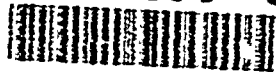


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IV Fluidmakers: Preparation of Sterile Water for Injection In a Field Setting

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ABSTRACT: Two approaches have been investigated for generating USP sterile, pyrogen-free water for injection (WFI) from potable water in the field. The first approach utilizes reverse osmosis (RO), ion exchange, a solid matrix filter containing activated carbon and zeta adsorbent, a final 0.2 μm pore size sterilizing filter and a device for transferring the WFI to an IV bag; prototype systems based on three different hand-operated RO units weigh 1.5–3.5 kg and are capable of producing WFI at rates of 1–10 L/hr. Parenteral solutions were made by adding WFI to an IV bag containing concentrated Ringer's lactate. The second approach, still in the breadboard stage, is similar but utilizes a larger ion exchange column in place of the RO unit and a multiport distribution head to fill a set of 18 1-L IV bags. This system, considered to be disposable, is capable of generating water of WFI quality at a fill rate of 0.5 L/min from a pressurized source.

Introduction

The U.S. Army has recognized a need to manufacture intravenous (IV) fluids under conditions where resupply of medical items is uncertain, and has called for development of a device to produce sterile water free of pyrogens (i.e., bacterial endotoxins) from a potable source. The product water is to be introduced directly into one-liter bags containing concentrated parenteral salts so as to make solutions suitable for IV infusion. Two configurations are envisioned: one, a hand-operated device capable of producing a minimum of 1 L/hr and small enough to be carried as part of the aidman's kit; the other, a disposable system capable of producing at least 50 L in two hours from a pressurized source and occupying no more than two cubic feet. At present, the smallest system for production of IV fluids projected to be available in the field is the Resuscitation Fluids Production System (REFLUPS), a 100 L/hr, desk-size device with substantial water and power requirements, employing reverse osmosis (RO) technology (1). A 2-kg device developed for the National Aeronautics and Space Administration (NASA), capable of producing 12 L of sterile water for injection, is based principally on ion exchange and ultrafiltration (2, 3).

We perceive that the target for the devices in question is sterile water for injection (WFI), as defined by USP XXII (4). 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) criteria, which specify maximum contam-

inant levels for a large number of organic and inorganic chemicals commonly found in water supplies. Army field potable water standards (Table I) are necessarily less stringent (5). For example, 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 by two-fold or more. For this reason, tests have been carried out with waters that would not meet EPA source criteria, and use of the term "WFI" in this paper does not address these criteria. We believe that use of potable water meeting Army standards will not compromise the safety of the product, while recognizing that this product will not qualify as USP WFI.

Materials

Reverse Osmosis Units

Specifications for three hand-operated RO units (Recovery Engineering, Inc., Minneapolis, MN) are presented in Table II. The smallest is the Survivor[™] 06 (S06). The Survivor[™] 35 (S35) is identical in configuration to the Survivor[™] A90 (SA90) but cannot be disassembled for storage. All three units use FilmTec[®] FT30 spiral-wound, thin-film composite membranes which provide 98% sodium chloride rejection at 225 psi (1600 kPa), 25°C and pH 7. Connections between all units used in these tests were made with Tygon[®] tubing of appropriate size. The RO membranes were protected from bacterial degradation by treatment with sodium bisulfite when not in use.

Ion Exchange (IE) Columns

Barnstead/Thermolyne Corp. (Dubuque, IA) D8902 IE columns containing 1.4 kg of strong acid/strong base

Received April 30, 1992. Accepted for publication September 23, 1992.

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TABLE I
Army Quality Standards for Potable Water^a

Constituent	Short Term Standard (7 Days or Less)	Long Term Standard (More than 7 Days)
Physical		
Color	—	50 units
Turbidity	Reasonably clear	5 units
Chemical		
Arsenic	2.0 mg/L	0.2 mg/L
Chloride	—	600 mg/L
Cyanide	20 mg/L	2 mg/L
Magnesium	—	150 mg/L
Sulfate	—	400 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

^a Reference 5.

mixed resin were utilized where large columns were required. For RO-based systems, a small ion exchange column was fabricated from a 15 cm length of PVC tubing of 1.75 cm inner diameter. The PVC tube was packed with resin from a fresh Barnstead D8902 cartridge, retained at each end with foam plastic filter material taken from the same cartridge.

