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DESIGN CONSIDERATIONS FOR PARENTERAL LIQUID SYSTEMS

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ABSTRACT

Considerable attention has been given to the external environment in designing facilities for the production of high quality pharmaceuticals and hospital products. The internal environment is even more important. The production of parenteral solutions of high quality depends on the ability to maintain extremely low levels of particulates, both viable and non-viable. This talk will discuss the effect of equipment such as piping, valves, mixers, pumps and controls on such ability, with information about the state of the art.

Note This paper is based on a presentation made in September, 1975, at the A.I.Ch.E. meeting, Boston.

INTRODUCTION

Recently, chemical engineers have given considerable attention to the construction of facilities for the housing of parenteral solution production equipment, the latest ones dealing with the use of the unidirectional air flow systems originally developed by the atomic energy and aerospace people, sometimes called "laminar flow air". The proper use of this technology includes detailed specifications for the construction of walls, ceilings and floors along with a host of other requirements to provide a clean air environment for the product. Not much has been said lately about the internal environment of piping, tanks, transfer equipment such as pumps and fillers, and of the processing equipment used in making parenteral solutions. After all, this is where the action is, and this is what this paper is about. And, we are only really going to talk about applying existing techniques, engineering methods already in use, and readily available equipment.

A "Parenteral" solution can be defined as a solution that is to be injected intravenously or intramuscularly to a patient. Large (50 ml. to 1 L.) volume parenterals are normally only injected intravenously. They are composed mainly of distilled water of high purity together with dextrose (5% or more) or

sodium chloride, or with other ingredients or drugs, and are used to restore electrolytic balance to the blood, to administer nutrition, or drugs and so on.

Small volume parenterals may be injected intravenously, subcutaneously or intramuscularly. We also make irrigating solutions used in urological procedures and for a number of other purposes, and which also have a high proportion of distilled water. The same design considerations apply to them.

GOALS

In order to protect the product quality of our solutions, our goals are to maintain an extremely low level of particulates, both viable and non-viable, and to exclude pyrogens or fever producing substances which are produced by certain organisms. Attainment of these goals depends on our ability to do the following:

First, to produce water for injection which meets U. S. Pharmacopoeia standards for chemical and microbiological purity;

Second, to clean, sanitize and maintain clean all of the parts of the piping, valves, pumps, tanks, and all the other equipment that the water or solution may come into contact with, in addition to the job of cleaning and sanitizing the product containers and closures;

Third, to effectively filter and reduce particulates in the solution before filling into containers; and

Fourth, to terminally sterilize the solution in the container. We do this to all large volume parenterals and to most small volume units as well.

Some small volume parenterals are filled aseptically, requiring a very high degree of cleanliness and sterility in all aspects of the equipment and functions. This involves smaller equipment and complete take apart or demounting ability, with each and every item clean and re-sterilized prior to use. In this paper we will address ourselves only to high volume parenterals, where the use of some techniques borrowed from other industries and some of our own have enabled parenteral solutions producers to utilize larger scale equipment, clean-in-place techniques, high speed equipment to turn out products of consistently high quality.

EXISTING GUIDELINES

First, let me list some of the guidelines we already have for design. They include the Good Manufacturing Practice Regulations as issued by the FDA and as amended since then, and the following:

The 3-A Sanitary Standards as published by the International Association of Milk, Food, and Environmental Sanitarians, Inc.

The Baking Industry Sanitation Standards of the Baking Industry Sanitation and Standards Committee.

The National Plumbing Code as published by ASME (L-10).

The National Fire Code by the National Fire Protection Association.

The ASME Boiler and Pressure Vessel Code.

The OSHA Standards of the Department of Labor.

The U. S. Pharmacopoeia.

ANSI-ASME Standard, F2.1-1975 Food, Drug and Beverage Equipment.

The baking industry and the dairy industry codes do a good job of defining and specifying what must be done to promote cleanliness.

But the manufacture of solutions involves some extra needs that require special design criteria. We will try to point these out as we get to them.

By the way, we have assumed that all readers are aware of the need for making certain that absolutely no asbestos is used as a gasket, packing, or seating material in connection with any pharmaceutical solution manufacture.

PROCESS

Fig. 1 shows a flow chart for large volume parenteral solution production, starting with incoming drug handling, on

