Determination of Inapplicability

for

A Regulation Entitled

"Asbestos-Form Particles in Drugs for Parenteral Injection"

The environmental assessment of this action has been accomplished on the basis of a complete Environmental Impact Analysis Report. None of the Department of Health, Education, and Welfare initial criteria were met.

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Enclosures:
Environmental Impact Analysis Report
Environmental Assessment Report

75P.0261

EIR 1

ENVIRONMENTAL ASSESSMENT REPORT

A. Summary of the Action

The Food and Drug Administration (FDA), based upon accumulating evidence that parenteral injection of asbestos fibers may be harmful to human health, promulgated proposed regulations on the utilization of asbestos filters on September 23, 1973. These regulations have been modified, are now in final form, and attempt to minimize asbestos contamination in parenteral drugs by: (1) eliminating the use of asbestos filters in the manufacturing process where possible or (2) requiring an appropriate non-asbestos filter downstream of the asbestos filter to maintain a safe and efficacious product. Only with special permission from the appropriate Bureau within the FDA will the utilization of an asbestos filter without such subsequent filtration be permitted.

B. Evaluation

The attached Environmental Impact Analysis Report is complete in that it lists all of the effects likely to occur, and is accurate in that it describes the expected results within the limits of existing knowledge with respect to environmental relationships. The action and secondary effects of the action have been evaluated against the Department of Health, Education, and Welfare initial criteria, and no effects approach these levels of significance. The benefits to human health likely to be derived from this action, therefore, greatly outweigh the slight effects on the environment (the consequences of process changes). All reasonable alternatives to this action do not accomplish the health objectives of the chosen alternatives, nor do they result in less environmental impact.

C. Application of Initial Criteria

1. Natural Resource Use. The regulation does not meet this criterion in that it could not cause a 1% increase in mineral or fuel consumption nationally, due to the small scale of the industry being regulated. Conversely, a slight decrease in total asbestos mined will result from this regulation.

2. Pollution. This regulation does not meet this criterion in that no identifiable increase in ambient air or water pollution will occur from the action or its secondary effects due to the small scale of the section of the industries to be affected by the regulation; nor will any emission standards be violated by any resulting shifts in the filter production industries. Similarly due to the small nature of this action, no identifiable increase in waste or storage will result from the promulgation and implementation of this regulation.

3. Populations. Although this regulation is designed to diminish the possible adverse health effects of asbestos injection, a change in the overall age characteristic of the human population to the extent that requirements for health, education, transportation or welfare services would be altered probably will not occur. Although the number of people receiving parenteral medications in the USA at least once in their lifetime is indubitably quite significant, there is no way to quantify a cause-effect health relationship with the possible presence of asbestos in these medications. Even qualification of effects is subjective, at best. It is hoped that this action will result in a health benefit to a portion of the population receiving injections on a routine basis, but not even the most ardent supporters of limiting regulations would claim that asbestos fibers in parenteral drugs has a definite

demographic significance and that the removal of asbestos fibers from these products would cause human population parameters to noticably change.

4. Services. The regulation is written in a manner to avoid the possibility of removing an important parenteral product from health services. Therefore, no change in capacity for health services will result.

5. Human Values. No effect on any historical structures or endangered species will result from this regulation, nor will any federal, state or local standards be violated by the regulation's implementation.

D. Recommendation

Whereas this action and the effects of the action do not meet any initial criteria, it is recommended that a Determination of Inapplicability be applied to the promulgation of the regulation entitled, "Asbestos-Form Particles in Drugs for Parenteral Injection."