Water Purification Filters

The First Need® water purification filter (General Ecology, Inc, Lionville, PA) is a plastic-encased, solid matrix cylindrical filter containing a proprietary mix of activated carbon and positive and negative zeta potential adsorbents; it is rated by the manufacturer at 0.1 micron nominal and 0.4 micron absolute and produces 400 to 500 mL/min at the recommended pumping rate. Total weight is 200 g, and water holdup is 20 to 30 mL. Seagull® filter cartridges (type RS1-SG), acquired from the same company, are of similar material. Each cartridge weighs 480 g, and the stainless steel housing weighs 725 g.

Sterilization Filters

The following filters, 0.2–0.22 µm pore size, were used: for the fluidmaker employing the S06, 25 mm cellulose acetate syringe filters, (Nalge Company, Rochester, NY); for the SA35, Cameo IV presterilized nylon syringe filters (Micron Separations Inc., Westborough, MA); for the SA90, 7.5 cm cellulose acetate REFLUPS filters (Abbott Laboratories, North Chicago, IL). For most tests the filter was connected on the downstream side to a REFLUPS concentrate transfer set (Abbott Laboratories), a 28 cm long, 4 mm diameter Tygon® tube with a spike pin at one end and a Luer-Lok® syringe connector at the other, thus providing a means for sterile transfer of the WFI to an IV bag.

TABLE II
Reverse Osmosis Units

Model	Length (cm)	Wt (kg)	Production Rate (mL/min)
Survivor® 06	20	1.1	20–25
Survivor® A90	38 ^a	3.2	200
Survivor® 35	57	3.2	100

^a Disassembleo.

Fine Particle Filters

A Whatman® (Maidstone, Eng.) Gamma-12 filter unit, fitted with the grade 20 filter tube (0.2 µm rating) was used for initial tests of the disposable fluidmaker. The tubes were autoclaved (121° for 30 min) before use. For all subsequent tests, a Filterite (Timonium, MD) UIA4A spiral wound string filter cartridge was used. The stainless steel and brass filter cartridge housing (Model 910562-000) weighed 2.5 g with fittings; the spiral wound string filter cartridges, which were autoclaved (121° for 30 min) before use, had a dry weight of 40 g each.

Receiver Set

REFLUPS receiver sets (No. 15257, Abbott Laboratories) were used for all tests of the disposable fluidmaker. Each sterile set consisted of 18 1-L IV bags, a 7.5 cm diameter, 0.22 µm pore size sterilizing filter and a docking device, all contained in a plastic wrapper. The dry weight of each 18 1-L bag receiver set was 1.2 kg.

Distribution Head

An indexed, 19-port valve constructed from stainless steel and Teflon® weighed 1.54 kg and was designed to accept the REFLUPS receiver sets (Fig. 1).

Parenterals

Lactated Ringer's concentrate (20:1) was manufactured by Abbott Laboratories for Sterimatics Corporation.

Methods

Challenge Waters

Various water sources were used to challenge the fluidmaker and its individual components. Total dissolved solid (TDS) levels from 600 to 1500 mg/L were achieved by amending Fort Detrick tapwater with sodium chloride and sodium sulfate. Source water was 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. The dechlorinated water was additionally allowed to stand for 1–2 weeks to build up naturally occurring bacteria and endotoxins.