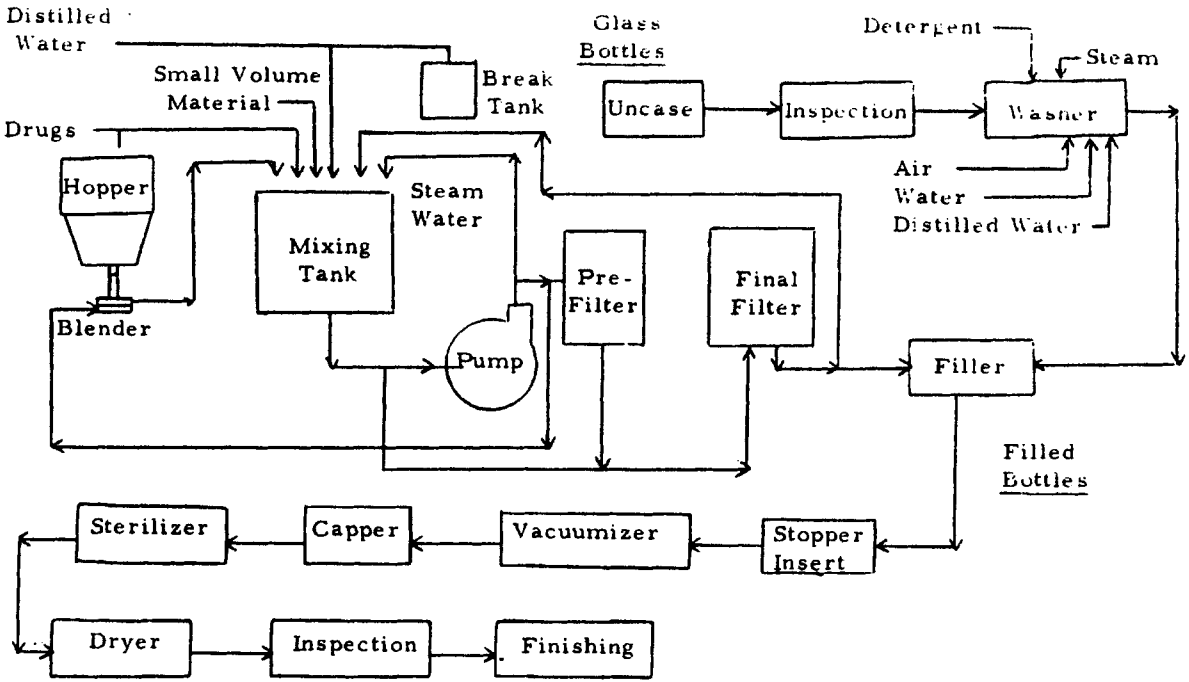

FIG. 1

PARENTERAL SOLUTION FLOW CHART

to solution preparation in mixing tanks and thence through prefilters and final filters to a filling machine where bottles or containers are filled with the solution. The bottles are closed or capped and placed in racks for sterilization in batch or continuous autoclaves. After terminal sterilization and cooling the bottles are dried, labeled and have a bail or metal handle attached before case packing. This sounds like a fairly simple straightforward production system, but it is under a lot of quality assurance constraints because the product is administered intravenously as compared to the oral consumption of a food or dairy product.

First, there is the need to prevent contamination to a greater degree than required in food or dairy products. It will be noted that the particles we are removing are in the submicron range for some particulates or organisms, and from 0.2 micrometers and above for many viable particulates, and colloidal substances, and from one to ten micrometers for some cellulosic and glass fibers. This is a whole order of magnitude less than the non-viable particulates the food industry is concerned with. Moreover, we try to prevent introduction of organisms to exclude pyrogens rather than rely only on sterilization to kill them. This requires proper cleaning, sanitation and maintenance of the system. It also requires greater effort

toward the elimination of human errors in handling ingredients or solutions.

DISTILLED WATER

The quality of the distilled water supplied will control the quality of the solution produced, and to a large extent the quality of the distilled water is controlled by the equipment and process used. Fig. 2 shows a simplified flow sheet for dis-

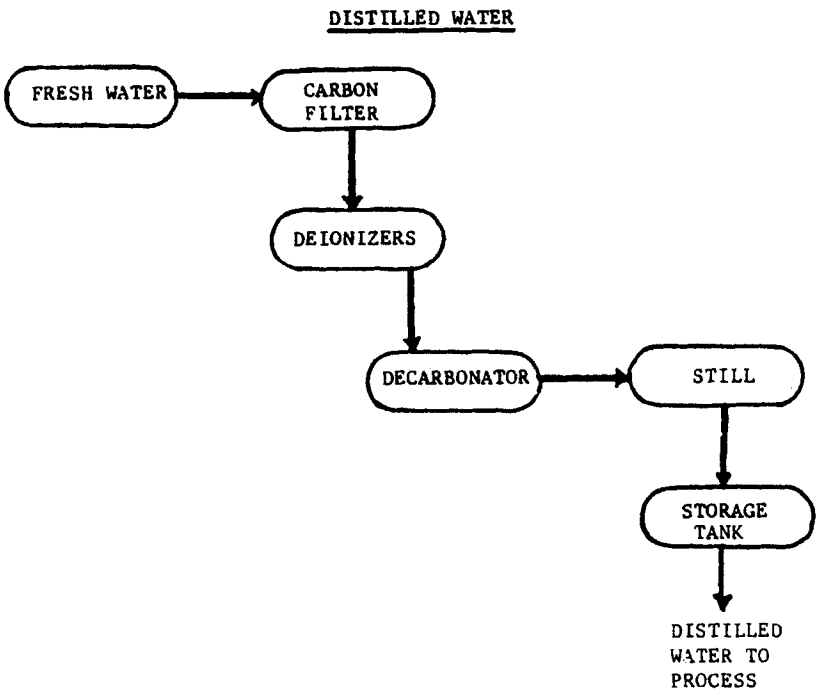

FIG. 2

DISTILLED WATER FLOW SHEET

tilled water using a vapor compression still which is the method of choice at Abbott Laboratories. The total installation needs to be designed carefully. The only acceptable materials for construction are type 304 or 316 stainless steel, Teflon(R), and Pyrex, although bronze has been okayed for moving parts on compressors because of the galling of stainless steel. Here the sanitary design criteria are a must for all elements in the system from the still to the use point. Sanitary type pumps with rotary seals and drains must be used and all piping must be welded, steamable and pitched 1/8" per foot for proper drainage. We use Schedule 5 pipe which has a pickle treatment. The absolute minimum of CIP (clean-in-place) type flanges must be used. No screwed fittings or ASME flanges are allowed and special heliarc welding techniques must be used. We use Saunders patent diaphragm valves only, which must be installed at a proper angle for complete draining and the piping system must be designed to eliminate pockets and dead ends where the water may be used only once in 24 hours. Wherever possible we loop the system to eliminate long branch lines with intermittent flow. All lines must be pitched for dainage to low points and a drain valve installed along with suitable stainless steel steam traps for sterilization by steaming. Our present steam filters are porous stainless steel with a three to seven micro-