1. Proposed Action

a. Purpose of the Action

The proposed action is the promulgation of regulations limiting the use of asbestos and microfibrous glass filters from the parenteral injectable drug and drug ingredient manufacturing processes by means of Food and Drug Administration Good Manufacturing Practices (GMPs) for these industries. The purpose of this action is to minimize the presence of asbestos and glass fibers as contaminants in injected drugs. The deleterious health consequences of injection of large quantities of these types of fibers has been demonstrated in laboratory animals, and thus prudence dictates that human exposure of this nature be minimized. The regulation accompanying this EIAR states that no asbestos containing or micro-fiberglass containing filter can be used in the preparation of parenteral drugs or drug ingredients in human use and allows for a 12 to 18 month period of process adaptation to permit the manufacturer to determine the best substitute for asbestos filtration without sacrifice in product safety or quality. Should no suitable substitute be found, a non-asbestos, non-fibrous glass filter of sufficient pore size will be required downstream of the fibrous filter to remove the fibers of sizes suspected to be the most hazardous. Only upon review and acceptance of submitted evidence that neither of the above procedures results in a safe and effective parenteral drug or drug ingredient will the FDA allow the continuation of present practices utilizing these types of fibrous filters.

b. Environments Affected

The primary environment to be affected by this action will be the environment of humans receiving parenteral drugs. Secondary affects of this action will be alterations in the demands for asbestos and non-asbestos filters and the raw materials for the production of these products.

2. Probable Impact of the Action on the Environment

a. Human Exposure

The environment of an organism can be defined as all external substances and forces which impinge upon that organism and thereby affect his existence. Therefore, the environment of patients receiving parenteral drugs includes the materials in those particular drugs, including the active ingredient, the solvent, salts, buffering agents, stabilizers, and impurities. This regulation is designed to eliminate or minimize the fibrous impurities in these drugs, as there are inferences from inhalation exposure to asbestos and from experiments in laboratory animals which imply that the parenteral administration of asbestos in humans can cause fibrosis and tumors. A "state of the art" review of the hazards of exposure to asbestos fibers was written for the preamble of the proposed regulations and is attached to this EIAR as Appendix I (General Background).

The impact of this action would be to minimize the human exposure to injected asbestos fibers which may have a deleterious effect on both the directly exposed tissues and respiratory tissues subsequent to circulation. There is no acceptable method of extrapolating the present data on experimental animals to man in a quantitative manner, but this regulatory action is the

result of a prudent analysis of the risks, benefits and analytical techniques associated with the inhalation, ingestion and parenteral administration of asbestos fibers. The major environmental effect will be a reduction in exposure of humans to fibrogenic and tumorogenic materials, and will contribute to an unquantifiable reduction in incidence of these pathological occurrences.

b. Effects on Raw Materials Utilization

The National Association of Filter Material Manufacturers has informed us that at least ten grades of filter sheets or pads are provided by the asbestos filter industry and that these filters vary in asbestos content from 5-40%. The other basic ingredient is cellulose wood pulp. Approximately 40 million pieces of asbestos filter material are produced annually of which 6 million pieces go to parenteral or injectable drug producers. These items are typically smaller than those provided to other users, such as commercial beverage producers, and therefore, an estimate of 40 tons of asbestos and 80 tons of cellulose wood pulp (of the total 400 tons asbestos and 1,600 tons of cellulose wood pulp used by the asbestos filter manufacturers) are required to produce the filters which are subject to this regulation.

The 1973 Bureau of Mines Minerals Yearbook lists apparent United States annual consumption of asbestos at 876,147 tons. The EPA, in correspondence accompanying their proposed standards for effluent guidelines for the pulp, paper and paperboard industries, has estimated that about 50 million tons of pulp were produced in the United States in 1973. Therefore, the asbestos demand for parenteral filter production is 0.0045% of the U. S. asbestos production. The amount of cellulose wood pulp required for this

production of the regulated filters is likewise insignificant (0.00016% of U. S. production).

Cellulose acetate or nitrate "membrane" filters are the most likely substitutes for asbestos filters. Roughly 90 percent of the U. S. production of these products is done by Millipore, Inc. and by the Gelman Company. These firms have provided information on their raw materials utilization and estimated market sizes which demonstrates the insignificance of increases in demand for natural resources, even assuming complete substitution of asbestos filters by membranes. The estimates are as follows:

At most, the regulations will increase the consumption of cellulosic materials by less than 130,000 lbs/year. These materials are derived from wood pulp (50 million tons produced in the U. S. in 1973) and are processed with a number of organic solvents (petroleum derivatives, alcohols, ketones). The precise identities of these solvents are confidential to these firms, but it can be estimated that if the regulation resulted in the replacement of all six million asbestos filters used annually, a maximum of one million pounds of solvents would be required to produce the membrane substitutes.

