestos in talc, and from consideration of the controversial nature of evidence to demonstrate the hazard to health presented by ingestion of the amounts of asbestos fibers normally to be expected in talc used in food or drugs, or in food or drug packaging materials containing talc, or in beverages, other foods and nonparenteral drugs prepared with the use of asbestos filters, the Commissioner concludes that the promulgation of regulations on the limitations or prohibition of the use of asbestos filters for the preparation of foods and nonparenteral drugs and of the amount of asbestos fibers in talc for use in food and drugs or which might migrate into food or drugs from talc-containing packaging materials is unwarranted until more reliable data can be obtained concerning these matters.

The Food and Drug Administration, in conjunction with other agencies, is planning extensive experiments to determine if long term exposure to ingested asbestos fibers represents a definitive hazard to human health. As noted, until this study is completed or other data become available, the Commissioner has determined ——→

that a prohibition of the use of asbestos-containing filters in the processing of food and beverages, and of asbestos-containing talc as a food or food additive or in drugs or drug ingredients is unwarranted due to lack of sufficient data. In the interim, manufacturers of food and drugs are urged to investigate all means of eliminating the use of such filters and talc, and to keep the Food and Drug Administration informed about changes in formulation and processing of this type.

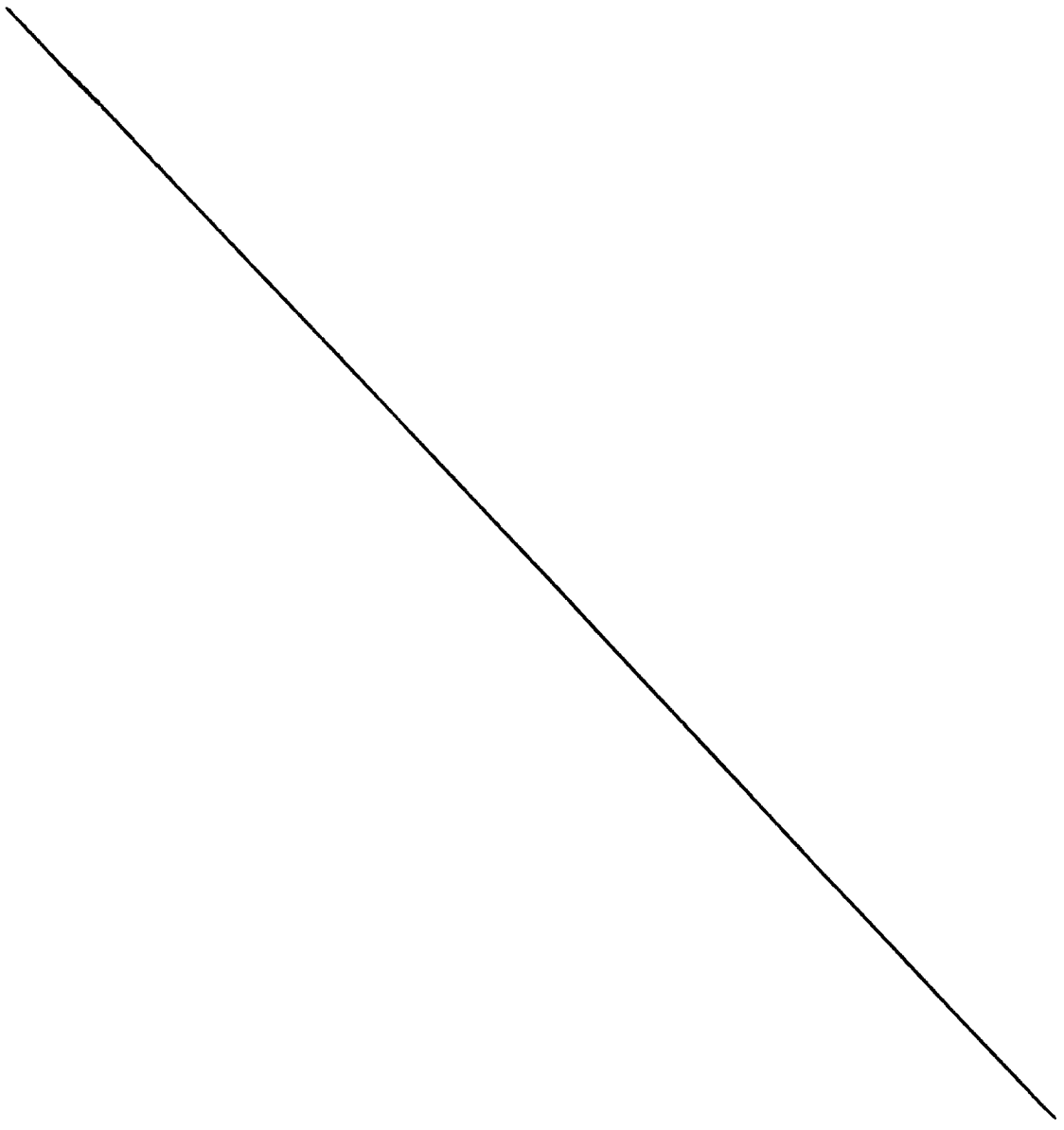
B. In order to deal with the injection potential of asbestos fibers, the Commissioner proposed that the good manufacturing practice regulations for drugs be amended to require that filtration procedures for parenteral drugs shall utilize either a non-fiber-releasing filter such as a membrane filter or, if an asbestos-containing filter is used because it is necessary, the procedures shall also utilize an additional non-asbestos-containing or non-fiber-releasing filter such as a membrane filter to reduce asbestos fiber content to the minimum level feasible unless such a subsequent filter will compromise the safety, identity, strength, quality, or purity of the product.