meter rating. The filter must be placed next to the distilled water equipment to be steamed, not before some steam hose connection to it. Also, the distilled water system must be acid treated after initial installation or after repair or revision to remove iron and iron oxides before use.

Distilled water may be added directly to a mixing tank, through a weigh tank, or through a fixed or controlled volume tank as shown on this slide. If a weigh tank or a controlled volume tank is used, it must be of sanitary design, free draining, of 304 stainless steel welded construction and be connected through demountable piping to the mixing tank. It must also have a bacterial filter on the breather pipe. An air-gap must be provided to prevent back siphonage from the tank to the distilled water system.

In heat exchangers that use gaskets the distilled water must be held at a higher pressure than the cooling medium, for gaskets can fail and contamination can result. The system must be monitored regularly to detect such problems, and this requires good instrument design, good sampling techniques and good sample ports. In Fig. 3 we show a welded sample valve and nipple that minimizes hold-up, is easily cleaned and drained, and is easily flamed to sterilize it before sampling. We are also working on the design of a steamed sample port

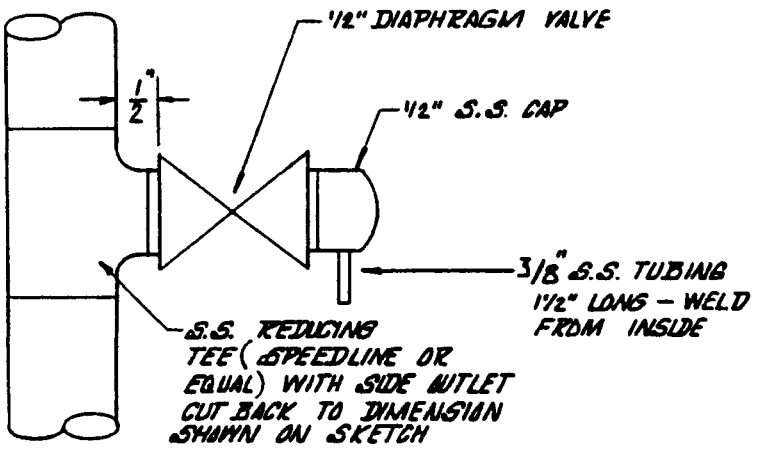

FIG. 3

WELDED SAMPLE VALVE AND NIPPLE

similar to that used in the fermentation industry. An alternative to the gasketed heat exchanger is the welded tubular type.

SOLUTION PREPARATION

Fig. 4 shows a hopper, or an optional hopper and blender system similar to that used in the milk industry as one method of transferring solid ingredients such as dextrose, sugar, or salt into a mixing tank using water and a pump to make a slurry. Obviously, bags can also be dumped through the manhole into the tank, or other fluidized solids conveying systems and weigh tanks can be used. The transfer system must be so designed that the inside of hoppers, chutes, or conveyors can be com-

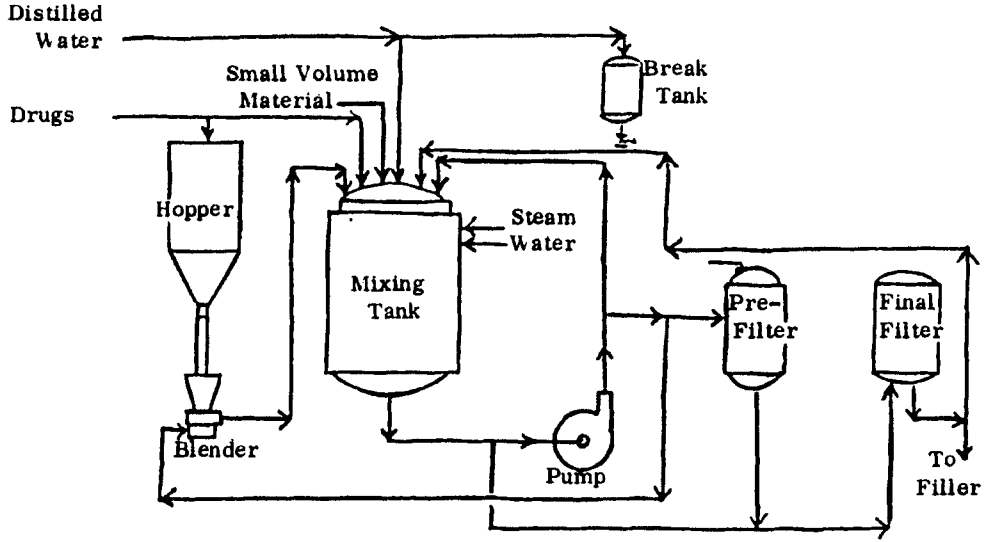

FIG. 4

SOLUTION PREPARATION

pletely cleaned, which means they must be of sanitary construction, type 304 or better stainless steel. From the mixing tank the solution is pumped to a pre-filter and a final filter before filling.

