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IV Fluidmaker: Preparation of Sterile Water for Injection in a Field Setting

by

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Two small, hand-operated systems have been devised for generating sterile, pyrogen-free water for injection (WFI) in the field. Both systems utilize reverse osmosis, ion exchange, a solid matrix filter containing activated carbon and zeta adsorbent, a final 0.2 micron pore-size sterilizing filter and a device for transferring the WFI to an IV bag. Both systems are capable of producing WFI according to U.S. Pharmacopeia XXI standards. The smaller system weighs approximately 1.5 kg and produces WFI at a rate of 1 liter in 45-50 minutes; the larger weighs approximately 3.5 kg and produces 1 liter of WFI in 5-6 minutes. Parenteral solutions were made by adding WFI to an IV bag containing concentrated Ringer's lactate. Keywords:

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PREFACE

Chemical analyses were performed under the direction of Dr. Steven H. Hoke, U.S. Army Biomedical Research and Development Laboratory (USABRDL). Pyrogen tests were conducted by Ms. Kathleen Connor of PRI, Inc., through the courtesy of Dr. Burton Lidgerding, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Sterile water tests were carried out under the direction of Ms. Linda L. Hildebrand, also of USAMRIID.

ABSTRACT

Two small, hand-operated systems have been devised for generating sterile, pyrogen-free water for injection (WFI) in the field. Both systems utilize reverse osmosis, ion exchange, a solid matrix filter containing activated carbon and zeta adsorbent, a final 0.2 micron pore-size sterilizing filter and a device for transferring the WFI to an IV bag. Both systems are capable of producing WFI according to U.S. Pharmacopeia XXI standards. The smaller system weighs approximately 1.5 kg and produces WFI at a rate of 1 liter in 45-50 minutes; the larger weighs approximately 3.5 kg and produces 1 liter of WFI in 5-6 minutes. Parenteral solutions were made by adding WFI to an IV bag containing concentrated Ringers lactate.

KEYWORDS

Water for injection	Reverse osmosis
Pyrogen-free water	Ion exchange
Sterile water	Carbon adsorption
Parenterals	Filtration

INTRODUCTION

The U.S. Army Medical Research and Development Command has the requirement for a device to manufacture intravenous (IV) fluids under circumstances of disadvantage, such as a field combat situation, where resupply of medical items is uncertain.[1] The device must produce sterile, pyrogen-free water which can be introduced directly into sterile bags with sterile salt solution so as to make one liter of Ringer's lactate or one liter of 5 percent dextrose in water suitable for IV infusion into humans. Approval by the Food and Drug Administration (FDA) will ultimately be required, but is not considered to be a part of this effort. Salient requirements for the device are:

a. It must fit into a protective mask container (ca 20 cm x 23 cm x 8 cm).

b. It must be hand-operated.

c. A minimum production rate of 1 liter per hour is required.

d. The feed will be taken from a potable source.

Presently, the smallest system for production of IV fluids projected to be available to the Army in the field is the Resuscitation Fluids Production System (REFLUPS), a 60 L/hr device about the size of a console piano with substantial water and power requirements, and employing reverse osmosis (RO) technology.[2] A literature review revealed no devices with the potential to meet the requirements listed above; therefore, a developmental initiative was necessary.

The United States Pharmacopeia (USP) defines four categories of water relevant to this study: Purified Water, Water for Injection, Sterile Water for Injection and Bacteriostatic Water for Injection, for which manufacturing and purity criteria are presented in Appendices A through D, respectively.[3] It is perceived that the target for the device in question, hereinafter the fluidmaker, is Sterile Water for Injection, which must be produced by distillation or RO. In addition, there are rigorous quality criteria, not only for pyrogens, but for many dissolved materials commonly found in potable water. The one criterion that cannot be met by any fluidmaker (including REFLUPS) at the outset is that the source water satisfy U.S. Environmental Protection Agency (EPA) regulations. Army potable water standards (Table 1) are necessarily much less stringent than EPA standards, which are based on lifetime health considerations for the general population and which specify maximum contaminant levels for a large number of organic and inorganic chemicals commonly found in raw water supplies. As an example of circumstances where EPA criteria cannot be met, potable water prepared from seawater by means of the 600 gallon/hour reverse osmosis water purification unit (ROWPU), the most advanced water treatment system in the Army inventory, has chloride levels exceeding the EPA secondary standard (250 mg/L) by two-fold or more.

TABLE 1. QUALITY STANDARDS FOR TREATED WATER

Constituent	Short Term Standard[a] (7 days or less)	Long Term Standard[a] (more than 7 days)	EPA
Physical			
Color	-	50 units	
Turbidity	Reasonably clear	5 units	
Chemical			
Arsenic	2.0 mg/L	0.2 mg/L	0.05 mg/L
Chloride	-	600 mg/L	250 mg/L
Cyanide	20 mg/L	2 mg/L	
Magnesium	-	150 mg/L	
Sulfate	-	400 mg/L	250 mg/L
Total dissolved solids	-	1500 mg/L	
Chemical Agent			
Hydrogen cyanide	20 mg/L	2.0 mg/L	
Lewisite	2 mg/L	0.2 mg/L	
Mustard	2.0 mg/L	0.2 mg/L	
Nerve agents	0.02 mg/L	--	
Bacteriological			
Coliform	1.0 per 100 mL	1.0 per 100 mL	
Radiological	no standard	no standard	

a. Reference 4

APPROACH AND RATIONALE

The performance requirements for the fluidmaker in terms of product quality are that it reduce dissolved inorganic and organic chemicals, including pyrogens, to very low levels; that it virtually eliminate residual suspended materials; and that it assure sterile transfer to an IV bag. For expedience, off-the-shelf items were used or items were fashioned from readily available materials. Selection of the the following devices for evaluation was strongly influenced by the studies of Duncan[5] and others in the course of development of REFLUPS.

REVERSE OSMOSIS. The fluidmaker concept was based on on RO technology, which is known to be highly effective in removal of dissolved organic and inorganic impurities and microorganisms, including viruses. RO will reduce all common ions (sodium, potassium, magnesium, chloride, sulfate and carbonate) to less than 10 mg/L, even from poor quality potable water, and will virtually eliminate heavy metals. (In principle, potable water prepared by ROWPU would qualify as RO-treated and, hence, could be converted to WFI by further treatment, as required. However, potable water rapidly loses its identity through distribution, and it was decided that development of the system should assume anonymity of the potable water supply.)

ION EXCHANGE. Mixed-bed ion exchange columns will reduce dissolved salts to levels acceptable for WFI, i.e., well below 1 mg/L. An ion exchange unit will be required for FDA approval, since RO alone can produce WFI according to USP criteria only from high quality potable waters. At this stage in development of the fluidmaker, ion exchange technology is considered to be optional because the product water from RO is believed to be safe for IV use in terms of its salt content. Ion exchange units have geometric constraints which make them inconvenient for field use, and a suitable commercial unit has not been identified.

WATER PURIFIER. A water purification filter, such as those used by campers or for end-of-pipe treatment in households, was chosen as the third main unit of the system. These filters commonly contain activated carbon, which is effective in trapping organic chemicals not removed by RO, and they provide an independent means of removing pathogens and pyrogens.