Test Procedures

Water treatment components were tested individually and in combination. For the RO system, the treatment

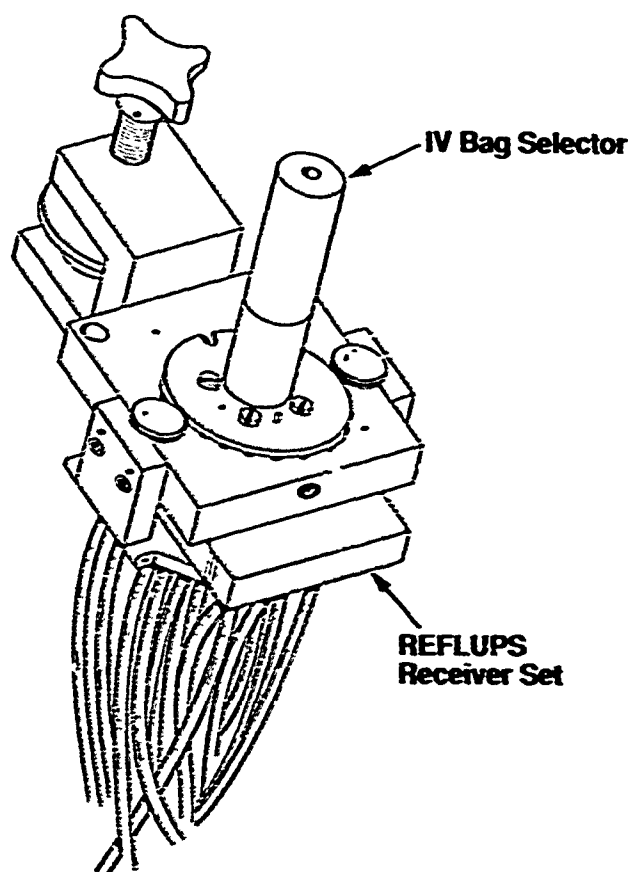


Figure 1—Distribution head for bagging WFI from disposable system.

train (Fig. 2) consisted of an RO unit, IE column (omitted for some tests), water purification filter, sterilizing filter, and transfer set with IV bag (omitted for some tests). The transfer set and sterilizing filter were replaced with each IV bag filled; both filters were replaced whenever there was a break in water production without bagging (i.e., every 5–20 L). IV bags were heat-sealed until sampling or sealed temporarily with a slotted plastic tab. For the disposable system, the treatment train (Fig. 3) consisted of a peristaltic pump, ion exchange column, water purification filter, fine particle filter, and receiver set with distribution head. Filling

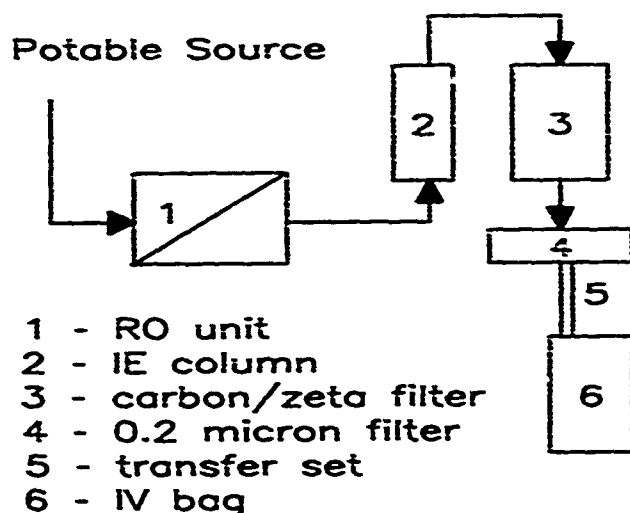


Figure 2—Schematic of water purifier based on reverse osmosis.

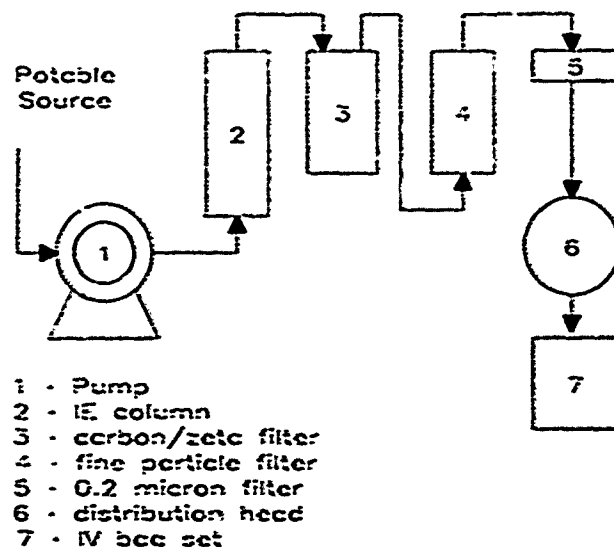


Figure 3—Schematic of disposable water purifier.

tubes were temporarily sealed with a pressure clamp after all bags were filled.