A chemical engineer will look at this batch mixing system and say, "I can do it better with a continuous slurry system, a small in-line blender or mixer; and with on-line instrument measurement and control and a computer, produce parenteral solutions continuously." We have been saying this for years, but we can't convince our pharmacists and the regulatory people who want a batch that can be identified, accounted for, and controlled as an entity. And frankly, there remain a few problems with developing sanitary type sampling and instrumentation systems. But we hope engineers will keep on trying to develop the equipment and data to do it on some high volume items such as 5% dextrose in water.

EQUIPMENT DESIGN

The mixing tank shown (Fig. 5 and 6) is of sanitary design and is also used as a storage tank during the subsequent filling operation. It may also be jacketed since some of the solutions require heating or cooling for reaction or for solution. Constructed of type 316 or 316L stainless steel with a type 304

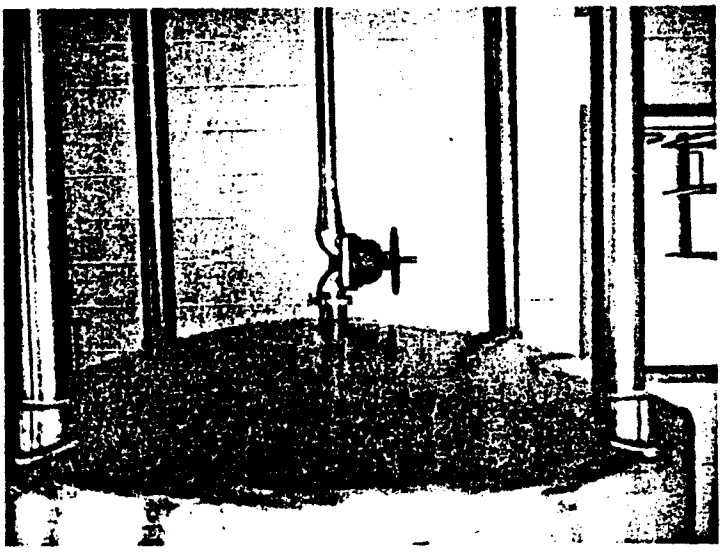

FIG. 5

PIPING AT BOTTOM PART OF MIXING TANK

jacket the internal surfaces should be a number seven finish or better, sometimes electropolished to make it very cleanable. Spray balls should be installed for cleaning and may be permanently mounted with sanitary fittings or they may be inserted through the manhole when needed. An agitator of sanitary design is provided for mixing soluble dry ingredients into the distilled water and for agitation without vortex formation to 1/3 of the vessel volume. We avoid the use of baffles, since they add to the cleaning problem. No stuffing box or packing is to be used so the agitator shaft (Fig. 7) is mounted on the

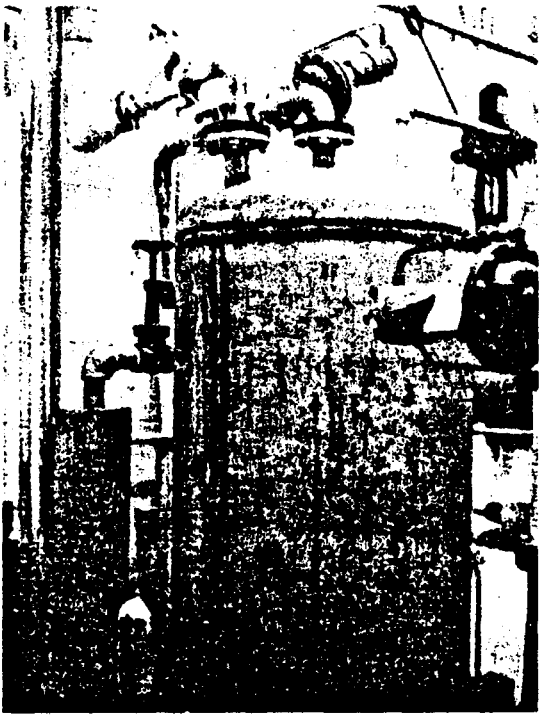

FIG. 6

UPPER PART OF MIXING TANK

tank through a small opening in the top head. A cover is provided. Gassing the solution with nitrogen puts the tank under positive pressure so that all gas and air flow is outward thus reducing the possibility of particulate entry. This is also helped by directing Hepa filtered air over the top of the tank. Otherwise, the agitator shaft may be designed with a rotary seal with special protection to remove particulates produced by the seal, and to prevent them from dropping into the solution. We

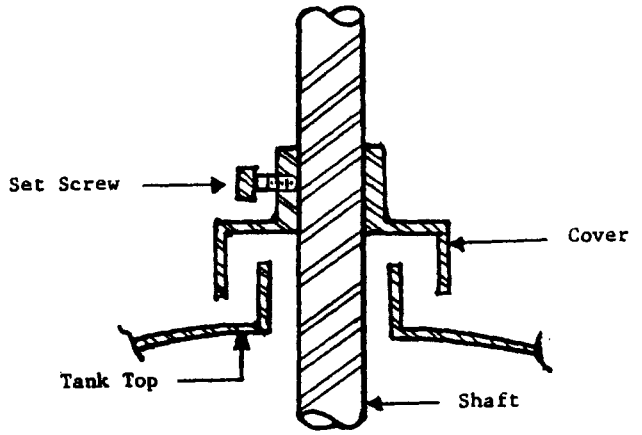

FIG. 7

STAINLESS STEEL COVER FOR AGITATOR INLET

do not presently steam tanks under pressure since this requires tanks built of stainless steel plate. We prefer the superior finish of the lighter gage tanks for cleanliness.