STERILIZING FILTER. A membrane filter of 0.2 micron limiting pore size is commonly used for sterilizing IV solutions. Although the water purification filter is expected to produce sterile water, the membrane filter is considered to be an essential backup.

MATERIALS AND METHODS

CHALLENGE WATERS. Various water sources were used to challenge the fluidmaker and its individual components. Challenge water sources were tapwater from different stations at Fort Detrick, Frederick city tapwater and water from the Fort Detrick post pond, containing suspended algae. " Worst case water" was prepared by amending tapwater with 900 mg/L of sodium chloride and 500 mg/L of anhydrous sodium sulfate. Synthetic ROWPU water was similarly prepared by amending tapwater with 600 mg/L of sodium chloride. For all tests involving the RO unit, source water was first dechlorinated either by allowing an open container of water to stand for several days or by adding 0.1 g of sodium bisulfite to each 5 gal (19 L) of tapwater.

REVERSE OSMOSIS. Two hand-operated RO units were evaluated, both manufac ured by Recovery Engineering, Inc., Minneapolis, MN. The Survivor™ 06 (S06) is 20 cm long, weighs 2.5 lbs (1.1 kg), and produces 20 to 25 mL/min from fresh water at a pumping rate of 80 to 100 up-and-down strokes per minute (spm). (This is greater than the pumping rate recommended by the manufacturer, but it is a rate easily maintained indefinitely without fatigue). The Survivor™ A90 (SA90) is 38 cm long disassembled, weighs 7 lbs (3.2 kg), and produces 200 to 300 mL/min from fresh water at a pumping rate of 60 spm. Both units use FilmTec® FT30 spiral-wound, thin-film composite membranes having a sodium chloride rejection of 98% at 225 psi (1.6 M Pa), 25°C and pH 7. The S06 will fit into a protective mask container; the SA90 will not.

ION EXCHANGE COLUMN: Because a small ion exchange column compatible with the fluidmaker was not readily available off-the-shelf, one was fashioned from a 15 cm length of PVC tubing of 1.75 cm i.d. End cap nipples fitted 6.25 mm i.d. Tygon® tubing. The PVC tube was packed with strong acid - strong base mixed bed ion exchange resin from a fresh Barnstead D8902 cartridge, retained at each end with foam plastic filter material taken from the same cartridge.

This resin is reported by the manufacturer to have a capacity of 12.7 equivalents of sodium chloride/ft^3 to produce water with a specific resistivity of 1 Megohm-cm or greater, which meets the USP criteria.

WATER PURIFICATION FILTER. The First Need^R water purification filter (General Ecology, Inc, Lionville, PA) used throughout this study is a solid matrix filter containing activated carbon and zeta adsorbents; it is rated at 0.1 micron nominal and 0.4 micron absolute. It is a cylinder 7 cm in diameter and ca. 10 cm long, weighs 0.20 kg and comes with a detachable pump weighing 0.11 kg. Inlet and outlet nipples fit the 6.25 mm inner diameter (i.d.) Tygon^R tubing used throughout this study. It produces 400 to 500 mL/min at the slow pumping rate recommended by the manufacturer. Holdup is 20 to 30 mL.

STERILIZATION FILTER. For the fluidmaker employing the S06, cellulose acetate syringe filters, 25 mm in diameter and 0.2 micron absolute pore size, were provided through the courtesy of the Nalge Company, Rochester, NY. This filter was connected by means of 4 mm i.d. Tygon^R tubing on the upstream side to the First Need^R filter, and on the downstream side was locked to a REFLUPS concentrate transfer set (a 28 cm long, 4 mm diameter Tygon^R tube with a spike pin at one end and a Luer-Lok^R syringe connector at the other, manufactured for Sterimatics Co., Bedford, MA), thus providing a means for sterile transfer of the WFI to an IV bag. The 25 mm filters would not accommodate the higher flow rate of the SA90. For this system the only filter available was a final sterilizing filter of 7.5 cm diameter and 0.22 pore size from REFLUPS lot packs. This filter was connected by large bore (6.25 mm i.d.) tubing directly to the First Need^R filter on the upstream side; on the downstream side a rubber stopper and stainless steel adapter were used to effect a connection to the REFLUPS transfer set after removing the Luer-Lok^R fitting (Figure 1).

MISCELLANEOUS ITEMS. The REFLUPS concentrate transfer set, empty 1 L IV bags, and lactated Ringer's concentrate are all manufactured by Abbott Laboratories, North Chicago, IL, for Sterimatics Company. Each IV bag has a rubber syringe port, a spike pin port, and an integral 0.8 m tube (4 mm i.d.) for filling with WFI from the REFLUPS system. Adapters for joining 6.25 and 4 mm i.d. tubing were fashioned from stainless steel (solid bar stock) as shown in Figure 2. Spring scales (used to monitor filling of IV bags), Model 8004-M0, manufactured by Ohaus Scale Corporation, Florham Park, NJ, have 25 g scale divisions and a capacity of 2000 g. The Super Cub butane torch (used for flame sterilization and to seal tubing, as described below) is distributed by Microflame, Inc., Minneapolis, MN.

TEST PROCEDURES. Water treatment units were tested individually and in combination. For the S06, 20 to 50 mL of test water was pumped through the system before taking samples or filling IV bags; for the S90, at least 500 mL was pumped through. Connection to the IV bag was made by means of the concentrate transfer set or through the integral filling tube. IV bags were sealed by heating the filling tube with a butane torch to the point of softening, then immediately pinching off the tube with flat-nose pliers; alternatively, the tube could be sealed off temporarily with a slotted plastic tab (Figure 3) included with REFLUPS transfer sets. First Need^R filters were flushed with Chlorox^R before reuse, and RO units were treated with sodium bisulfite after use, as recommended by the manufacturers (Appendices F, G and H).