Analytical Methods

The samples for bacteriological and Limulus amoebocyte lysate (LAL) testing were collected in sterile Falcon® 2027 screw cap tubes. In general, a single sample was collected for each liter of product water. The Pyrogen Plus® LAL gel test kit was supplied by Whittaker Bioproducts, Inc., Walkersville, MD. Using the manufacturer's test procedure, the sensitivity was 0.06 eu/mL; triplicate tests were conducted for all samples. Bacterial testing was conducted using prepared BBL® sheep blood media (Becton Dickinson Microbiological Systems, Cockeysville, MD). Plates were incubated at 37° for 48 hours, and in most cases duplicate tests were performed. Conductivity was determined using either a VWR Scientific (Medix, PA) portable conductivity meter or a Presto-Tek® conductivity meter (Preston Scientific, Anaheim, CA). Chloride (detection limit <0.1 mg/L), sulfate (detection limit <0.1 mg/L) and ammonium (detection limit <1 mg/L) ions were determined by ion chromatography (Dionex 4000 series, Sunnyvale, CA) (6). Other water quality parameters were determined by procedures given in USP XXII (4).

Results and Discussion

RO-Based Systems

The prototype fluidmaker developed in this study is based on RO technology. Known to be effective in removal of most dissolved organic and inorganic impurities and microorganisms, including viruses (7). An ion exchange unit is required to further reduce dissolved salts. Depyrogenation of WFI is commonly achieved by ultrafiltration; however, this would have required incorporation of an additional pump into the system, since the hand-operated RO units employed are designed to operate with very little net increase in water pressure. Instead, a water purification filter, such as those used by campers or for end-of-pipe treatment in households, is

the third main unit of the system. These filters commonly contain activated carbon, which is effective in trapping many low molecular weight organic chemicals not removed by RO, and they also remove pathogens and pyrogens. A sterilizing filter of 0.2–0.22 μm limiting pore size is the final element in the treatment train (Fig. 2). Various considerations dictated the use of off-the-shelf items where available.

Three hand-operated RO units were investigated: the Survivor[™] 06 (S06) with its associated components is small enough to fit into a protective mask container (a desired constraint); the Survivor[™] A90 (SA90) and Survivor[™] 35 (S35) are not. Polyamide membranes of the type used generally remove 98% of dissolved sodium chloride, and all RO units achieved this removal. The small ion exchange column fabricated for this study has an exchange capacity of 1 g of sodium chloride, sufficient to demineralize 100 L of water containing 10 mg/L of sodium chloride to a specific resistivity ≥ 1 megohm-cm. (This column must be supported in an upright position to avoid flow channeling; however, the Army has developed under contract several small ion exchange units that can be operated in any orientation.) Sterile, pyrogen-free water (but not WFI) was prepared from various water sources using only a First Need[®] solid matrix water purification filter. Pond water and other waters with pyrogenicity exceeding 100 endotoxin units/mL (eu/mL) were tested, but in no instance did pyrogens exceed the detection limit of 0.06 eu/mL, in product water from a fresh First Need[®] filter, much less the USP XXII standard of 0.25 eu/mL.

All three RO-based systems consistently provided sterile, pyrogen-free water; when the small ion exchange unit was included in initial studies, the product water was equivalent in all parameters measured to USP XXII Sterile WFI (Table III) (8, 9). Samples bagged and stored for seven days (with or without IV concentrate) remained sterile and pyrogen-free. However, in an extended series of tests, with up to 50 L of water collected from each of five S06- and S35-based systems, product water exceeded the USP XXII chloride limit (0.5 mg/L), whether or not an ion exchange unit was employed, due in part to leaching of salt from the First Need[®] filter matrix (10, 11). Future systems will have an ion exchange unit with high purity resin following, rather than preceding, this filter. (Commercial grades of ion exchange resins may be contaminated with bacteria and

leach endotoxins.) A second concern with the First Need[®] filter is discharge of small quantities of fine particles, which eventually plug the sterilizing filter. For future systems the sterilizing filter will be protected by a disposable fine particle filter, further discussed below.