The 1973 U. S. production figures on common solvents have been provided by the U. S. Tariff Commission as follows:

	Million lbs. produced		Million lbs. produced
Methanol	7,064	Benzene	28,000
Isopropanol	1,635	Cyclohexane	2,122
Acetone	1,995		

Therefore, increased demand for solvents resulting from this regulation will amount to fractions of percents, even in the unlikely case of 100% conversion to cellulose acetate filters by the parenteral product industry. The actual conversion figures will depend on the success of process modifications.

3. Probable Adverse Effects Which Cannot be Avoided

The adverse effects of this action which cannot be avoided are minimal. The production of non-asbestos filters will of necessity increase. This will result in a shift in raw materials utilization from asbestos to cellulose and petrochemical-based solvents. The magnitude of these effects was discussed in the previous section.

4. Alternatives to the Proposed Action

a. Different Regulations

(1) A ban on the use of asbestos filters in the process of parenteral drug and drug ingredients without the phase-in period and without the allowances for the use of asbestos filters with subsequent downstream filtration, should the scientific filters sacrifice product quality, would result in the loss of a number of medically important parenterally administrative materials. Asbestos filters are unique in their filtration properties in that the fibrous mesh can remove large proteins and other pyrogens without the rapid decline in filtering capacity associated with conventional surface filters. This "depth filtration" has been responsible for the successful purification of many blood fractionation products. It is not the intent of this regulation to remove all asbestos fibers from parenteral drugs, no matter what the cost. The loss of a lifesaving parenterals due to difficulties in adapting non-asbestos filters to the production scheme should be avoided.

(2) A regulation based on asbestos particle count rather than process requirements is not a viable option at this time due to the uncertainties

in predicting dose-response with carcinogenic materials and due to difficulties in quantification methodologies presently associated with asbestos fiber counting. Electron microscopy for both qualitative and quantitative fiber determination is a time-consuming, expensive technique requiring well-trained technicians for both measurement and interpretation. Even then, results are often capricious. Thus, the lack of standard methodologies for analyses precludes the promulgation of regulations based on fiber count in the product.

b. No Action

The "no action" alternative would allow the present use of asbestos filters in the manufacture of parenteral drug and drug ingredients to continue unrestricted. Although it has been argued that asbestos fibers are ubiquitous in the environment and that man has always been exposed to a background of asbestos in his air and water, we see a significant difference between this natural background and the presence of asbestos contamination in materials administered by subcutaneous, intravenous or intramuscular injection. These administration routes circumvent the natural barriers to internal contamination and have proven pathogenic and laboratory animal studies. Therefore, this alternative was rejected for an alternative which attempts to minimize the public's exposure to parenterally administered asbestos.

5. This action will not affect local, short-term use of the environment nor long-term productivity as the magnitude of resourse use is negligible in comparison with other industrial activities.

6. Irreversible, irretrievable commitment of natural resources resulting from this action will be negligible due to the minor nature of the industries affected, as discussed in section 2(b).

7. All known objections to this regulation, as proposed, are discussed in the final regulation itself. The reader is referred to this document.

8. The Cost-Benefit Considerations of these Actions are Listed Below

a. Costs

The costs to the drug manufacturing industry of this regulation will not be prohibitive. No comments on the proposed regulation from the drug industry, directly or through trade associations, claimed that the cost of process modification for parenteral drug production would cause hardships. However, several vociferous communications from asbestos filter manufacturers indicate a fear of a significant loss in business.

b. Benefits

The benefit from this action is solely in the human health area. The minimization of public exposure to parenterally administered asbestos fibers is expected to have a positive long-term effect on public health, as discussed in previous sections of this EIAR.