Mixing tanks may have load cells for weight measurement, or they may be calibrated for liquid level measurement by hydrostatic head or other gaging methods. Load cells also make it easy to record the amount of solution left in a tank after a run is completed and provide complete accountability. If jacketed, tanks must be insulated with a watertight covering. Temperature sensors with recorders are a must.

A sanitary centrifugal pump (available from several manufacturers) with a recirculating line back to the tank completes the mixing system. This pump (Fig. 8) must have a

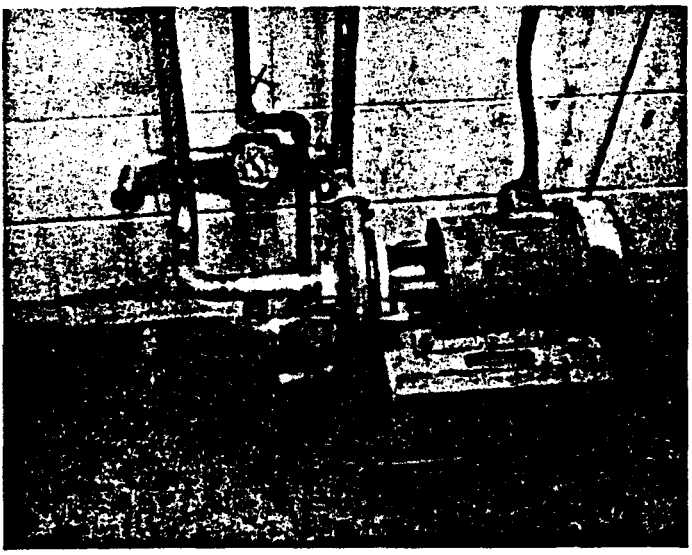

FIG. 8

SANITARY PUMP

sanitary seal and a drain with a valve and a stainless steel steam trap. A properly located sample port in the return line to the tank enables the operator to take samples to determine whether or not anything needs to be added to bring the solution to proper strength.

The solution is pumped through a horizontal plate pre-filter with filter pads pre-coated with activated carbon (Fig. 9).

The rate of solution flow through the pre-filter is critical since flow surges may break the paper or disturb the pre-coating, and must be regulated carefully by proprer valving and

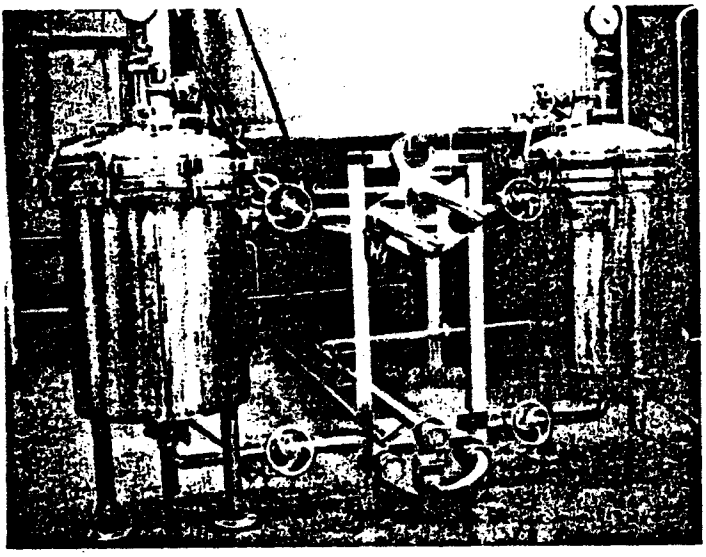

FIG. 9

PREFILTER

controls. The same goes for the final filter, shown in Fig. 10, especially since the pressure drop changes and translates into surges from beginning to end of the run. This filter should be as close as possible to the filling machine and contain a set of membrane discs for microbial and other particulate removal. Before and after a batch is run, the filter must be tested for integrity by a bubble test or forward flow test using filtered compressed air. If the filter fails the test, showing a ruptured membrane, anytime after the lot is started filling, the product to that time may be rejected. These filters must be changed

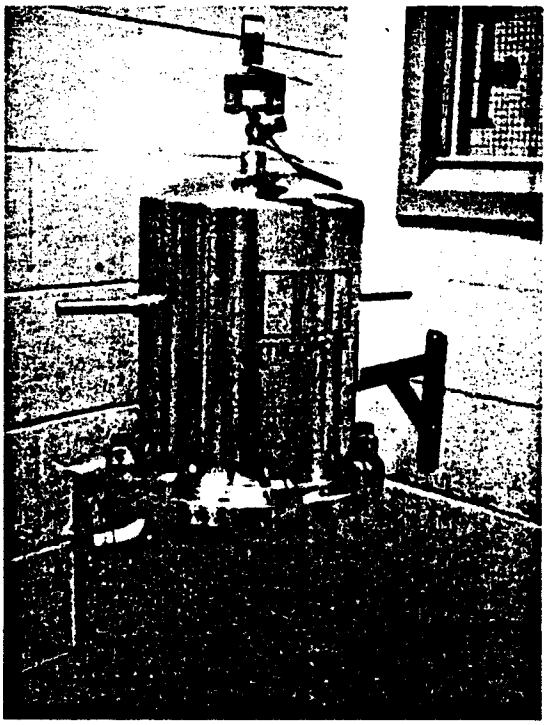

FIG. 10

FINAL FILTER (MILLIPORE)