Wetted components of the fluidmakers, when exposed to air, were rapidly colonized by mixed gram-negative bacteria, thereby compromising both pyrogenicity and sterility. Field sanitization of the system is not practical. Because there are no suitable field tests to assure that the product is pyrogen free and sterile, quality must be assured by system design and operating procedures. Thus, to assure production of sterile, pyrogen-free water the sterilizing filter, transfer set and IV bag should be replaced as a unit after each liter of WFI is produced, and the water purification filter and ion exchange unit should be discarded after every 25 L, or whenever production of WFI is discontinued.

Disposable System

The disposable system was conceived with the thought that the high production requirement and the uncertainty of an external power supply rule out the use of reverse osmosis; on the other hand, the 50-L limit and system disposability permit the use of disposable ion exchange columns for total salt and heavy metals removal. (Neither this system nor the NASA system mentioned above can produce WFI according to USP XXII, which specifies that WFI be generated by RO or distillation) (4). The studies reported above showed that pyrogen and pathogen removal can be achieved through use of a solid matrix activated carbon and zeta adsorbent filter of the kind used for household tapwater purification. The breadboard treatment system devised for the present study consisted, in series, of a strong acid/strong base mixed resin ion exchange column, carbon filter, fine particle filter and a 0.2 μm sterilizing filter (Fig. 3). For product collection we utilized an IS-bag transfer set originally developed for RIFLUPS; a hand-operated, multiport indexed valve directed fluid flow (Fig. 1). Fluid transfer to individual IV bags was readily achieved, and no leakage occurred. Feed-water flow was maintained using a peristaltic pump. The combined weight of all components (except the pump) was less than 10 kg, and the complete device with three bag sets (total capacity 54 L) occupied no more than two cubic feet, as required.

TABLE III
Performance of Fluidmakers^{a,b}

Sample	Cl ⁻ (mg/L)	SO ₄ ²⁻ (mg/L)	Ca ²⁺ (mg/L)	NH ₄ ⁺ (mg/L)	Pyrogens (eu/mL)	Sterility ^c (colonies/mL)
Challenge water	550.0	420	ca. 36	11	38.1	< 10,000
S06 w/o IE	1.5	10	MI	< 1	NM	NM
SA90 w/o IE	3.7	31	MI	< 1	NM	NM
S06 with IE	0.1	BD	MI	< 1	< 0.06	No growth
SA90 with IE	0.06	BD	MI	< 1	< 0.06	No growth

^a Complete data are provided in Ref. 5.

^b IE = ion exchange, NM = not measured, BD = below detection limit, MI = meets limit for calcium according to USP XXII, eu = endotoxin units.

^c Growth 48 hours after plating.

The breadboard test system produced sterile, pyrogen-free water at a rate of 0.5 L/min at a feed pressure of one atmosphere from challenge water containing levels of bacteria ($\geq 11,000$ colony forming units (cfu)/mL) and pyrogens (≥ 60 eu/mL) much higher than would be expected for any potable source (12). However, endotoxin breakthrough at the detection limit with the Seagull® RS1-SG filter occurred at 38 L of product from a challenge greater than 100 eu/mL. To assure 54 L of pyrogen-free water it may be necessary to install a new filter for each 18 L bag set, or to substitute the larger RS2-SG filter (700 g vs. 450 g) and housing (1.2 kg vs. 725 g). Combined weights would be about the same for either alternative.

