

MEMORANDUM

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

TO : Armand R. Casola, Ph.D.
Chief Chemist
Bureau of Drugs

DATE: May 10, 1972

FROM : Pharmacologist
Bureau of Drugs

SUBJECT: Report of a Seminar Attended May 10, 1972

The Bureau of Drugs seminar for this date was entitled "Particulate Matter in Parenterals," and was given by Dr. Salvatore J. Turco of the College of Pharmacy, Temple University, Philadelphia. It should be of interest to your committee on asbestos, especially with regard to methodology on light microscopy.

Dr. Turco pointed out that parenterals should be sterile, pyrogen free and free of particulate matter. Dr. Turco began with a review of the literature on the subject, and the two papers by Garvin and Gunner of Australia in 1963 and 1964. There have been more than 100 papers related to the subject since that time, including 3 on which Dr. Turco was co-author. FDA held a Symposium on the subject July 28-29, 1966 at which time Dr. J. D. Lockhart reviewed the medical literature and Dr. A. Gross presented his studies on dogs following injection IV of ground filter paper particles.

The human studies indicated that particulate matter could be fibers or crystalline material, or even fungi. (Drug addicts who use tablets IV can have starch and talc granulomas.) The lung is the most frequent site of deposit, with fibrous pneumonitis and granulomas produced by agglutinated platelets and thrombic formation. Particles can also be found in the occipital lobe, or in the blood vessels of the eye. Particles in parenterals vary from one manufacturer to another, and from year to year, depending on quality controls.

The problem extends beyond large volume IV infusions, for IV antibiotics and ophthalmic solutions are involved. There are many particles in antibiotics, more in the dry powder than in lyophilized preparations according to Beckerman of UCLA. Norman Jaffe reported eye granulomas from particles in ophthalmic solutions, especially those used in eye surgery.

Techniques of detection may be destructive or non-destructive. The non-destructive are visual inspection, the most sophisticated being with a Tindall beam and photomultiplier tubes. The "sensitivity" of visual methods is particles of $>25-50 \mu$ for the unaided eye, or $>5-600 \mu$ for the Tindall beam. The Emhart Autoscan is used by the Parenteral Drug Association.

Destructive methods are the Coulter counter and the millipore filter with light microscope counting. The objection to the Coulter counter is that it does not distinguish between shapes, or sizes. A "count" relates to "mass", a long thin fiber being given the same value as a small sphere. Also a clump of particles will be counted as one. Ideally a method should indicate the number, size and shape of particles as well as the identity (cellulose, cotton, asbestos, etc). The millipore filter collection plus light microscope will give fairly accurate ($\pm 10\%$) counts on particles $> 5 \mu$, and with the electron microscope the method may be extended to particles below 5μ .

Dr. Turco's studies reported here represent 6 months work and 500 samples. The results are published in Am. J. Hosp. Pharm. 28: 620-623, (Aug. 1971). A similar study, done in 1969 on products of 4 firms identified only by A.B.C.D. code, was compared. The techniques used were the same. Two firms, Abbott and Baxter, supported financially the 1970 study. In the 1970 study there were also reported results of a "final filter" in the administration sets, for Baxter and for Abbott. The technique involves use of a laminar flow hood, careful cleaning of the containers and components of the millipore collection device with particle-free Freon TF solvent and the running of "blanks" after every 6 samples to control techniques. The millipore filter is removed after vacuum filtration of liter flasks of IV fluids, stored in ultraclean Petri plates, and examined with the light microscope at 40 and 100X magnification. Counts are made for particles, by size, and the fibers are given special attention because of the potential for thrombus formation. A fiber is defined as being at least 10 X as long as it is thick. An automated method of counting, using a "TTC" system with TV monitor and computer module was used sometimes (it was borrowed). Results were much the same as published. The firms were rated: Abbott $>$ Baxter $>$ Cutter $>$ McGaw for relative freedom from particulates. Each firm had improved over 1969. The addition of administration sets, or additives such as KCl, or vitamins, added materially to the particle count. The use of a final filter, downstream, was very effective in reducing the particle count, and most of the particles were very small (pg. 622 of the Aug. 71 publication).

Temple U. Pharmacy distilled water gave 361 particles/liter, and a community pharmacy distilled water gave 933. Tap water gave almost 28,000/liter.

A few analyses of fibers were done by Walter C. Mc Cone Associates of Chicago. Rubber particles predominated, followed by red iron oxide and limestone, glass, paper fibers, etc. Dr. Turco stated he thought some asbestos fibers were present but he could not specify which kind.

The Abbott final filter is an acetate, with 1 μ pore size, while the Baxter final filter is millipore, 0.45 μ pore size. Electron micrographs of the pores show they are tortuous, not straight pores.

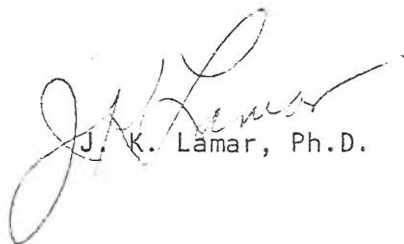
Sources of particles could be the ingredients, the package and components, or the administration sets, or additives. There may be reaction products, also, because particles are more numerous with long shelf-life. Manipulations at the bedside add more particles.

No systematic studies for adverse effects have been done in the USA, but a program of autopsies is being started at Temple, on persons having infusions who later die.

Dr. Turco advocates use of final filter sets, especially when additives are used, or there are multiple infusions. He also advocates setting of standards (by USP and FDA) for tolerances of particles in parenterals. Dr. Turco stated his studies had deficiencies, in that the sampling was not of all production nationwide, in 1969 and 1970. A third study is being conducted with broader sampling. His technique might be improved, in that replicate counts by the same person show with $\sim 10\%$ variation, and the studies were not "blinded," but I think these are trivial criticisms. He plans to study peritoneal dialysis fluids soon.

Dr. Turco then introduced his graduate student, Mr. Steve Lamancha, who has studied ophthalmic solutions, both OTC and Rx, and both topical and for eye surgery. He used the same technique, with control blanks usually zero. There was tremendous variation among the various products, with some showing as few as 10-12, others showing 535 particles/ml. In some cases the small particles were too numerous to count. He suggested use of Swinnex millipore filtration (2.2 μ) of all solutions for use in eye surgery.

Both speakers stated that plastic containers had generally less particles than those made of glass.


J. K. Lamar, Ph.D.