APPENDIX I

GENERAL BACKGROUND

"Asbestos" is a generic term for a number of hydrated silicates that, when crushed or processed, separate into flexible fibers made up of fibrils. Although there are many asbestos minerals, only six are of commercial importance. Chrysotile, a tubular serpentine mineral, accounts for 95 percent of the world's production. The others, all amphiboles (crystals with three groups of metal ions), are amosite, crocidolite, anthophyllite, tremolite and actinolite. These asbestos minerals differ in their metallic elemental content, range of fiber diameters, flexibility, harshness, tensile strength, surface properties, and other attributes that determine their industrial uses and which may affect their respirability, deposition, retention, translocation and biologic reactivity (Ref. 1).

Many products such as cement, flooring, shingles, pipes, filters, textiles, etc. contain asbestos of one kind or another. There are great variations among such products with respect to the chances of fiber release during the use of the product. The likelihood of such fiber release depends predominantly on the ease with which the fibers can be dislodged and on the degree to which the use of the product destroys the fibers. Almost all asbestos fiber used in the United States for manufacturing products becomes tightly bound within the products and usually undergoes little actual abrasion or wear before being discarded. Asbestos cement products (accounting for most of the asbestos used in the United States), shingles and floor tiles are in this category. Some asbestos-containing products, such as brake linings, are subjected to great friction; their rate or wear is considerable, and at times they are almost completely worn away. In the case of brake linings, the application

of force is so intense and the heat created so great that most chrysotile fibers are destroyed by being converted into another substance which is non-fibrous. Nevertheless, an appreciable percentage (1 to 3 percent) remains as fibrous asbestos, and fiber release from products such as asbestos cloth, paper and sprayed fireproofing materials is a serious source of emission. This usually occurs in densely populated areas. Most of the pipes delivering drinking water are of a mixture of cement and asbestos.

Solid wastes produced during manufacture of asbestos-containing products, use of such products, and demolition can be emission sources. These waste materials are usually disposed of without regard to their potential as emission sources. Alternate methods of disposal often result in commingling of asbestos-containing wastes with municipal wastes in open dumps and thus create a long-term emission source.

Asbestos fibers thus are ubiquitous in air, water and a large percentage of the earth's crust. The amount of this material which additionally is added to the environment and to food and drugs by the use of asbestos filters is not known. Therefore, it is obvious that the presence of asbestos in these products is only one small source of exposure.

Asbestos inhalation has been known to be an occupational hazard in workers in asbestos mines. The asbestos is inhaled and lodges in the lungs causing the development of a fibrotic disease known as "asbestosis." Asbestosis, or abestotic pneumonoconiosis, was the first clearly demonstrated adverse effect of asbestos in man. It is characterized by a pattern or roentgenographic changes in the lung consistent with diffuse interstitial fibrosis of variable degree and at times with fibrosis and calcification of the pleura; clinical

changes that include fine rales, finger clubbing and shortness of breath, each of which may be absent in an individual case; and physiologic changes consistent with a restrictive lung disorder (Refs. 2 through 8).

In these workers in asbestos mines, malignancies of the lung and of the body lining tissues, namely lung cancer and mesothelioma, occur at rates greater than in persons not so occupationally exposed. There is a 5 to 7 fold increase in lung cancer in asbestos workers which is noted as early as 10 to 14 years after onset of exposure and is significant at 20 years (Refs. 9 through 15). Seven percent of deaths in asbestos workers are caused by pleural and peritoneal mesothelioma (Refs. 16 through 33). This is a marked increase since this tumor is extremely rare in the general population. There is suggestive evidence concerning an increase in the rate of gastrointestinal malignancies in asbestos workers (Ref. 34).