Comments received in response to this part of the notice, dealing with the injection potential of asbestos fibers, are as follows:

1. A number of comments stated that there is no conclusive evidence that asbestos filters add fibers to the filtrate, or that asbestos has caused deleterious effects as a result of parenterally administered drugs.

Asbestos fibers were found in a number of samples of parenteral drugs by Nicholson et al. (Ref. 10) and also by a subsequent Food and Drug Administration investigation of parenterals. Although the Food and Drug Administration has demonstrated that filtration through asbestos of a water sample highly contaminated with asbestos fibers can significantly reduce the number of fibers present, the Food and Drug Administration also has direct evidence that the utilization of asbestos filters can cause asbestos contamination. The preliminary report of the latter study is on public display in the office of the Hearing Clerk. The evidence of the deleterious effects of parenteral asbestos administration (Ref. 1, 11, 12 and 13) requires that the amount of contamination in these products be minimized. Consequently, the Commissioner has determined that it is important that asbestos-containing filters be replaced with non-fiber-releasing filters unless it is demonstrated that it is not possible to manufacture a safe and effective parenteral drug or parenteral drug ingredient without the use of such an asbestos-containing filter. In the latter instance, a final non-fiber-releasing filter shall be used to reduce the content of any asbestos-form particles in the drug or drug ingredient. Use of an asbestos-containing filter with subsequent use of an additional non-asbestos-containing, non-fiber-releasing filter shall be permissible only upon submission of evidence to the appropriate bureau of the Food and Drug Administration that substitution for the asbestos filter of a non-fiber-releasing filter will or is likely to compromise the safety or effectiveness of the drug. Use of an asbestos-containing

filter without subsequent use of an additional non-asbestos-containing, non-fiber-releasing filter shall be permissible only upon submission of evidence that neither the substitution for the asbestos-containing filter nor the use of a subsequent non-fiber-releasing filter can be accomplished without compromising the safety or effectiveness of the drug.



2. One comment noted that, although there have been several demonstrations of the addition of nonasbestos filters as final filters in the production of injectable biologics, there remains concern that the replacement of asbestos filters with non-asbestos-containing filters would upset delicate filtration parameters of the product preparation process. An 18-month period was suggested as the allowable period of time for technical development of the new processes.

The Commissioner agrees that a specific period for process development and modification should be provided in the regulations. Therefore, 18 months will be allowed for compliance. Firms not conforming to these regulations within 12 months of the date of publication of this regulation will be required to submit monthly progress reports thereafter concerning attempts to implement the required procedures and any difficulties in maintenance of product quality.

3. A large number of comments stated that many parenteral products would suffer in safety and quality because of a requirement to replace asbestos-containing filters in the manufacturing process.

The Commissioner agrees that it is essential that there be no increase in risk to the public as a result of this action. The regulation provides for continued use of asbestos filters where no alternative is feasible. The responsibility for demonstrating that the replacement of asbestos filters or the utilization of a final non-fiber-releasing, non-asbestos-containing filter decreases product quality and effectiveness or safety remains that of the manufacturer. Evidence for such product alteration must be submitted to the appropriate bureau of the Food and

Drug Administration for approval of the continued use of the unmodified asbestos filtration processes.