with every batch change and can only be used for one shift. This is another area in which our problems differ from the food industry. If viable and non-viable particulate barriers were all that we required in solution making for protection, it would make life easy. However, some bacteria produce exotoxins during their life cycle, and endotoxins as they break up during or after death. These substances, "pyrogens," pass through

the membrane filters and could produce fever reactions in patients receiving solutions containing small amounts. Therefore, we must change rather expensive membrane filters very often to prevent bacteria build up on the membrane.

Solution is then fed to a pressure tank in the filler by a flow control valve regulated by the level in the tank. When this valve does not call for solution, the solution is recirculated back to the mixing or storage tank. Since this whole system is cleaned with hot water at 190° to 200°F., and also steamed, all of it must be able to withstand the temperature and pressures involved. The filter membranes will not withstand steaming so it is necessary to bypass the filter when steaming the lines.

PIPING DESIGN

We should talk about solution piping now. Type 316 stainless steel sanitary tubing, welded wherever possible with no threads, crevices, dead ends, or pockets is called for. Clean-in-place fittings as previously shown are used, and no ASME flanges are used. There is considerable argument as to which is more easily cleanable, highly polished interior pipe or tubing, or pipe with a pickled interior surface. The process of polishing actually scratches the surface of the stainless steel. We believe that a bright annealed finish is the choice for dis-

tilled water, and for solutions, that a bright annealed finish is probably as good as a number seven and better than a number four finish for cleaning; but we also believe that an electropolished number seven interior should be investigated in the future. All solution piping must be welded, steamable and pitched for dainage. Unless electropolished, all piping and equipment must be acid treated before use.

Saunders type diaphragm valves with Teflon(R) or silicone rubber diaphragms are used. Teflon(R) does shed particulates so diaphragms must be checked carefully and replaced often. Buna N will not withstand distilled water and cannot be used. Gaskets and 0 rings in piping service must be silicone rubber or Teflon(R) Going back to the piping itself, we demand a high degree of weld quality, with inert gas shielded electrode techniques. Don't let contractors or vendors put you off by saying they can't control weld quality. By having our welders work with contractor's welders, we found we can show them how to make welds of high quality. Fig.'s 11 and 12 show what I mean. Fig. 11 shows an unpurged weld with large crevices. Fig. 12 shows a purged weld with no crevices. Generally, control valves must be carefully checked for 0 ring channel design for ease of cleaning, and for liquid hold up. We use flow diverter panels with U-bend connections to eliminate problems with

FIG. 11

UNPURGED WELD

trying to maintain control valves clean and particle free and self-draining (Fig. 13). In this case the use of the 3A (John Perry) Acme thread fittings is permitted in order to obtain a tighter joint in repeated use, and these can be cleaned daily.

Mixing tanks, pumps, valves, piping, filter bodies, and filling machines are cleaned and sanitized at the end of a run by pumping hot water, 190° to 200°F., through the system to the sewer at from six to ten feet per second velocity for a period of 20 minutes. They are sanitized daily by steaming for one hour with 15 to 25 psig steam where possible and with

FIG. 12

PURGED WELD WITH NO CREVICES

atmospheric steam where necessary, followed by a cold distilled water rinse. Since the effectiveness of this method depends on the smoothness of the piping and equipment, we emphasize this element in design.

In designing for minimum particulates we really start with the product containers which range in size from 150 ml. to 3 litres. Fig.'s 14 and 15 show the two ends of a typical glass bottle washer. Usually there is a detergent wash for glass bottles with several rinses of resh or tap water, chlorine treated and/or filtered, and with final rinses of distilled water.

FIG. 13
FLOW DIVERTER

Considerable testing must be done to establish the absence of any detergent carry-over, that particulates have been removed, and that no organisms have been added.

Sample ports must be provided on washers so that representative samples of all the waters used can be taken and they must be flamed or sterilized to reduce the possibility of microbial contamination by outside sources. The location of these ports requires help from microbiologists also.

OTHER DESIGN CONSIDERATIONS

In trying to cut down on the use of detergents in cleaning containers and maximize use of hot distilled water, design