There is considerable evidence that most human lungs harbor thousands or millions of asbestos fibers although most people do not have asbestosis (Refs. 35 through 37). This is due to the ubiquity of the substance. Some of these fibers are chrysotile asbestos, and amphiboles are probably present also. This number of fibers is relatively small in most persons not occupationally exposed to asbestos compared with the numbers found in the occupationally exposed. The systematic application of quantitative techniques, measuring both coated and uncoated fibers, is needed to define a gradient of accumulated fibers for correction with incidence of disease, on the one hand, and history of environmental exposure, on the other.

The methodology for quantification of asbestos fibers of varying sizes is such that the results obtained in one laboratory may vary substantially

from those in another. An inter-agency governmental task force together with other scientists working in this field is currently attempting to develop standard technology which can be applied to the identification and qualification of asbestos fibers. The Environmental Protection Agency is currently investigating four separate techniques in order to establish the best method for identification, quantification, sizing and typing of asbestos particles and fibers. At present, the National Institute for Occupational Safety and Health (NIOSH) recommends, as a technique for sampling of air, a method based on counting fibers greater than 5 microns in length using phase contract illumination at 430x magnification with a 4 millimeter objective (Refs. 38 and 39). This technique is currently recommended for liquid materials until more accurate and sensitive practical methods are developed. Similarly, difficulties exist with other methods proposed for analysis of asbestos fibers in a material such as talc.

The evidence concerning the possible hazard from ingestion of asbestos particles is contradictory and inconclusive.

In an unpublished study by L. M. Swinburn (Ref. 40), asbestos particles were fed once a week to SPF Wistar rats for 16 and 18 weeks. The material was administered in butter. Although the particles were of the size range known to produce tumors by other modes of administration, no tumorgenic effect was noted. With a single large dose, the fibers were totally cleared by the gastrointestinal tract in 48 hours and no asbestos was detected in the animal tissues at the end of 1 week. The gastrointestinal tract of the rat seemed to provide an effective barrier to penetration.

In a published study by W. E. Smith et al. (Ref. 41), hamsters maintained on a diet of 1 percent chrysotile or amosite through life had no gastrointestinal tumors.

A report by Westlake, Spjut and Smith (Ref. 42) indicates that the rat colonic mucosa is penetrated by chrysotile after feeding a diet containing 5 percent asbestos for 3 months.

Cunningham and Pontefract (Ref. 43 and 44) injected chrysotile fibers (9.4 and 94×10^9) directly into stomachs of rats. Fibers were found in blood and other organs 2-4 days after treatment. Control rats, although having no asbestos in blood, also had high levels of asbestos in tissues.

These workers found that, whereas the tap water in Ottawa (having a filter plant) contained about 2 million fibers per liter, the quality of fibers in soft drinks and alcoholic beverages purchased in the Ottawa area ranged from 1 to 12 million fibers per liter. Even with the technical problems of methodology, this seems to indicate that in some beverages the asbestos content may be about the same as in water, whereas, in others, it may be increased. Thus, it is reasonable to conclude that water and many other beverages for human consumption contain substantial amounts of asbestos fibers.

There is some evidence that asbestos filters may remove some asbestos material. In a preliminary experiment performed by the Food and Drug Administration, asbestos was added to distilled water and dispersed evenly by the action of an ultrasonic generator. Electron microscopy of this material clearly showed large numbers of asbestos fibers. This material was then filtered through an asbestos filter, and electron microscopic examination of the filtered material showed a reduction in the number of asbestos fibers.

Nicholson and his colleagues (Ref. 45) investigated a number of samples of parenteral drugs and found asbestos fibers. Based on their report a study was undertaken by the Food and Drug Administration concerning contamination of parenteral drugs with asbestos. Although the data are still preliminary, the the following observations are pertinent. Parenteral drug samples were collected from a number of firms. Based on phase contrast microscopy, 11 of 13 samples had clear-cut evidence of the presence of asbestos, one sample was questionably positive, and one was negative. The number of fibers ranged from 2 to 27 in the positive specimens of variable sample size. Using electron microscopy, 12 of the 12 samples examined were positive. Quantitation is not yet complete.