4. One comment objected to the utilization of the terms "membrane filter" and "non-fiber-releasing filter," stating that the former term was too limiting as a recommendation for a replacement of filters which may release asbestos fibers and that the latter phrase should be changed to "asbestos-containing or media-migration-exhibiting filter." This comment claimed that the term "non-fiber-releasing" should be replaced since small quantities of the fibrous support used in many cellulose-ester membrane filters, as well as fibers and particles from the manufacturing process for cartridge and other type filters, are released by cleaning and flushing prior to marketing of the product. Another comment stated that the proposed regulations did not contain a definition of a non-fiber-releasing filter. Comments also stated that § 133.8 should not use the terms "fiber-releasing" and "asbestos-containing" interchangeably, and one comment objected to the synonomous use of the terms "fiber" and "asbestos fiber."

The Commissioner agrees that the regulation should not specify only one type of filter which would satisfy the new requirements, and thus has deleted the term "membrane filter." The Commissioner also concludes that, for the purposes of these regulations, a non-fiber-releasing filter shall be defined as a nonasbestos, nonglass fiber filter which, after any appropriate pretreatment such as washing or flushing, will not continue to release fibers into the drug or drug ingredient which is to be filtered. The distinction is, therefore, made between filters

which release fibers by media migration, i.e., continuous release due to the nature of the filter, and filters which contain fibers from structural supports and contamination. The utilization of nonasbestos, nonglass fiber filters in the latter category will be permitted provided that appropriate pretreatment, which eliminates fiber contaminant release, has been accomplished. As the similarity between the carcinogenicities of asbestos and fibrous glass has been noted, fibrous glass filters have been added to this definition to prevent the widespread conversion from asbestos to this type of filter (Ref. 14 and 15). A fiber is defined as "any particle with length at least three times greater than its width" (Ref. 15 and 16).

The Commissioner realizes that the definition of a fiber-releasing filter excludes the possibility of the use of an asbestos or fibrous glass filter locked into a matrix which precludes the release of fibers. However, no such technology was presented as feasible by any of the comments. Therefore, the Commissioner concludes that the definition of a fiber-releasing filter is appropriate for this regulation and that, should a method for production of such a non-fiber-releasing asbestos or glass containing filter become available, the definition will be subject to review.

5. One comment suggested that the proposed requirement that "no asbestos-containing filter may be used unless it is not possible to manufacture a drug without the use of such a filter" be replaced by

"when an asbestos-containing filter is utilized, a suitable after-filter must also be utilized to retain fibers."

The Commissioner concludes that such a change would be unacceptable since the purpose of these regulations is to minimize the amount of asbestos or asbestos-form fibers in parenteral drugs thereby minimizing the possibility of deleterious effects, and although an after-filter will substantially reduce the number of these fibers in the product, it cannot be assumed that it will remove all of this material. Hence, the Commissioner has determined that the best means to eliminate asbestos contamination from parenteral drugs is by removal of the asbestos filters from the process whenever possible. As stated in paragraph B.3. of this

preamble, the Commissioner agrees that there must be no increase in risk to the public from any product the manufacturing process of which is required to be changed. However, he reiterates that the use of an asbestos filter will be permissible only upon a demonstration by the manufacturer that the replacement of an asbestos filter by a non-fiber-releasing filter or the utilization of a final or after-filter which is non-fiber-releasing adversely affects the quality, safety, and effectiveness of the product.

6. One comment objected to the statement in the proposal that the use of asbestos filters in parenteral drug manufacturing is prohibited "unless it is not possible to manufacture that drug or drug ingredient without the use of such a filter," claiming that the lack of a more specific statement will lead to capricious regulatory decisions.

The Commissioner concludes that there is no more reasonable method by which to make a determination of the impossibility of achieving the desired product quality and effectiveness without the use of asbestos-containing filters than by individual evaluation by knowledgeable scientists. No automatic decision scheme was suggested in the comment. Therefore, the responsibility for submission of the evidence required for this determination will rest with the manufacturer and the responsibility for accepting or rejecting the request for use of asbestos-containing filters will rest with the appropriate bureau in the Food and Drug Administration.

7. Two comments objected to the fact that the regulations were limited to the release of asbestos and asbestos-form fibers and suggested

that all extraneous material such as diatomaceous earth, carbon, silica, micro-fiberglass, etc. also be regulated.

The Commissioner agrees that there is reason to be concerned about all particulate contamination in parenteral drugs, but concludes that this problem should be considered separately from the subject regulations. Therefore, except for fibrous particulates, the Commissioner has decided to await clarification of the degree of other types of contamination and the possible health effects of such other particulates prior to developing applicable regulations. A call for scientific information in this regard will be published in the FEDERAL REGISTER in the future.