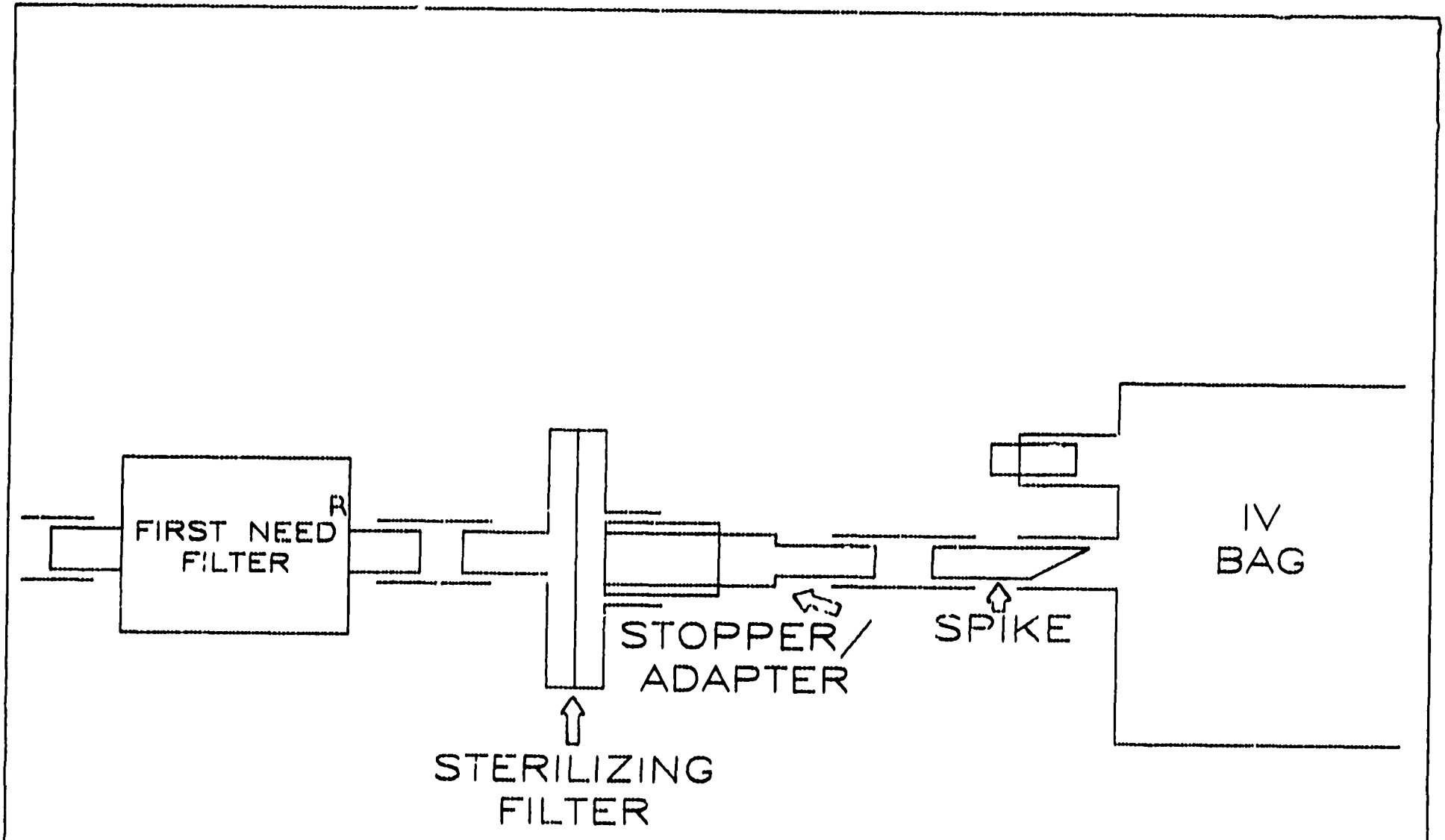

Figure 1. Schematic of Sterile Docking Set for System A90.

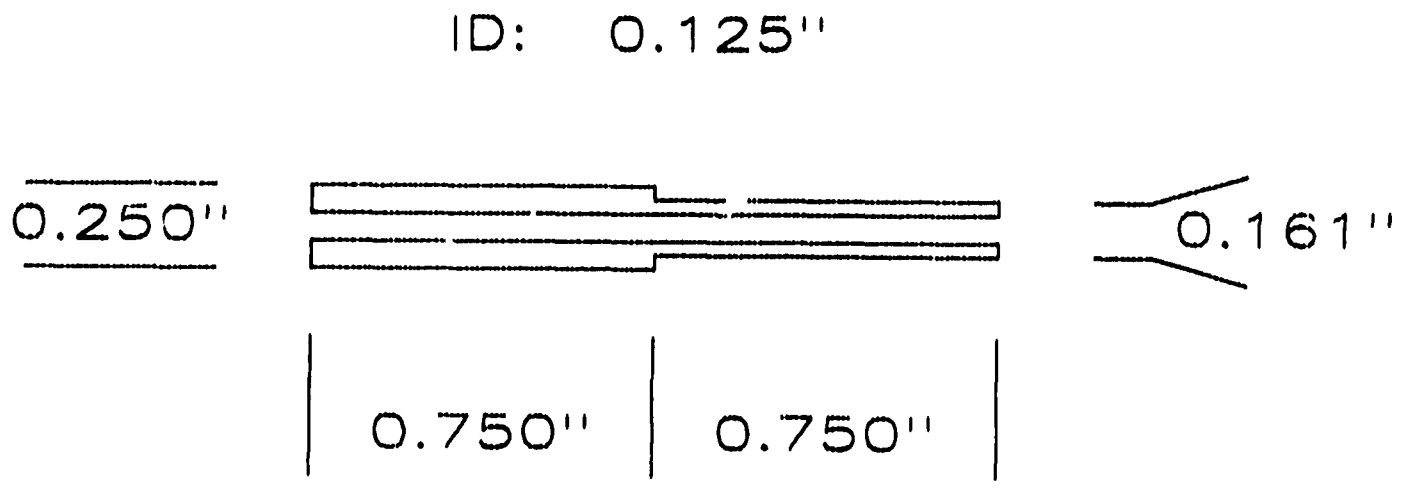

Figure 2. Adapter for Connecting Tygon® Tubing.

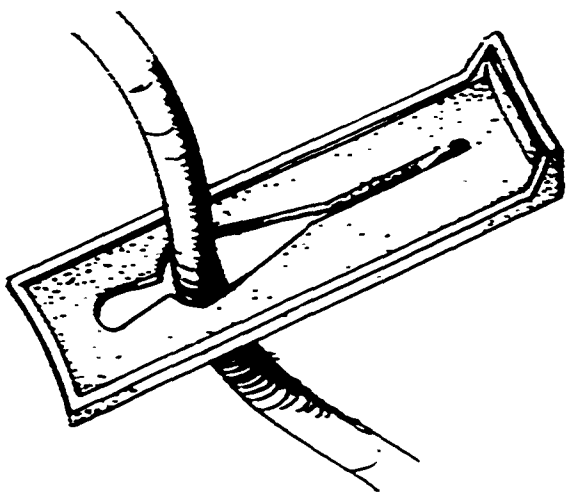

Figure 3. Device for Temporary Sealing of Tygon® Tubing

TRANSFER OF CONCENTRATE. Individual IV bags containing lactated Ringer's concentrate were prepared by transferring 50 mL of concentrate from a 1 L REFLUPS pack to each bag by means of a 50 mL syringe with a 5 cm, 13 gauge hypodermic needle. The transfer was carried out in a Class 2 biological safety hood equipped with ultraviolet disinfection lights, and every effort was made to maintain sterility. The bags were sealed in lots of three in plastic overwraps using a TISH 300 impulse sealer (Taiwan Electric Heating Equipment Company, Ltd). Sterility was checked for only a few samples, but it was found that concentrate samples that remained clear after a few weeks were sterile, while non-sterile samples soon developed visible microbial colonies. Sterile transfer was thereby achieved in 12 of 15 samples.