In this survey, seven of 13 manufacturers of parenteral drugs do not use asbestos filters; four firms use such filters followed by final membrane type filters (one of these uses asbestos filters for its rinse water without final filtration of such water); and two firms use asbestos filters only for their rinse water, without final filtration.

The preliminary report of these studies is on display at the Office of the Hearing Clerk. Any other scientific data in this regard should be submitted to the Hearing Clerk.

Certain parenteral drugs, such as blood fractionation products, may be filtered several times through asbestos filters. Thus far, it is not known with certainty whether the more viscous products could be successfully processed through terminal membrane filters without compromising safety, identity, strength, quality or purity. The precise effect of asbestos pad filtration on

removal of pyrogens (Ref. 46 and 47) is not completely known at the present time. Currently, the Food and Drug Administration is surveying the industry for information concerning the use of asbestos filters. Results of this survey will be incorporated in the public record.

Although the major experimental studies of asbestos have involved inhalation of fibers so as to simulate occupational exposure, several studies have been performed to investigate the effect of parenteral inoculation of asbestos fibers. In 1958, Schmahl (Ref. 48) reported that implantation of asbestos fibers and crumbs in either the subcutaneous tissue or in the peritoneum lead to the development of malignant tumors (sarcomas) in 11 of 30 rats which survived longer than 15 months after such implantation. Roe and his colleagues (Ref. 49, 50, 51) have performed a number of studies in which asbestos fibers were injected subcutaneously (Ref. 49) into the flanks of mice. In the first experiments, crocidolite, amosite and chrysotile asbestos fibers were used and each animal was injected twice subcutaneously in both flanks with 10 milligrams of fibers in saline with an interval of five weeks between the injections. Seven of seventy-one mice which survived 40 weeks or more developed injection site tumors. In addition, one mouse developed a mesothelioma of the peritoneum underlying the injection site. The injection site sarcomas were produced by all three types of fibers. In addition, Roe et al. (Ref. 49) showed that the asbestos fibers were widely disseminated from the local injection sites being deposited rather selectively on the serosal surfaces of the abdominal organs and the retroperitoneal structures as well as on the pericardium, diaphragm, pleura and adjacent parts of the lungs and heart. These serosal surfaces reacted

vigorously to the presence of the asbestos fibers and in 10 of 71 mice, malignant mesotheliomas of the thorax and/or abdomen developed. In a later study (Ref. 51) Kanazawa et al. showed that, after subcutaneous injection of asbestos fibers in mice, fibers could be found to have disseminated to regional and distant lymph nodes, spleen, kidneys and occasionally to brain tissue suggesting that some asbestos may enter the circulation.

Thus, there is experimental evidence that parenteral administration of asbestos fibers may lead to wide dissemination of such fibers in animals and to the development of local malignant tumors as well as malignant mesotheliomas of the pleura and peritoneum similar to those that occur after inhalation of asbestos fibers.

The problem of asbestos in the total environment, to which the worldwide scientific community is addressing itself, is very complex. The Environmental Protection Agency has published in the Federal Register of April 6, 1973 (38 FR 8820) national emission standards for asbestos milling and manufacturing based on the determination that asbestos is a hazardous air pollutant. This standard has been developed despite the fact the EPA also recognizes that a "standardized reference method has not been developed to quantitatively determine the content of asbestos in a material."

The present status of this problem is summarized by the report of a committee prepared subsequent to a meeting sponsored by the International Agency for Research on Cancer (Ref. 52). The Food and Drug Administration's review of this report indicates the following areas of further research are necessary:

(1) Further epidemiology, particularly with respect to past exposure to asbestos and cancer of sites other than lung, pleura, and peritoneum.

(a) Assessment of excess cancer risks following exposure to only one type of fiber.

(b) Investigation of whether reduction of asbestos exposure in lungs below those causing asbestosis abolishes excess risk of carcinoma.

(c) Investigation of evidence of an increased risk of cancer resulting from asbestos in water, beverages, food, or liquids used for the administration of drugs.

(2) Development of methods of quantitative assessment, size analysis and characterization of particles and fibers.

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