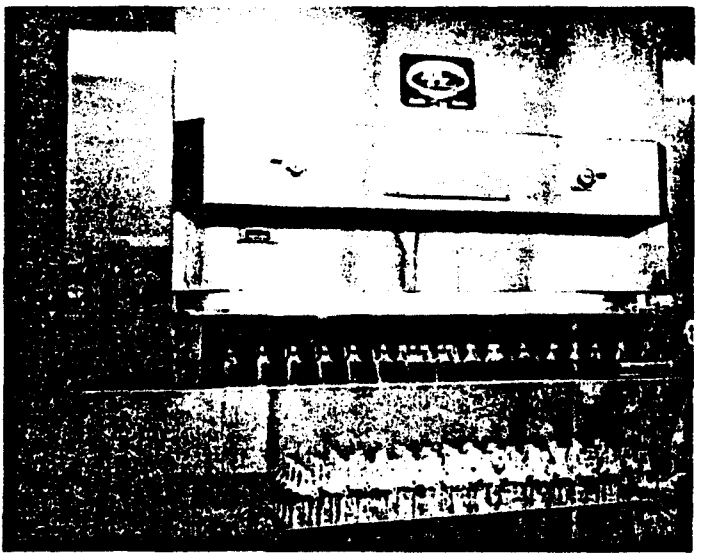

FIG. 14

BOTTLE WASHER - MAIN LINE

becomes more difficult, and considerable engineering work and development time can be expended on water flow systems, pumps, nozzles and container carriers. Off the shelf units are just not suited for our industry unless modified considerably. Washing units, pumps, heat exchangers, and accessory equipment must all be designed according to sanitary standards so that they may be completely cleaned in place. Temperature, pressure and flow control instrumentation is necessary to provide good results in container washers. Remember however, that a stainless steel turbine or mechanical meter will not handle or measure distilled water flow accurately. They just don't go together.

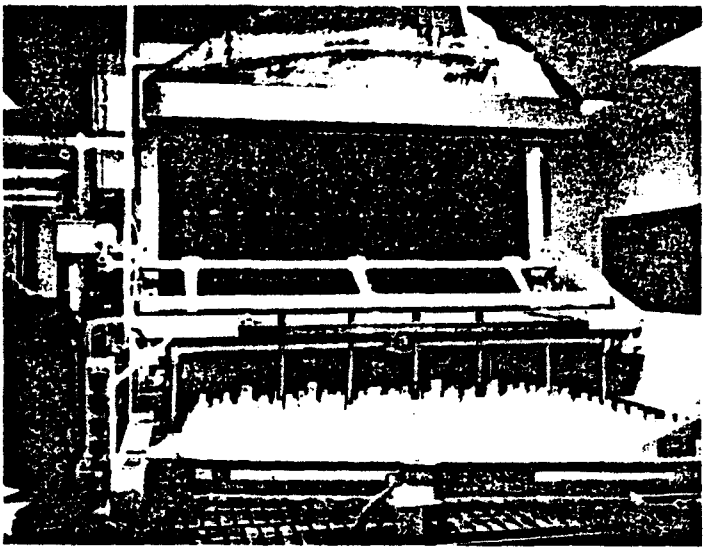

FIG. 15

BOTTLE WASHER

We are now at the filling machine. There are a number of types on the market, but the choice will be one of completely sanitary construction and design, easily cleaned and accurate. Seals and gaskets and 0 rings must be carefully examined to determine that they do not pose problems in cleaning. The selection should also be made on the basis of the cleaning process to be used, particularly if the unit is to be sanitized with steam.

Some units will not rotate if heated. Much of the framework and moving parts of fillers is classed as non-product

contact surface but if poorly designed and fabricated can be a cause of product contamination from moisture drippage into the container or by adding particulates under the laminar air flow system (Fig. 16).

Until the bottle is closed there is a threat to internal purity from outside. So until a rubber bung is inserted and vacuumized and then overcapped, or until a screw cap is threaded, the threat exists, from excessive lubrication or excessive wear on the machine. Fig. 17 shows a typical vacuumizer and Fig. 18 shows the overcapping machine.

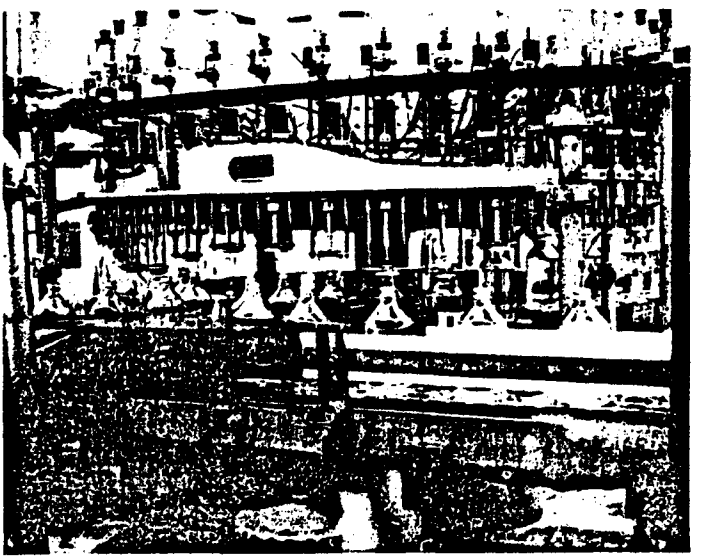

FIG. 16

FILLER

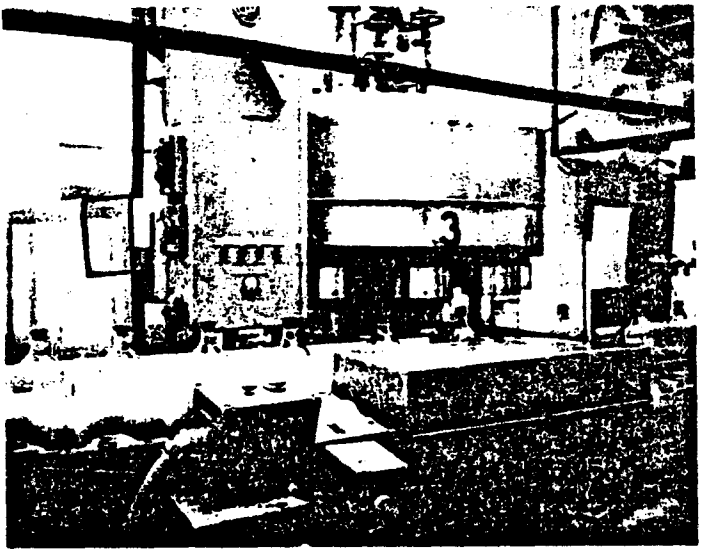

FIG. 17

VACUUMIZER

It is not our intention to discuss the terminal sterilization process in this talk. And, our packaging and case packing lines are typical of any in any bottling operation (Fig. 19).