ANALYTICAL METHODS. Pyrogen content was determined using the Limulus amebocyte lysate (LAL) chromogenic assay. Sterility of water samples was tested by plating on sheep's blood agar and MacConkey's agar. Chloride, sulfate, sodium, potassium, ammonium, calcium and magnesium ions were determined by ion chromatography. Other water quality parameters were determined by procedures given in USPXXI (Appendices A and C).[3]

RESULTS AND DISCUSSION

REVERSE OSMOSIS. Two hand-operated RO units were investigated for removal of dissolved solids. The Survivor™ 06 (S06), designed for emergency production of drinking water from seawater, meets the specified size limitation[1]; the Survivor™ A90 (SA90) does not, but the purified water flux is ten times that of the smaller unit. The principal function of the RO unit is to remove dissolved salts, especially chlorides, sulfates and heavy metals. Polyamide membranes of the type used in the S06 and SA90, as well as the ROWPU, generally remove 98 percent of dissolved sodium chloride. In practice, both RO units achieved this removal, with the S06 giving superior results (Table 2). Reverse osmosis will also remove most organic compounds, pyrogens, viruses and other microbes; hence, a device to prepare sterile, pyrogen-free water could in principle be based on reverse osmosis alone. However, experience has shown that the S06 and SA90 are soon colonized by gram negative bacteria downstream from the membranes, thereby necessitating further treatment.

Because Army potable water may have free chlorine residuals exceeding 5 mg/L,[4] it is essential that the RO feed water be dechlorinated to protect the membranes. This can be achieved in the field by addition of sodium bisulfite, which destroys chlorine by the following reaction:

$$2HSO_3^- + HOCl \longrightarrow HS_2O_5^- + Cl^- + H_2O$$

This corresponds to 5.9 mg/L of sodium bisulfite for each mg/L of free available chlorine, or 0.56 g of sodium bisulfite to dechlorinate 5 gallons (19 L) of potable water with an initial 5 mg/L residual. It should be noted that potable water drawn for RO treatment from a finite reservoir, such as a 5-gallon container, will deteriorate in quality as rejected salts build up in the reservoir. In the case of potable water with high levels of dissolved solids, it may be necessary to replenish the source water frequently. The

principal disadvantage of batch chemical dechlorination is that the dechlorinated water may need to be discarded and the replenished water dechlorinated anew. Alternatively, a granular carbon filter could be used to dechlorinate the water, but because the SA90 must draw 4 liters and the S06 10 liters for each liter of purified water produced (the reject stream being returned to the source), the carbon filter would be of such a size as to cause a significant pressure head loss and a consequent reduction in purified water flux, besides adding a bulky component to the system.

TABLE 2. REMOVAL OF SALTS BY RO AND ION EXCHANGE

Sample	Salt content, mg/L					
	Cl^-	$SO_4^=$	Na^+	K^+	Ca^{2+}	Mg^{2+}
Tapwater, untreated	25.5	48	13.9	4.6	51.6	8.8
After S06	0.26	ND[a]	1.5	ND	2.9	ND
Tapwater, untreated	28.6	37.3	16.4	5.7	54.0	8.4
After SA90	0.45	tr[b]	1.4	ND	3.1	ND
"Worst case water"	580	420	556	11	ca.56	9.4
After S06	1.8	10	<1	<1	3.1	ND
After S06 and IE	0.1	ND	<1	<1		
After SA90	3.7	31	14	<1	2.2	ND
After SA90 and IE	0.06[c]	tr[b]	<1	<1		
"ROWPU water"	405	52.8	250	6.9	41.2	7.5
After S06	1.3	8.9	4.4	<1	4.4	ND
After S06 and IE	0.04[c]	ND	1	<1		
After SA90	3.9	15.3	11.5	<1	2.2	ND
After SA90 and IE	0.1	tr[b]	1	<1		

a. None detected
b. Trace; below quantitation limit
c. Approximate; below quantitation limit

ION EXCHANGE. As defined, WFI has a salt content corresponding to an electrical resistivity of 1 Megohm-cm or greater. This level of purity can be achieved using RO alone only from water of low mineral content (<50 mg/L), and Army field water supplies are virtually certain to exceed this number. The RO product may be satisfactory for WFI in the field, but it will not meet USPXXI standards unless further treated by ion exchange (IE). The small IE unit fabricated for this study had an exchange capacity of 1 g as sodium chloride, presumably sufficient to demineralize 100 L of water containing 10 mg/L of sodium chloride to a specific resistivity of 1 Megohm-cm. Although no special effort was made to optimize this unit, it appeared to achieve the further purification necessary to meet USPXXI standards for WFI (see Table 2 and Appendix Table I3), and was small enough to be included in the protective mask container with other components.

Inclusion of an IE column in the fluidmaker concept is not without complications. Unlike the other components, the IE column must be supported in an upright (upflow) position; otherwise, flow channeling will occur, and deionization will be incomplete. It may be possible to procure or devise an IE unit without this limitation, although probably at the expense of size and flow restriction. The IE unit must be followed by depyrogenation and sterilization, since ion exchange resins for water purification, as delivered, usually contain adsorbed bacteria, which produce pyrogens (Table 3).

WATER PURIFICATION FILTER. Sterile, pyrogen-free water could be prepared from various water sources using only a First Need[R] solid matrix water purification filter (Table 3). Freshly drawn tapwater had a pyrogen content of 7 to 10 endotoxin units per milliliter (eu/mL); 50 L was passed through a single filter without pyrogen breakthrough. Pond water and other waters with pyrogenicity exceeding 100 eu/mL were tested, but in no instance were pyrogens detected in product water from a freshly unwrapped First Need[R] filter.

TABLE 3. FIRST NEED[R] FILTER PYROGEN TESTS

Sample	Pyrogens, eu/mL before filtration	Pyrogens, eu/mL after filtration
Frederick municipal water	8.3	<0.06
Fort Detrick tapwater	7.3	<0.06
Post Pond water	106.1	<0.06
Ion exchange water	7.1	<0.06
Tapwater, after 1 L	10.2	<0.06
" 12 L		<0.06
" 25 L		<0.06
" 50 L		<0.06

On standing, wetted First Need[R] filters were rapidly colonized by mixed gram-negative bacteria downstream from the filter matrix, thereby compromising both pyrogenicity and sterility. Attempts to restore contaminated First Need[R] filters for reuse met mixed success (Table 4). Flushing with fresh water reduced product pyrogenicity only slightly. Backflushing with chlorinated water, as recommended by the manufacturer (Appendix E) restored sterility, but did not reduce pyrogenicity sufficiently. Autoclaving at 120° C for 20 minutes restored sterility and achieved adequate reduction in pyrogenicity. A combination of disinfection, flushing and autoclaving achieved sterility and undetectable pyrogenicity, but one filter was permanently blocked by this process. Restoration of First Need[R] filters for reuse in the field may be feasible, but at this time the only way to assure production of sterile, pyrogen-free water is to discard the filter after each production run, and not attempt to retain the wetted filter for reuse for more than a few hours.

TABLE 4. RESTORATION OF CONTAMINATED FIRST NEED[R] FILTERS[a]

Sample	Filter treatment	Pyrogen content, eu/mL After 50 mL	Pyrogen content, eu/mL After 500 mL	Sterility[b]
#1 Filter product	none	41.3	36.3	+
#2 Filter product	disinfected		0.93	-
#3 Filter product	autoclaved	0.56	0.14	-
#1 Filter product	dis/flush/auto[c]		<0.06	-
#2 Filter product	dis/flush/auto[c]		<0.06	-
#3 Filter product	dis/flush/auto[d]		blocked	

a. Filters were challenged with tapwater containing 149 eu/mL.
b. "+" = 3-5000 colonies/mL mixed gram negative bacteria; "-" = no growth in 48 hours
c. Disinfected, flushed and autoclaved
d. Disinfected, flushed and twice autoclaved

The manufacturer of the First Need[R] filter recommends that the first few ounces of water be discarded when the filter is initially put into use in order to eliminate any dust particles. Experience has demonstrated that these particles will rapidly plug a sterilizing filter (see below), and for this reason it is advised that at least 100 mL of water be passed through the system and discarded before the sterilizing filter is installed.

STERILIZING FILTERS AND STERILE DOCKING. Although freshly opened First Need[R] filters consistently produced sterile water, these filters are not intended for medical use, and it was considered essential that a sterilizing filter of 0.2 micron pore size follow the First Need[R] filter. For the S06 system, a 25 mm diameter cellulose acetate syringe filter connected to a REFLUPS transfer set permitted sterile docking to the IV bag in the laboratory, and should assure sterile docking even under field conditions. The transfer tube was closed temporarily using a slotted plastic tag (Figure 3), or permanently heat-sealed. For the SA90 system, a REFLUPS final filter was used; it was connected to the transfer set using a rubber stopper rather than the Luer-Lok[R] connector used with the 25 mm filter (Figure 1). This permitted sterile docking to the IV bag in the laboratory, but a more satisfactory connection from filter to transfer set will be necessary for field use, particularly since rubber stoppers are known to shed small particles, which are themselves pyrogenic, though undetectable in the LAL test. The Nalge Company is presently developing a 50 mm diameter cellulose acetate syringe filter, which should be suitable for use with the SA90; introduction is planned for mid-1989.[6] With either system, a fresh transfer set must be used for each bag of IV fluid, and the sterilizing filter should be replaced at least as often as the water purification filter.

PRODUCT WATER. Both S06 and SA90 systems consistently provided sterile, pyrogen-free water; when the IE unit was included, the product water was equivalent in all parameters measured to USPXXI Sterile WFI (Appendix I). Where the fluidmaker is used to prepare parenterals, it is necessary to provide IV bags containing the parenteral concentrate in either liquid or solid form. For this study, IV bags were prepared containing 50 mL of lactated Ringer's concentrate taken from a REFLUPS lot pack. Unless sealed in plastic overwraps, these bags tended to dehydrate, losing 1 gram of water per bag over a period of 11 days at 85 percent relative humidity and 85°C and about twice as much under ordinary room conditions. FDA specifications call for an accuracy of ± 5 percent in finished parenteral concentrations, corresponding to ± 50 g of WFI per 1 liter bag. This level of accuracy can probably be achieved volumetrically; alternatively, small spring scales are available which provide an accuracy of ± 25 g.*

SUMMARY

Two complete IV fluidmaker systems were tested for their ability to provide sterile WFI in 1-liter IV bags from potable water of various quality. Both systems produced sterile, pyrogen-free water equivalent in all parameters measured to USPXXI water for injection. The fluidmaker S06 system, weighing approximately 1.5 kg, met all requirements and produced WFI at a rate of 1 L in 45 to 50 minutes; the fluidmaker SA90 system, weighing approximately 3.5 kg, met all requirements except size, and produced WFI at a rate of 1 liter in 6 to 7 minutes. The components and their sequence of assembly are as follows:

S06 System (Figure 4)

1. Survivor™ 06
2. Adapter (Figure 1)
3. Tygon® tubing (6.25 mm i.d., 4" or 10 cm long)
4. Ion exchange column
5. Tygon® tubing (6.25 mm i.d., 10" or 25 cm long)
6. First Need® filter
7. Tygon® tubing (6.25 mm i.d., 2" or 5 cm long)
8. Adapter (Figure 1)
9. Tygon® tubing (4 mm i.d., 2" or 5 cm long)
10. Sterilizing filter (25 mm diameter, 0.2 micron pore size)
11. Transfer set
12. IV bag suspended from spring scale

*The USABRDL has learned that the National Aeronautics and Space Administration, Johnson Space Center, has contracted with Baxter International to undertake research on the problem of IV concentrates.[7]

Figure 4. S06 System on Test Stand.

SA90 System (Figure 5)

1. Survivor™ A90
2. Adapter (Figure 1)
3. Tygon® tubing (6.25 mm i.d., 4" or 10 cm long)
4. Ion exchange column
5. Tygon® tubing (6.25 mm i.d., 10" or 25 cm long)
6. First Need® filter
7. Tygon® tubing (6.25 mm i.d., 4" or 10 cm long)
8. Sterilizing filter (7.5 cm diameter, 0.22 micron pore size)
9. Adapter and #00 rubber stopper
10. Transfer set less Luer-lok (Figure 2)
11. IV bag suspended from spring scale

For field use, the following items should be included in each kit:

1. Small butane torch
2. Lighter
3. Knife or scissors
4. 4" flat-nose pliers
5. Packages of sodium bisulfite (0.6 g and 10 g)

The number of First Need® filters, sterilizing filters, transfer sets and IV bags included in the kit will depend upon the mission.

RECOMMENDATIONS

At this time, circumstances favor the S06 system. Besides being smaller and lighter, all components (except ion exchange) are immediately available off-the-shelf. However, in the event that the Survivor™ A90 becomes readily available under the same scenario as projected for use of the fluidmaker, or if its greater size and weight are acceptable, then the SA90 system should be considered favorably for its high production rate. Preliminary operational instructions for S06 system are presented in Appendix J.

Regardless of the system selected, it is recommended that the ion exchange unit be omitted until a unit suitable for field use can be located or developed. Although the water produced will not then meet USPXXI criteria for Sterile WFI, USABRDL believes that it will be safe for the intended use.

It is recommended that the fluidmaker(s) be made field-ready, principally by devising pressure-secure, quick-release connectors between tubing and components and between tubing of different sizes.

It is recommended that efforts be made to identify or develop (1) a small ion exchange unit suitable for field use and (2) a sterilizing filter and transfer set suitable for System A90.

Figure 5. SA90 System on Test Stand.

REFERENCES

1. Memorandum, U.S. Army Medical Research and Development Command, SGRD-PLB, 21 April 1988, subject: IV Fluidmaker.

2. U.S. Army. 1987. Operator's and Organizational Maintenance Manual, Resuscitation Fluids Production System (REFLUPS), Advanced Development Model (ADM). Draft. Sterimatics Co., Bedford, MA.

3. The United States Pharmacopeia, Twenty-First Revision. 1985. United States Pharmacopeial Convention, Inc., Rockville, MD.

4. U.S. Army. 1986. Occupational and Environmental Health. Sanitary Control and Surveillance of Field Water Supplies. TB MED 577. Headquarters, Dept. of the Army, Washington, DC.

5. Duncan, J.B. 1985. The Field Production of Water for Injection. Technical Report 8502, AD A168145. U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD.

6. Dan Dwyer, Nalge Company, personal communication, November 1988.

7. Kenneth Broadwell, MD, NASA Johnson Space Center, personal communication, July 1988.

APPENDIX A

PURIFIED WATER[3]

Purified water is obtained by distillation, ion-exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the regulations of the federal Environmental Protection Agency with respect to drinking water. It contains no added substance. [Note -- Purified water is intended for use as an ingredient in the preparation of compendial dosage forms. Where used for sterile dosage forms, other than for parenteral administration, process the article to meet the requirements under Sterility Tests <71>, or first render the Purified Water sterile and thereafter protect it from microbial contamination. Do not use Purified Water in preparations intended for parenteral administration. For such purposes, use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection.]

