

PHARMACY PRACTICE



A New Single Use Sterile Line for Sterile Filtration of Parenteral Nutrition Solutions

P. Leglise, P. Arnaud and F. Brion

INTRODUCTION

Pharmacy departments throughout North America and Europe prepare total parenteral nutrition solutions. In North America it is very common to use sterile solutions prepared by manufacturers and mix them in a closed system under a laminar airflow hood using aseptic technique. However, in Europe it is very common for hospital pharmacy departments to virtually manufacture parenteral nutrition solutions starting with sterile solutions, using open vessel techniques and aseptic technique. This requires that both the personnel and the department follow Good Manufacturing Practices (GMP). This paper briefly describes how parenteral nutrition solutions are prepared in France using a new single use sterile filtration device.

Hôpital Robert Debré in Paris, France is a 500-bed acute care pediatric hospital. The department of pharmacy provides unit dose distribution and a complete IV additive service, including preparation of parenteral nutrition solutions. On average, approximately 50 bags of parenteral nutrition solution are prepared each day for 50 patients. These solutions are prepared from commercially available sterile solutions within the pharmacy

department by qualified personnel using sterile technique and laminar air flow equipment.

Prior to the development of a single use sterile line, we had used a conventional method to filter parenteral nutrition solutions. The components were put in a stainless steel container and the solution was pumped into a sterile ethyl vinyl acetate (EVA) bag through a sterile membrane 0.22 μm filter with a surface area of 45.5 cm^2 using positive pressure. This method required that the sterile membrane holder, membrane, and the tubing system be cleaned to remove pyrogens; that a membrane integrity test be completed after the sterilization operation to ensure membrane integrity; that filtration be carried out under 3 bars (approximately 43.5 psi) of positive pressure using sterile nitrogen. There were a number of problems with this method. During the filtration process the solution could not be visualized, a number of teflon joints could develop particles and sealing problems, the low surface area of the filter increased filtration time, the life of the tubing was only 60 sterilization operations, and the system occupied most of the area available under the laminar airflow hood which made working conditions difficult.

As a result of these problems, the reusable filter was eventually replaced by a single use filter which offered many advantages.¹ However, the filtration line was not ready to use¹ and had to be assembled using reusable tubing and a single use filter under sterile working conditions in a laminar air flow hood. In order to reduce the risks of pyrogenic and microbial contamination associated with such an assembly procedure, and in order to improve the quality of sampling conditions for chemical, physical and microbial testing, a sterile single-use set filtration was developed in the pharmacy department (Figure 1). We have now used this device for more than two years and believe that since assembly, cleaning, and sterilization times were reduced, productivity increased without a change in patient safety. All parenteral nutrition solutions are prepared in a class 100 vertical laminar airflow hood in an environmentally controlled area (class 10,000) in accordance with good manufacturing practices.

Method of Parenteral Nutrition Preparation.

The first step in the preparation of a parenteral nutrition bag under a class 100 laminar airflow hood using this single use sterile filter is to attach the

P. Leglise, is a Staff Pharmacist in the Department of Pharmacy at Hôpital Robert Debré, Paris, France.

Philippe Arnaud, Ph.D., is Pharmacien Praticien Hospitalier, in the Pharmacie et laboratoire de Toxicopharmacologie at the Hôpital Robert Debré.

Françoise Brion, Ph.D., is Chef de Service, in the Pharmacie et laboratoire de Toxicopharmacologie at the Hôpital Robert Debré.

Address correspondence to: Philippe Arnaud, Ph.D., Pharmacien Praticien Hospitalier, Pharmacie et laboratoire de Toxicopharmacologie, Hôpital Robert Debré, AP-HP, 48, boulevard Serurier, 75019 Paris, France.

silicone tubing to a variable speed peristaltic pump (Millipore XX80000230, Molsheim, France) (Figure 2). Then, prior to preparation of the first bag and immediately following preparation of the last bag,

500 mL of sterile water is processed through the line. Samples from each of these 500 mL volumes are tested for sterility according to USP XXIII to ensure process quality. During parenteral nutrition solution

preparation, the maximum flow rate is set at one litre per minute. The filter is placed vertically on a holder so that the entire surface of the membrane is in contact with the liquid to be processed. The parenteral nutrition solution is prepared using sterile components (dextrose, amino acids, electrolytes, oligoelements, vitamins, etc.), the volumes of which are measured either using graduated cylinders after opening the flasks, or using single use syringes and needles through rubber stoppers. Component mixing is carried out in a food grade sterile container. The free end of the silicone tube is then dipped into the container and the peristaltic pump is operated. The solution is transferred into plastic bags through the filter without any contact with air.

Microbial, physical, and chemical testing is carried out on samples drawn from each bag. In this procedure, the bag is first shaken, clamp 4 in Figure 1 is closed, and clamp 5 in Figure 1 is opened. Then the first Vacutainer® tube is filled ensuring that the lines between the bag connection and Robert clamps (assembled parts 4, 5, and 7 - see Figure 1) are primed. Then a second Vacutainer® tube is filled for microbial tests; and a third Vacutainer® is filled for physico-chemical tests. The samples taken from each bag are used to complete quality control tests. These tests include tests for sodium and potassium content. The samples taken for microbial tests are stored at 4°C for one week for sterility. The sample taken from the bag is not suitable for sterility testing according to USP XXIII. However, it does allow a sample of each manufactured bag to be available for testing at a later time by the health authorities, if required.