Performance with respect to removal of TDS was measured in terms of conductivity. The upper limit on conductivity for WFI is 20 μ siemen/cm (3); however, to assure that chloride does not exceed 0.5 mg/L, WFI should have conductivity no greater than ca. 1 μ siemen/cm. The Barnstead DS902 cartridges employed (exchange capacity 78 g as sodium chloride) met this limit ($\pm 25\%$) from a challenge water with a TDS of ca. 1000 mg/L and conductivity of 1250 ± 50 μ siemen/cm (Fig. 4); breakthrough did not occur until total product volume had exceeded 60 L. There is significant leaching of conductive materials from the RS1-SG filter (Fig. 4), but this problem should be correctable by means of a second, much smaller, high purity ion exchange column following the filter. The size and shape of this column would be dictated by flow considerations rather than exchange capacity, which need not in any event exceed 1 g as sodium chloride. Electrodeionization would be an attractive alternative to ion exchange for this polishing step (13), if such a system could be adapted to operate from the 24 volt power supply of military vehicles.

The function of the fine particle filter is to protect the sterilizing filter, part of the receiver set, from blockage by small particles shed by the RS1-SG filter. A Whatman® paper tube filter rated at 0.2 μ m pore size served this function, but plugged after 45 L of product water. A Filterite® wound string cartridge protected the sterilizing filter, which showed no signs of restricted flow after more than 100 L of product. The weight of the stainless steel and brass housing, 2.5 kg, is a disadvantage, but we

have learned that a plastic housing of lighter weight is available. The string filters tested incorporated a spin finish which gave a false positive LAL indication for the first few liters of filtrate; however, the manufacturer has informed us that a prewashed medical grade filter, identical in all other respects, is available.

Further Research Needs

Devising and validating a system to introduce parenteral concentrates into the WFI may present the greatest challenge in fielding the fluidmakers. For this study, some IV bags were prepared containing 50 mL of lactated Ringer's concentrate (20:1). U.S. Pharmacopeial specifications call for an accuracy of ± 5 percent in sodium chloride concentration, corresponding to ± 50 mL of WFI per 1-L bag. We achieved this level of accuracy using small spring scales calibrated to ± 25 g. NASA has undertaken research on the problem of IV concentrates; a report is in preparation (14).

Sterile closure of filled IV bags also requires further research. To simulate capabilities available in the field, some IV bags were permanently sealed by heating the filling tube with a small butane torch to the point of softening, then immediately pinching off the tube with flat-nose pliers; this procedure was effective if cumbersome. A better solution may be to have slotted plastic tags or other clamping devices incorporated during manufacture of the receiver sets. Alternatively, a battery-operated heat sealer could be devised. It should be noted that most of the test items incorporated in the systems described have not yet been approved for medical use; extensive testing needs to be performed under Good Laboratory Practices and Good Manufacturing Practices before these systems can be fielded.

Summary

Two approaches have been investigated for generating water of WFI quality under field conditions from portable equipment. One, in late prototype stage, utilizes reverse osmosis, while the other, still in the breadboard stage, relies solely on ion exchange for salt removal. Although the systems devised consistently produce sterile, pyrogen-free water from tapwater containing high bacterial levels, the product water will require additional treatment to consistently meet USP XXII standards for WFI with respect to salt levels. Further research is needed to develop a procedure for introduction of parenteral concentrates and to devise a method for sterile closure of IV bags in the field.

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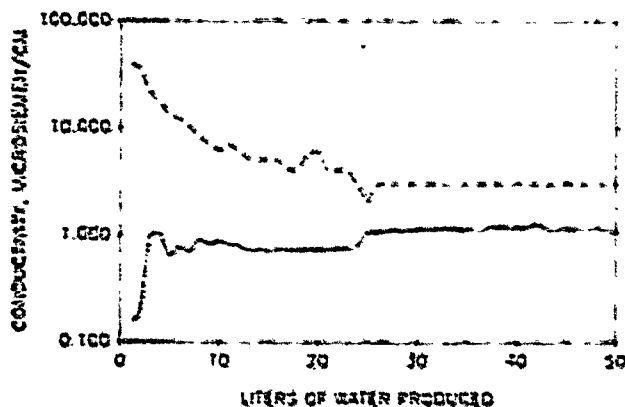


Figure 4—Conductivity of product water from disposable system: top, ion exchange column plus RS1-SG carbon filter; bottom, ion exchange column only.

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