We will conclude by stating that there is a need for more developments in equipment, valves, filters, etc., in order to advance the state of the art. For example; we need:

1. Flow control valves that are fully sanitary and cleanable in place, and with tight shutoff. This means no leakage at all.

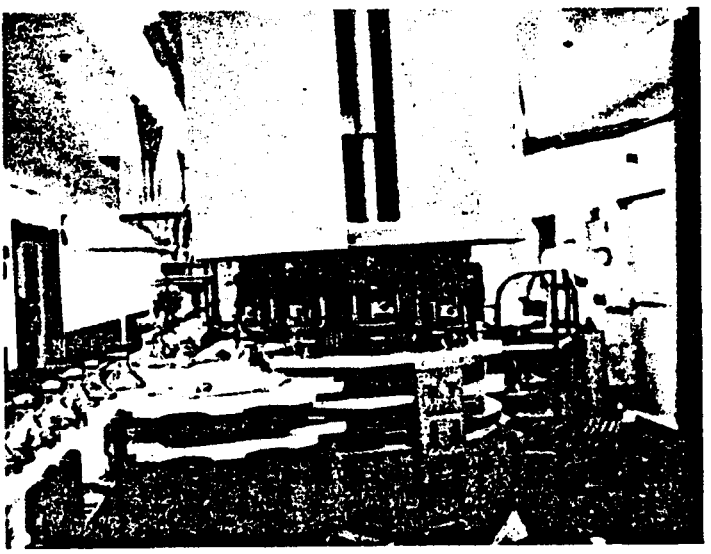

FIG. 18

CAPPER

2. Filter bodies and filter plates that are more easily cleaned than existing units.

3. Better sanitary gaging systems for tanks.

4. A completely sanitary, cleanable, and sterilizable flowmeter that will measure distilled water accurately.

5. A hose that will not shed particulates and that will withstand steam, for flexible connections without a crevice.

6. Filters for steam at .5 micrometer absolute rating that are not hydrophobic or membranes of .22 micrometer rating that are steam sterilizable.

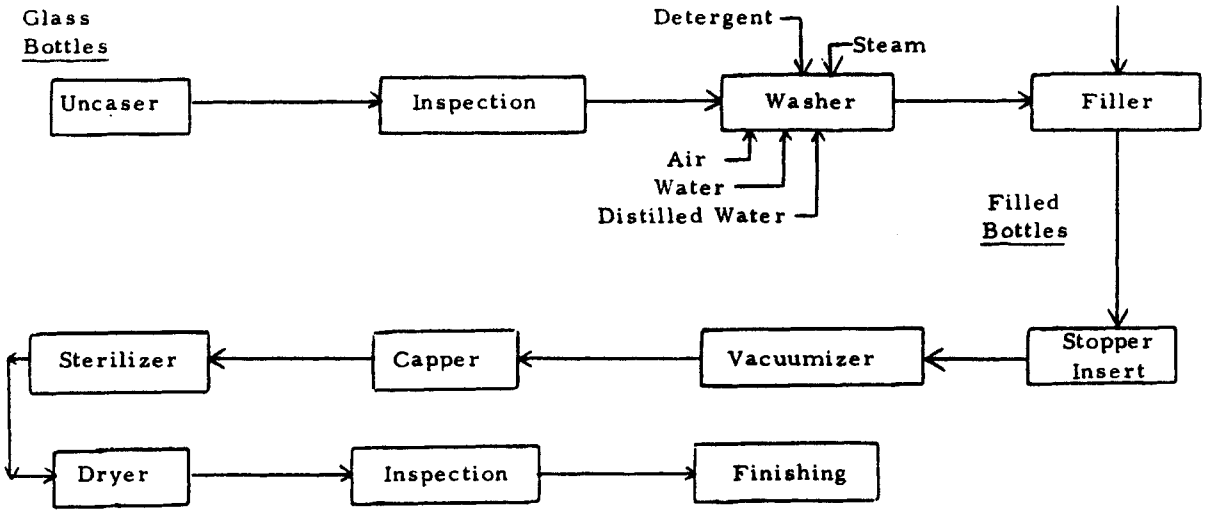

FIG. 19

PARENTERAL SOLUTION FILLING FLOW CHART

We believe that instruments and controls can be designed so as to provide that all the equipment will be handled by the operator as planned. The use of proximity switches at flow diverters, load cells, counters, instruments and controls can be programmed with a computer to provide a monitored, accountable system. It should produce a printout showing all weights, account for all solution used or lost due to rejects, etc. and that all operating procedures required were followed in producing the lot or batch.

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