Packaging and storage -- Where packaged, preserve in tight containers.
Labeling -- Where packaged, label it to indicate the method of preparation.
pH <791>: between 5.0 and 7.0, determined potentiometrically in a solution prepared by the addition of 0.3 mL of saturated potassium chloride solution to 100 mL of test specimen.
Chloride -- To 100 mL add 5 drops of nitric acid and 1 mL of silver nitrate TS: no opalescence is produced.
Sulfate -- To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.
Ammonia -- To 100 mL add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 ug of added NH_3 in High-purity Water (see under Reagents in Containers <661>) [0.3 ppm].
Calcium -- To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.
Carbon dioxide -- To 25 mL and 25 mL of calcium hydroxide TS: no turbidity is produced.
Heavy metals -- Adjust 40 mL of Purified Water with 1 N acetic acid to a pH of 3.0 to 4.0 (using short-range pH indicator paper), add 10 mL of freshly prepared hydrogen sulfide TS, and allow the liquid to stand for 10 minutes: the color of the liquid, when viewed downward over a white surface, is not darker than the color of a mixture of 50 mL of the same Purified Water with the same amount of 1 N acetic acid as was added to the test specimen, matched color-comparison tubes being used for comparison.
Oxidizable substances -- To 100 mL add 10 ml of 2 N sulfuric acid, and heat to boiling. Add 0.1 mL of 0.1 N potassium permanganate, and boil for 10 minutes: the pink color does not completely disappear.
Total solids -- Evaporate 100 mL on a steam bath to dryness, and dry the residue at 105° for 1 hour: not more than 1 mg of residue remains (0.001%).
Bacteriological purity -- It complies with the federal Environmental Protection Agency regulations for drinking water with respect to bacteriological purity (40 CFR 141.14; 141.21).

APPENDIX B

WATER FOR INJECTION[3]

Water for Injection is water purified by distillation or by reverse osmosis. It contains no added substances. [Note -- Water for Injection is intended for use as a solvent for preparation of parenteral solutions. Where used for the preparation of parenteral solutions subject to final sterilization, use suitable means to minimize microbial growth, or first render the water for Injection sterile and thereafter protect it from microbial contamination. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and thereafter protect it from microbial contamination.]

Packaging and storage -- Where packaged, preserve in tight containers. Where packaged, it may be stored at a temperature below or above the range in which microbial growth occurs.
Reference standard -- USP Endotoxin Reference Standard.
Bacterial endotoxins -- When tested as directed under Bacterial Endotoxins Tests <85>, the USP Endotoxin RS being used, it contains not more than 0.25 USP Endotoxin Unit per mL.
Particulate matter <788>: meets the requirements under Small-volume Injections.
Other requirements -- It meets the requirements of the tests under Purified Water, with the exception of the test for **Bacteriological purity.**

APPENDIX C

STERILE WATER FOR INJECTION[3]

Sterile Water for Injection is Water for Injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Packaging and storage -- Preserve in single-dose containers, preferably of Type I or Type II glass, of not larger than 1-liter size.
Labeling -- Label it to indicate that no antimicrobial or other substance has been added, and that it is no suitable for intravascular injection without its first having been made appropriately isotonic by the addition of a suitable solute.
Reference standard -- USP Endotoxin Reference Standard.
Bacterial endotoxins -- When tested as directed under Bacterial Endotoxins Test <85>, the USP Endotoxin RS being used, it contains not more than 0.25 USP Endotoxin Unit per mL.
Sterility -- It meets the requirements under Sterility Tests <71>.
Ammonia -- For Sterile Water for Injection in glass containers holding a volume up to 50 mL, dilute 50 mL with 50 mL of High-purity Water (see Reagents under Containers <661>), and use this dilution as the test solution; where larger volumes are held, use 100 mL of Sterile Water for Injection as the test solution. To 100 mL of the test solution add 2 mL of mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 ug of added NH_3 in High-purity Water (see Reagents under Containers <661>)(0.6 ppm for Sterile Water for Injection packaged in volumes up to 50 mL in containers; 0.3 ppm for larger volumes).
Chloride -- To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of High-purity Water (see under Reagents in Containers <661>) containing 10 ug of Cl^- (0.5 ppm), viewed downward over a dark surface with light entering the tubes from the sides.
Oxidizable substances -- To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Injection in containers holding a volume up to 50 mL, add 0.4 mL of 0.1 N potassium permanganate, and boil for 5 minutes; for larger volumes, add 0.2 mL of 0.1 N potassium permanganate, and boil for 5 minutes: the pink color does not completely disappear.
Total solids -- Proceed as directed in the test for Total solids under Purified Water. The following limits apply for Sterile Water for Injection in glass containers holding up to 30 mL, 0.004%; from 30 mL up to 100 mL, 0.003%, and for larger volumes, 0.002%.
Other requirements -- It meets the requirements of the tests for pH, Sulfate, Calcium, Carbon dioxide, and Heavy metals under Purified Water.

APPENDIX D

BACTERIOSTATIC WATER FOR INJECTION[3]

Bacteriostatic water for Injection is Sterile Water for Injection containing one or more suitable antimicrobial agents. [Note -- Use Bacteriostatic Water for Injection with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.]

Packaging and storage -- Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type II glass, of not larger than 30-mL size.
Labeling -- Label it to indicate the name(s) and proportion(s) of the added antimicrobial agent(s). Label it also to include the statement, "NOT FOR USE IN NEWBORNS," in boldface capital letters, on the label immediately under the official name, printed in a contrasting color, preferably red. Alternatively, the statement may be placed prominently elsewhere on the label if the statement is enclosed within a box.
Reference standard -- USP Endotoxin Reference Standard.
Antimicrobial agent(s) -- It meets the requirements under Antimicrobial Preservatives -- Effectiveness <51>, and meets the labeled claim for content of the antimicrobial agent(s), as determined by the method set forth under Antimicrobial Agents -- Content <341>.
Bacterial endotoxins -- When tested as directed under Bacterial Endotoxins Test <85>, the USP Endotoxin RS being used, it contains not more than 0.5 USP Endotoxin Unit per mL.
Sterility -- It meets the requirements under Sterility Tests <71>.
pH <791>: between 4.5 and 7.0, determined potentiometrically in a solution prepared by addition of 0.30 mL of saturated potassium chloride solution to 100 mL of test specimen.
Particulate matter <788>: meets the requirements under Small-volume Injections.
Other requirements -- It meets the requirements of the tests for Sulfate, Calcium, Carbon dioxide, and Heavy metals under Sterile Water for Injection.

APPENDIX F

TEST SOLUTIONS (TS)[3]

Ammonium Oxalate TS -- Dissolve 3.5 g of ammonium oxalate [$(NH_4)_2C_2O_4.H_2O$] in water to make 100 mL.

Barium Chloride TS -- Dissolve 12 g of barium chloride [$BaCl_2.2H_2O$] in water to make 100 mL.

Calcium Hydroxide TS -- Use Calcium Hydroxide Topical Solution [a solution containing, in each 100 mL, not less than 140 mg of $Ca(OH)_2$].