8. One comment objected to the requirement of proof of reduction of asbestos fibers by the use of subsequent non-asbestos-containing filters in the manufacture of a parenteral drug or drug ingredient when submitting a request for approval of a process in which asbestos filters are used. This and one other comment claimed that the National Institute for Occupational Safety and Health (NIOSH) analytical method, as well as other analytical methods for determination of asbestos-form fibers in parenteral drugs, is inadequate quantitatively to demonstrate reduction and is immensely difficult to perform.

The Food and Drug Administration and other government agencies are presently attempting to develop reproducible, practical and useful methodologies for these analyses, and amendments to these regulations will be promulgated upon the satisfactory completion of this research. The Commissioner has decided that until these studies are completed, the

evidence for reduction of asbestos-form fiber content need not be obtained if adequate downstream filtration is accomplished. Thus, the requirement of proof of reduction of asbestos fiber content is omitted and the use of a non-fiber-releasing filter of 0.22 micron maximum pore size is added to this regulation (0.45 micron maximum, if the manufacturing conditions so dictate).

9. One comment claimed that it is inappropriate to control all types of asbestos fibers uniformly, as asbestos filters are composed primarily of chrysotile which is less hazardous to human health than amphiboles.

The Commissioner concludes that this differential in hazard has not been established for parenterally administered asbestos. Studies by Reeves et al. (Ref. 17) have demonstrated mesotheliomas in rats and rabbits from pleural and peritoneal injections of both chrysotile and crocidolite fibers. Further studies have been initiated by the Food a Drug Administration on the effects of parenteral injections of chryso fibers in experimental animals.

10. One comment indicated that, in the study of parenteral a tration of asbestos to animals by Schmahl (Ref. 11), the tumors t occurred were not related to asbestos since they were sarcomas r than mesotheliomas.

Although mesotheliomas are closely related to inhalation there also has been an association of carcinoma of the lung inhalation. As with other carcinogens, several types of t

occur as a result of exposure to a particular carcinogen depending upon the route of exposure. The Commissioner therefore concludes that the data in this reference are valid and may possibly implicate asbestos in the development of these malignant tumors of soft tissues, namely, sarcomas.

11. One commenter presented data demonstrating that membrane filtration was capable of removal of all asbestos particles from his asbestos-filtered product (beer) as measured by electron microscopy. However, even though the container for this product was subjected to a final rinse by municipal water, the packaged product contained a significant number of asbestos fibers. Similarly, the Food and Drug Administration has found asbestos particles in parenteral drugs produced by manufacturers who do not use asbestos filters in their processes.

These indications of substantial contamination of the product from typical liquid containers have led the Commissioner to conclude that cleansing and rinse water for the containers for parenteral drugs shall be filtered through non-fiber-releasing filters equivalent to those required for post-asbestos-filter filtration to remove inherent fiber contamination.

12. The Environmental Impact Analysis Report (EIAR) and other relevant materials have been reviewed and it has been determined that the proposed use will not have a significant environmental impact. Copies of the EIAR are available in the office of the Assistant Commissioner for Public Affairs, Rm. 15B-42, or the office of the Hearing Clerk, Rm. 4-65, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852.

The indications to references set forth in the preamble are to the following, which are on display in the office of the Hearing Clerk:

1. "Parenteral Preparations, Pyrogens," in Remington's Pharmaceutical Sciences, 14th ed., Chapter 82, p. 1542, 1970.

2. Mason, T. J., F. W. McKay and R. W. Miller, "Asbestos-Like Fibers in Duluth Water Supply: Relation to Cancer Mortality," Journal of the American Medical Association, 228:1020, May 20, 1974.

3. Comment from Asbestos Research Council, March 1, 1974.

4. Cunningham, H. M. and R. Pontefract:

   (a) "Asbestos Fibers in Beverages and Drinking Water," Nature 232:332-333, 1971.

   (b) "Symposium on Industrial Chemicals as Food Contaminants," Journal of the Association of Official Analytical Chemists, 56:976-981, 1973.

5. Pontefract, R. and H. M. Cunningham, "Penetration of Asbestos through the Digestive Tract of Rats," Nature, 243:352-353, 1973.

6. Davis, J. M. G., Institute of Occupational Medicine, Edinburgh, Scotland, unpublished report.

7. Bonser, G. M., and D. B. Clayton, "Feeding of Blue Asbestos to Rats," 1967 Annual Report, British Empire Cancer Campaign for Research, p. 242.

8. "Report of the Advisory Committee on Asbestos Cancers to the Director of the International Agency for Research on Cancer," British Journal of Industrial Medicine, 30:180-186, 1973.

9. Kleinfeld, M., J. Messite, and M. H. Zaki, "Mortality Experiences Among Talc Workers: A Follow-up Study," Journal of Occupational Medicine, 16:345-349, 1974.