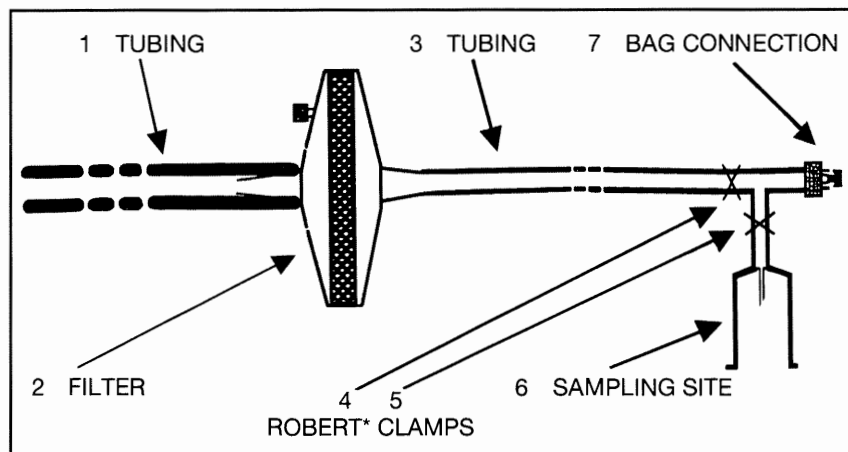


Figure 1: Sterile parenteral nutrition filtration line. In this figure '1' shows 100 cm of silicone tubing with a 10 mm external diameter and 4 mm internal diameter able to withstand a 1.4 bar pressure. '2' shows the single use 0.22 μm hydrophilic filter (Millipack 40®, Millipore, Molsheim France) with a surface area of 200 cm^2 , suitable for filtration up to 500 mL/min at a maximum pressure of 0.5 bar. '3' shows, the placement of the 20 cm of PVC tubing with an internal diameter of 4 mm and an external diameter of 7 mm, fitted with a male Luer Lock conical adapter suitable for connecting 500 mL to 4000 mL ethyl vinyl acetate (EVA) bags (Pharmacia, Noisy le Sec, France). '4' and '5' show the placement of Robert - 22® clamps used for the sampling procedure. '6' shows the sampling site consisting of a 5 cm tube branch equipped with a Luer Vacutainer Adaptor® (Becton Dickinson, Grenoble, France) and a Vacutainer® holder enabling samples to be taken in sterile evacuated tubes. The sampling needle is covered with a retractable rubber sleeve. '7' shows the placement of a male Luer Lock tip with a sliding ring made of polycarbonate. All connections are secured with adhesive (cyclohexanone/methylethylcetone 75/25 v/v). The whole set is sterilized by Ethylene Oxide. The dosages of the sterilizing agent residue are effected to avoid any health safety risks. This set is manufactured by CAIR, a pharmaceutical company in Civrieux d'Azergues, France.

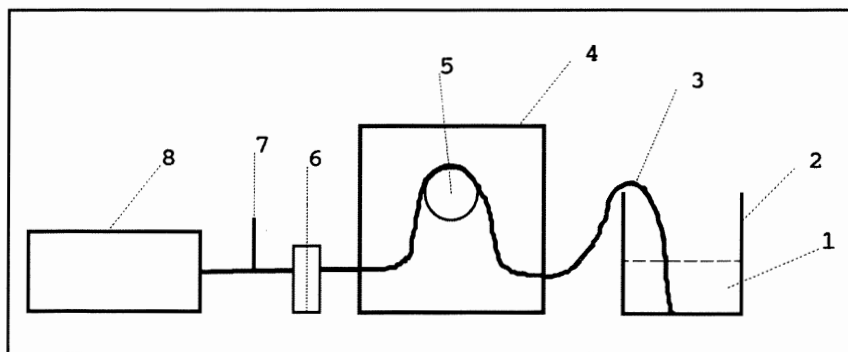


Figure 2: New method of preparation of TPN. '1' indicates the TPN solution; '2' represents the vessel; '3' represents silicone tubing; '4' shows the placement of the peristaltic pump; with '5' representing the rotor of the pump; '6' represents the single use 0.22 μm filter; '7' shows the placement of the sampling site; and '8' represents the EVA bag.

RESULTS - DISCUSSION

Using a sterile non-pyrogenic single-use filter (Cair, Civrieux d'Azergues, France) has reduced the time devoted to assembly of components, and

eliminates washing and sterilization of components, and helps to improve quality assurance. The use of a line with an integrated sampling site avoids contamination of the line and the bag during sampling of quality control tests. A 20 cm length of PVC tubing was selected to allow easy shaking for better homogeneity, while avoiding filter motion. The 20 cm length does not give excessive dead space between the filter and the bag.

The set must be changed after filtration of 75L of solution. The filtration rate is not reduced during filtration of the first 75L of dextrose mixed with other components (aminoacids, electrolytes, water). A 40% reduction in filtration rate may occur with viscous solutions such as 70% dextrose.

We have used this sterile filtration device for more than two years. During one year, 15,000 bags were

processed with this line without detection of any microbial contamination. ☒

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