Hydrogen Sulfide TS -- A saturated solution of hydrogen sulfide made by passing H_2S into cold water. Store it in a small, dark amber-colored bottles, filled nearly to the top. It is unsuitable unless it possesses a strong odor of H_2S, and unless it produces at once a copious precipitate of sulfur when added to an equal volume of ferric chloride TS. Store it in a cold, dark place.

Mercuric-Potassium Iodide TS, Alkaline (Nessler's Reagent) -- Dissolve 10 g of potassium iodide [KI] in 10 mL of water, and add slowly, with stirring, a saturated solution of mercuric chloride [$HgCl_2$] until a slight red precipitate remains undissolved. To this mixture add an ice-cold solution of 30 g of potassium hydroxide [KOH] in 60 mL of water, then add 1 mL more of the saturated solution of mercuric chloride. Dilute with water to 200 mL. Allow the precipitate to settle and draw off the clear liquid. A 2-mL portion of this reagent, when added to 100 mL of a 1 in 300,000 of ammonium chloride [NH_4Cl] in ammonia-free water produces at once a yellowish brown color.

Silver Nitrate TS -- Use 0.1 N silver nitrate.

APPENDIX F

FIRST NEED® BACKWASH PROCEDURE

1. Disconnect the pump from the canister and pump a little sclution* through the open end of the assembly.

2. Place entire pump in solution and allow to stand for about five minutes and then rinse thoroughly in clean water.

3. Connect pump to the end of the canister marked "OUT", being sure the spring clip is in place on the hose, and pump a couple pints of solution slowly and steadily through the canister in a reverse direction. Increase the rate of pumping during the last few strokes.

4. Reconnect the pump hose to the end of the canister marked "IN", again being sure the spring clip is in place.

5. Again, rinse the unit with pure water to be sure all the bleach solution is out of the canister and the pump.

6. The backwashed First Need is now ready for additional service.

* The manufacturer recommends 1/4 teaspoon of household bleach per gallon [about 30 mg/L of free available chlorine].

APPENDIX G

SURVIVOR™ 06 STORAGE INSTRUCTIONS (7 days or longer)

After the unit has been operated for any length of time and before it is stored again, the unit should be flushed with biocide to prevent growth of bacteria according to the following procedure:

a. Prepare a biocide solution containing one quart of clean fresh water and one package of biocide powder [10 g of sodium bisulfite].

b. Turn the desalinator [Survivor™ 06] upside down and pump it with the intake strainer out of the water until water stops coming from the reject tube. This fills it with air.

c. Place the intake strainer in the biocide solution and pump for approximately 100 strokes. Once the unit is flushed, pump the unit with air again until water stops coming from the reject tube.

d. Store the unit in a cool place, but do not allow it to freeze.

e. This procedure should be repeated at least once a year if the desalinator is not used. If the desalinator is being used once a week the biocide procedure is not required.

APPENDIX H

SURVIVOR™ A90 STORAGE INSTRUCTIONS (4 hours or longer)

To store the unit after the desired amount of water is obtained, remove the prefilter from the water. Pump the unit (with air) for ten strokes to depressurize it.

Unscrew the membrane housing [from the pump body] and pour one package of biocide [10 g of sodium bisulfite] onto the top of the membrane.

Reassemble the unit. Place the prefilter into the water and pump the unit for 30 strokes.

Remove the prefilter from the water and pump the unit (with air) for 10 strokes to depressurize it.

Disassemble the unit, being careful not to get any dirt, sand or debris into the pump body or pump membrane housing. Screw the dust covers back onto the membrane housing and pump body.

APPENDIX I

DATA TABLES

TABLE II. SUMMARY OF ENDOTOXIN TESTS

Sample no.	Source	Treatment				Endotoxin eu/ml
		RO	IE	First Need[R] filter[a]	Sterilizing filter	
1	Fort Detrick tapwater	--	--	--	--	14.2
2	Fort Detrick tapwater	--	--	--	--	2.2
3.	REFLUPS WFI	--	--	--	--	<0.06
4.	Fort Detrick tapwater	--	--	--	--	8.94
5.	Frederick tapwater	--	--	--	--	8.3
6.	Post pond water	--	--	--	--	143.7
7.	Tapwater (Sample 8)	--	--	#1	--	<0.06
8.	Fort Detrick tapwater	--	--	--	--	7.3
9.	Tapwater (Sample 5)	--	--	#1	--	<0.06
10.	Post pond water	--	--	--	--	106.1
11.	Pond water (Sample 10)			#1	--	<0.06
12.	REFLUPS water, bulk[b]	--	--	--	--	68.0
13.	REFLUPS (Sample 12)	--	--	#1 f	--	<0.06
14.	IE water	--	yes	--	--	7.12
15.	IE water (Sample 14)	--	--	#1 f	--	<0.06
16.	Fort Detrick tapwater	--	--	--	--	10.2
17.	Tapwater (S16, 1st L)	--	--	#2	--	<0.06
18.	Tapwater (S16, 12th L)	--	--	#2	--	<0.06
19.	Tapwater (S16, 25th L)	--	--	#2	--	<0.06
20.	Tapwater (S16, 50th L)	--	--	#2	--	<0.06
21.	Fort Detrick tapwater[b]	--	--	--	--	75.5

TABLE 11 (Continued)

22.	Tapwater (Sample 21)	S06	--	--	--	<0.06
23.	Fort Detrick tapwater[b]	--	--	--	--	138.8
24.	Tapwater (Sample 23)	S06	--	#2[c]	--	0.55
25.	Tapwater (Sample 23)	SA90	--	--	--	6.7
26.	REFLUPS WFI	--	--	--	--	<0.06
27.	Fort Detrick tapwater[b]	--	--	--	--	382.3
28.	Tapwater (Sample 27)	S06	--	#1 d	--	0.07
29.	Tapwater (Sample 27)	SA90	--	#1 d	--	<0.06
30.	Fort Detrick tapwater[b]	--	--	--	--	123.3
31.	Tapwater (Sample 30)	--	--	--	7.5 cm	18.2
32.	Tapwater (Sample 30)	S06	--	#1 d[c]	--	28.8
33.	Tapwater (Sample 30)	S06	--	#2 d[c]	--	53.3
34.	Tapwater (Sample 30)	S06	--	#3	--	<0.06
35.	Sample 28[d]	--	--	--	--	111.2
36.	Tapwater (Sample 39)	--	--	#1[c]	--	41.3
37.	Tapwater (Sample 39)	--	--	#2 df	--	0.93
38.	Tapwater (Sample 39)	--	--	#3 a	--	0.46
39.	Fort Detrick tapwater[b]	--	--	--	--	149.0
40.	Tapwater (Sample 39)	--	--	#1 f	--	36.3
41.	Tapwater (Sample 39)	--	--	#3 af	--	0.14
42.	Water (Sample 44)	S06	yes	#2 dfa	25 mm	<0.06
43.	Water (Sample 44)	SA90	yes	#2 dfa	7.5 cm	<0.06
44.	Worst case water[b,e]	--	--	--	--	38.1
45.	Tapwater (Sample 27)[d,f]	SA90	--	#2 df	--	112.0

TABLE II. (Continued)

46.	Tapwater (Sample 30)	S06	--	--	7.5 cm	<0.06
47.	ROWPU water[b,e]	S06	yes	#4	25 mm	<0.06
48.	ROWPU water[b,e]	SA90	yes	#4	7.5 cm	<0.06
49.	Sample 42[d]	--	--	--	--	<0.06
50.	Sample 43[d]	--	--	--	--	<0.06
51.	Sample 47[d]	--	--	--	--	<0.06
52.	Sample 48[d]	--	--	--	--	<0.06
53.	ROWPU water[b,e,f]	SA90	yes	#4	7.5 cm	<0.06

a. Letters d, f and a describe the treatment of the First Need® filters before use; d means the filter was disinfected according to Appendix F; f means the filter was additionally flushed with at least 0.5 L water; a means the filter was autoclaved. No letter following the filter number means that the filter was newly opened or that less than one hour had elapsed since previous use, unless otherwise indicated.
b. Water sample stood for more than 24 hours after dechlorination before use.
c. Wetted First Need® filter was stored for at least 24 hours before use following last treatment.
d. Sample was bagged and allowed to stand for at least 7 days before testing.
e. For description of worst case and ROWPU waters see Table 4.
f. IV bag contained 50 mL of lactated Ringer's concentrate.

TABLE I2. SUMMARY OF STERILITY TESTS

Sample	Source	Test results colonies/mL
M1	Sample 32, Table I1	10 - 20,000 (gram negative)
M2	Sample 33, Table I1	20 - 30,000 (gram negative)
M3	Sample 34, Table I1	No growth in 48 hours
M4	Sample 35, Table I1	>100,000 (gram negative)
M5	Sample 29, Table I1[a]	>100,000 (gram negative)
M6	Survivor™ 06 + sterilizing filter	No growth in 48 hours
M7	Sample 36, Table I1	3 - 5,000 (gram negative)
M8	Sample 37, Table I1	No growth in 48 hours
M9	Sample 38, Table I1	No growth in 48 hours
M10	Sample M6[a]	No growth in 48 hours
M11	Sample M6[b]	No growth in 48 hours
M12	Sample 45, Table I1	10^4 - 10^6 (bacillus)
M13	Sample 42, Table I1	No growth in 48 hours
M14	Sample 43, Table I1	No growth in 48 hours
M15	(no sample)	
M16	Sample 47, Table I1	No growth in 48 hours
M17	Sample 48, Table I1	No growth in 48 hours
M18	Sample 49, Table I1	No growth in 48 hours
M19	Sample 50, Table I1	No growth in 48 hours
M20	Sample 51, Table I1	No growth in 48 hours

TABLE I2. (Continued)

M21	Sample 52, Table I1	1 (Staphylococcus)[c]
M22	Sample 53, Table I1	No growth in 48 hours
M23	Repeat of M21	1 (staphylococcus)[c]

a. Sample was bagged and allowed to stand two weeks before sampling.
b. Sample was bagged and allowed to stand two months before sampling.
c. Assumed to be external contamination incidental to sampling and testing of M21.

TABLE I3. TESTS FOR USPXXI CHEMICAL STANDARDS[a]

Sample	Cl^- mg/L	$SO_4^=$ mg/L	NH_3 mg/L	Ca^{2+}	CO_2[b]	Heavy metals	pH[c]
Worst case water	580	420	17	+	+	-	
System 06 w/o IE	1.8	10	<1	-	+	-	
System A90 w/o IE	3.7	31	3	-	+	-	
System 06 with IE	0.1	tr[d]	<1	-	+	-	
System A90 with IE	0.06	ND[e]	<1	-	+	-	
ROWPU water	405	52.8	<1	+	+	-	
System 06 w/o IE	1.3	8.99	<1	-	+	-	
System A90 w/o IE	3.9	15.3	<1	-	+	-	
System 06 with IE	0.04	ND[e]	<1	-	+	-	
System A90 with IE	0.1	tr[d]	<1	-	+	-	5.85

a. Results indicated as + or - were performed according to USP procedures, IAW Appendix A.
b. Samples believed to be contaminated with carbon dioxide during collection and/or testing.
c. One sample tested only
d. Trace: below quantitation limit
e. None detected

APPENDIX J

PROVISIONAL OPERATING INSTRUCTIONS FOR SOS SYSTEM

1. Prepare potable water source, and test for free available chlorine (FAC) using a test kit such as the Water Quality Analysis Set - Preventive Medicine (NSN LIN Y36849). For water containing 5 mg/L or less of FAC, add 1 unit (0.56 g) of sodium bisulfite to 5 gal; for water containing more than 5 mg/L of FAC, add 2 units. Mix well.

2. Place inlet filter of RO unit into water source. Pump at a rate of about 100 upstrokes and down strokes per minute until water is moving freely in the outlet tube.

3. Connect RO outlet tube to First Need^{R} inlet tube (large bore, 2-3", Tygon^{R}) with stainless steel adapter. If system contains an ion exchange (IE) unit, follow instructions 3a-3b; otherwise go directly to 4.

3a. Connect RO outlet tube to IE unit inlet tube (large bore, 2-3", Tygon^{R}) with stainless steel adapter. Mount IE column in vertical position with arrow pointing up.

3b. Connect IE outlet tube (large bore, 10-12", Tygon^{R}) to First Need^{R} filter inlet.

4. Open package containing new First Need^{R} filter and attach inlet tube.

5. Pump at least 100 mL of water through the system and discard the water produced. This will take about 5 minutes.

6. Attach outlet tube (large bore, 2-3", Tygon^{R}), adapter and small bore tube to First Need^{R} filter.

7. Open packages containing sterilizing filter and transfer set. Remove protective cover from Luer-Lok end of transfer set and attach sterilizing filter.

8. Connect sterilizing filter to First Need^{R} filter by means of the small bore tube.

9. Hang spring scale from suitable support and suspend IV bag from scale.

10. Remove caps from IV bag spike port and spike pin end of transfer set and force spike pin into spike port as far as it will go.

11. Suspend First Need^{R} filter from support at level such that the IV bag hangs free.

12. Pump RO unit until scale reads 1025 to 1050 g. This will take 45 to 50 minutes.

13. Seal transfer tube with slotted plastic tag. Detach sterilizing filter from small bore tube. (Alternatively, detach transfer set from final filter, which can be reused.)

14. To fill more bags, return to step 7. After 25 bags return to step 4. If feeding from 5 gal container, discard remaining water after making 10 liters of WFI and dechlorinate a fresh 5 gal batch.

15. When finished producing water, discard First Need^{R} filter.

APPENDIX K

GLOSSARY OF TERMS

USABRDL	U.S. Army Biomedical Research and Development Laboratory
EPA	U.S. Environmental Protection Agency
eu	endotoxin units
FAC	free available chlorine
FDA	U.S. Food and Drug Administration
i.d.	inner diameter
IE	ion exchange
IV	intravenous
REFLUPS	Resuscitation Fluids Production System
RO	reverse osmosis
ROWPU	Reverse Osmosis Water Purification Unit
SA90	Survivor™ A90
SO6	Survivor™ 06
spm	strokes per minute
TS	Test Solution (see Appendix E)
USP	U.S. Pharmacopeia
WFI	Water for Injection

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