10. Nicholson, W. H., C. J. Maggiare and I. J. Selikoff, "Asbestos Contamination of Parenteral Drugs," Science, 177:171-173, 1972.

11. Schmahl, D., "Carcerogene Wirking von Asbest bei Implantation von Ratten," Zeitschrift fur Krebsforschung, 62:561-567, 1958.

12. Roe, F. H. C., R. L. Carter, M. A. Walters and J. S. Harrington, "The Pathological Effects of Subcutaneous Injections of Asbestos Fibers in Mice: Migration of Fibers to Submesothelial Tissues and Induction of Mesotheliomas," International Journal of Cancer, 2:628-638, 1967.

13. Kanazawa, K., M. S. C. Birbeck, R. L. Carter and F. J. C. Roe, "Migration of Asbestos Fibers from Subcutaneous Injection Sites in Mice," British Journal of Cancer, 24:96-106, 1970.

14. "Symposium on Occupational Exposure to Fibrous Glass," sponsored by National Institute for Occupational Safety and Health, University of Maryland, June 26-27, 1974.

15. Stanton, Mearl F., "Fiber Carcinogenesis: Is Asbestos the Only Hazard?" Journal of the National Cancer Institute, 52:633 (1974).

16. "Occupational Exposure to Asbestos," Criteria document, U.S. Public Health Service, National Institute for Occupational Safety and Health, Chapter VIII, pg. 6, 1972.

17. Reeves, A. J., H. E. Puro, R. G. Smith and A. J. Vorwald, "Experimental Asbestos Carcinogenesis," Environmental Research, 4:496-511, 1971.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 501, 502, 701, 52 Stat. 1049-1051, 1055-1056, as amended; 21 U.S.C. 351, 352, 371) and under the authority delegated to the Commissioner (21 CFR 2.120), Part 133 is amended as follows:

1. By amending § 133.8 by adding new paragraph (j), to read as follows:

§ 133.8 Production and control procedures.

* * * * *

(j) Use of asbestos-containing or other fiber-releasing filters: (1) Filters used in the manufacture, processing or packaging of components of drug products for parenteral injection in humans shall not release fibers into such products. No asbestos-containing or other fiber-releasing filter may be used in the manufacture, processing or packaging of such products unless it is not possible to manufacture that drug product or component without the use of such a filter. Filtration, as needed, shall be through a non-fiber-releasing filter. For the purposes of this regulation a non-fiber-releasing filter is defined as a nonasbestos, nonglass fiber filter which, after any appropriate pretreatment such as washing or flushing, will not continue to release fibers into the drug product or component which is being filtered. A fiber is defined as any particle with length at least three times greater than its width.

(2) If use of a fiber-releasing filter is required, an additional non-fiber-releasing filter of maximum pore size of 0.22 microns (0.45

microns if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of any asbestos-form particles in the drug product or component. 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 the appropriate bureau of the Food and Drug Administration that use of a non-fiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the drug.

(3) Substitution for a fiber-releasing filter shall be achieved on or before (insert date 18 months after date of publication in the FEDERAL REGISTER). If such substitution is not achieved on or before (insert date 12 months after date of publication in the FEDERAL REGISTER), the manufacturer of the drug product for parenteral injection who requires the additional 6 months to develop new manufacturing procedures so as to utilize non-fiber-releasing filters in place of fiber-releasing filters shall submit monthly reports to the appropriate bureau of the Food and Drug Administration indicating progress in substituting the new filters. Such a substitution shall be shown to have been effected without loss of the safety or effectiveness of the drug.

2. By revising § 133.9 to read as follows:

§ 133.9 Product containers and their components.

Suitable specifications, test methods, cleaning procedures, and when indicated, sterilization procedures shall be used to assure that containers, closures, and other component parts of drug packages are

suitable for their intended use. Containers for parenteral drugs, drug products or drug components shall be cleansed with water which has been filtered through a non-fiber-releasing filter equivalent to that indicated in § 133.8(j)(2). Product containers and their components shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug or its components beyond the official or established requirements and shall provide adequate protection against external factors that can cause deterioration or contamination of the drug.

Effective date. This order shall be effective (insert date 30 days after date of publication in the FEDERAL REGISTER).

(Secs. 501, 502, 701, 52 Stat. 1049-1051, 1055-1056, as amended; 21 U.S.C. 351, 352, 371.)

Dated: February 28, 1975.
FEB 28 1975

A. M. Schmidt

A. M. Schmidt
Commissioner of Food and Drugs

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL