Medical Grade Water Generation for Intravenous Fluid Production on Exploration Missions

Charles E. Niederhaus, Karen L. Barlow, and DeVon W. Griffin
Glenn Research Center, Cleveland, Ohio

Fletcher J. Miller
National Center for Space Exploration Research, Cleveland, Ohio

NASA STI Program . . . in Profile

Since its founding, NASA has been dedicated to the advancement of aeronautics and space science. The NASA Scientific and Technical Information (STI) program plays a key part in helping NASA maintain this important role.

The NASA STI Program operates under the auspices of the Agency Chief Information Officer. It collects, organizes, provides for archiving, and disseminates NASA's STI. The NASA STI program provides access to the NASA Aeronautics and Space Database and its public interface, the NASA Technical Reports Server, thus providing one of the largest collections of aeronautical and space science STI in the world. Results are published in both non-NASA channels and by NASA in the NASA STI Report Series, which includes the following report types:

- TECHNICAL PUBLICATION. Reports of completed research or a major significant phase of research that present the results of NASA programs and include extensive data or theoretical analysis. Includes compilations of significant scientific and technical data and information deemed to be of continuing reference value. NASA counterpart of peer-reviewed formal professional papers but has less stringent limitations on manuscript length and extent of graphic presentations.

- TECHNICAL MEMORANDUM. Scientific and technical findings that are preliminary or of specialized interest, e.g., quick release reports, working papers, and bibliographies that contain minimal annotation. Does not contain extensive analysis.

- CONTRACTOR REPORT. Scientific and technical findings by NASA-sponsored contractors and grantees.

- CONFERENCE PUBLICATION. Collected papers from scientific and technical conferences, symposia, seminars, or other meetings sponsored or cosponsored by NASA.

- SPECIAL PUBLICATION. Scientific, technical, or historical information from NASA programs, projects, and missions, often concerned with subjects having substantial public interest.

- TECHNICAL TRANSLATION. English-language translations of foreign scientific and technical material pertinent to NASA's mission.

Specialized services also include creating custom thesauri, building customized databases, organizing and publishing research results.

For more information about the NASA STI program, see the following:

- Access the NASA STI program home page at *http://www.sti.nasa.gov*

- E-mail your question via the Internet to *help@sti.nasa.gov*

- Fax your question to the NASA STI Help Desk at 301–621–0134

- Telephone the NASA STI Help Desk at 301–621–0390

- Write to:
  NASA Center for AeroSpace Information (CASI)
  7115 Standard Drive
  Hanover, MD 21076–1320

Medical Grade Water Generation for Intravenous Fluid Production on Exploration Missions

Charles E. Niederhaus, Karen L. Barlow, and DeVon W. Griffin
Glenn Research Center, Cleveland, Ohio

Fletcher J. Miller
National Center for Space Exploration Research, Cleveland, Ohio

National Aeronautics and
Space Administration

Glenn Research Center
Cleveland, Ohio 44135

May 2008

Level of Review: This material has been technically reviewed by technical management.

Medical Grade Water Generation for Intravenous Fluid Production on Exploration Missions

Charles E. Niederhaus, Karen L. Barlow, and DeVon W. Griffin
National Aeronautics and Space Administration
Glenn Research Center
Cleveland, Ohio 44135

Fletcher J. Miller
National Center for Space Exploration Research
Cleveland, Ohio 44135

1.0   Introduction

This document describes the intravenous (IV) fluids requirements for medical care during NASA's future Exploration class missions. It further discusses potential methods for generating such fluids and the challenges associated with different fluid generation technologies. The current Exploration baseline mission profiles are introduced, potential medical conditions described and evaluated for fluidic needs, and operational issues assessed. Conclusions on the fluid volume requirements are presented, and the feasibility of various fluid generation options are discussed. A separate report will document a more complete trade study on the options to provide the required fluids.

At the time this document was developed, NASA had not yet determined requirements for medical care during Exploration missions. As a result, this study was based on the current requirements for care onboard the International Space Station (ISS). While we expect that medical requirements will be different for Exploration missions, this document will provide a useful baseline for not only developing hardware to generate medical water for injection (WFI), but as a foundation for meeting future requirements. As a final note, we expect WFI requirements for Exploration will be higher than for ISS care, and system capacity may well need to be higher than currently specified.

1.1   Future Exploration Missions

The Vision for Space Exploration outlined a new direction for NASA, consisting of missions unlike those accomplished before. These missions will return astronauts to the Moon and test the technologies required for Mars missions. The ISS will be used as a testbed for some of these new technologies. NASA's Exploration Systems Architecture Study presents the design reference missions (DRMs) that are being used to facilitate the derivation of requirements for the essential technologies (ref. 1).

1.1.1   International Space Station (ISS)

The ISS is planned to expand to a crew complement of six before the shuttle retires in 2010. These six astronauts will be from the United States and its international partners. U.S. astronauts will focus on validating technologies required for the Lunar and Martian missions. The ISS is the only platform currently available with long-duration microgravity to validate medical water generation and mixing.

1.1.2   Lunar Sortie

A crew of up to four will be able to explore any site on the Moon for up to 7 days. This includes the ability to explore polar regions as well as the equatorial region. No prepositioned infrastructure such as habitat or provisions is included. Daily extravehicular activities (EVAs) with all crewmembers are possible. The Lunar Sortie DRM includes the capability to return to Earth in 5 days or less at any time from any site.

1.1.3 Lunar Outpost

The Lunar Outpost DRM will establish a continuous presence on the Moon's surface. A crew of up to four will occupy an outpost on an expedition lasting up to 6 months. A new crew will arrive every 6 months, and the existing crew will return to Earth. The outpost will help validate technologies required for Mars exploration. The 5-day, anytime return capability of the Sortie DRM is available for the Outpost DRM if the outpost is located at a polar or equatorial site. Remaining on the surface may be required at other sites, extending the return time.

1.1.4 Mars Exploration

The Mars DRM is for a conjunction-class mission, with 6-month transit to and from Mars, and an 18-month stay. These missions will be launched when the Earth and Mars are in conjunction, thus minimizing radiation exposure by minimizing transit time. A crew of six will be included on this 2.5-year mission. No early return is possible in the case of an emergency because of the mission profile.

1.2 Medical Need for Fluids

These longer duration missions increase the likelihood of a medical incident and thus the need for medical fluids. The patient condition database (PCDB) provides a list of over 400 medical conditions that may present and require treatment during ISS missions. These conditions are a subset of possible conditions that could be encountered during long-duration, EVA-intensive, Exploration missions. Of the 442 conditions, approximately 115 may require medical fluids during the course of treatment. Terrestrial treatment would typically include fluids such as normal saline (NS) (0.9% NaCl), 5% dextrose, Lactated Ringer's solution (LR), or blood products. Operational constraints such as mass limitations and lack of refrigeration may limit the type and volume of such fluids that can be carried onboard the spacecraft. Representative conditions that may require fluid treatment include trauma, burns, and hemorrhagic shock. Section 2.0 will include a more detailed discussion of these conditions likely requiring IV fluid administration.

1.3 General Issues With Providing Fluids

Choosing a technology to generate sterile water for injection (SWFI) and produce IV fluids requires balancing capabilities with mission and medical requirements. For example, the type, volume, and timeline over which IV fluids are required are key drivers in selecting an appropriate technology. Additionally, the system must operate in various gravity environments, such as microgravity, lunar gravity, and Martian gravity, while also functioning in Earth normal gravity for testing and verification. Propulsive thrusting events may also produce an effective gravitational level and could possibly occur during fluid production. Successful operation requires maintaining sterility, which can be handled in different ways depending on technology. Some technologies might be sealed until use, requiring only seal integrity, while other systems may require internal recirculation or periodic maintenance to ensure proper operation. Instrumentation will likely be required to verify compliance of United States Pharmacopeia (USP) standards of operation of the system. Crew time may be especially limited in an emergency situation, and the time needed to deploy, prepare, activate, and operate the system should be taken into account. Any system must be relatively simple to use, safe, and reliable. Section 4.0 discusses many of these issues in greater detail.

1.4 Brief Review and Analysis of Previous Work

In the late 1980s and early 1990s, NASA conducted a detailed investigation to determine the possibility of producing IV fluids on orbit as part of the Health Maintenance Facility of what was then Space Station Freedom. The Johnson Space Center led this effort, which included contracts with Krug

International (Wyle Laboratories since 1997), Sterimatics Corporation, and Baxter Healthcare Corporation, culminating in a flight experiment on Space Transportation System (STS)–47 from September 12, 1992, to September 20, 1992. Krug International of Houston, Texas, was the prime contractor and flight integrator, with subcontracts to specialists Sterimatics and Baxter. The final decision at the time was not to produce sterile water on Space Station Freedom, but to use prepackaged IV fluids. No flight-ready hardware was fabricated for sterile water production. A brief description of the results follows.

1.4.1 IV Fluids Requirements White Paper

A white paper titled "An Evaluation of IV Fluids Requirements for the Space Station Freedom Health Maintenance Facility Assuming a 10-Day Therapeutic Stay" was written by Gerry Creager of Krug Life Sciences in 1991 (ref. 2). This report evaluated six medical scenarios requiring fluids for treatment. The scenarios included (1) cardiac arrest with rapid resuscitation, (2) 40 percent body surface burn of full thickness, (3) a fracture of the radius and ulna with complications requiring surgical intervention, (4) a relatively uncomplicated femur fracture, (5) space motion sickness, and (6) a myocardial infarction requiring polypharmaceutical intervention. The basic assumptions in the study were (1) maximum length of treatment is 10 days, (2) patient is a 90-kg, 95th percentile American male, (3) IV fluids are packaged in 1 L volumes, (4) parenteral (i.e., external to the gastrointestinal tract) nutrition is not included, (5) infusible pharmaceuticals can be mixed in one of the solutions provided, (6) no accommodations for additional fluids beyond those identified, and (7) entire fluid administration set changeout every 48 hr consistent with terrestrial infection control practices.

Fluid volumes were calculated for each scenario for seven types of solutions. The volume required to cover a particular scenario ranged from 11 to 90 L, averaging 37 L. The total volume required to treat all individual scenarios in a mission and the minimum volume required to any one individual scenario in a mission were also calculated. The total volume of the seven types of solutions required to cover one incident of each scenario was 220 L, while 141 L was required to cover any one scenario. The report suggested that the minimum was 123 L, but we found an 18 L error in the calculations for the minimum amount of NS required.

1.4.2 Sterile Water for Injection System

Krug International, as lead contractor for the health maintenance facility on Space Station Freedom, contracted with Sterimatics Corporation to develop a sterile water for injection system (SWIS) as part of a system to produce IV fluids. The SWIS was a filter/adsorption-based technology to produce WFI. The design goal was to be able to use hygiene water, a proposed ISS water designation that was lower in quality than potable water. Specifications for hygiene water were not available in the early design stages. Therefore, system designers assumed this water would not be more than 10 times worse than the potable water specification for all contaminants. System requirements included producing at least 6 L of WFI at 6 L/hr with a sterile shelf life of 90 days, utilizing a filter with a minimum shelf life of 1 year.

The SWIS produced WFI utilizing filter and adsorption bed technologies. In order, the process included particle prefiltration, carbon adsorption, mixed-bed deionization, ultrafiltration, and sterilizing microfiltration. As developed, the SWIS had a dry mass of 2 kg and produced 9 L of WFI from hygiene water with contamination levels 10 times the ISS potable water specification. Testing indicated that at least 20 L of WFI could be produced from potable water. The flow rates were 6 L/hr at 30 psia and 4 L/hr at 20 psia. The SWIS was flown on STS–47 in September 1992 as part of the fluid therapy system (FTS) on the Spacelab–J (Spacelab–Japan). The results of this work will be discussed further in Section 1.4.4.

1.4.3 Zero-Gravity IV Mixing System

Krug International contracted with Baxter Healthcare to produce a system for mixing constituents in custom IV bags. Baxter worked on developing methods to mix both powders and concentrates, but was unable to overcome problems in mixing powders (ref. 3). The development was constrained by a passive system requirement, utilizing only water pressure to produce the mixing. The method developed utilized a mixing bag separate from the IV bag. The mixing bag contained a serpentine channel similar to blood warming bags. The concentrate to be mixed was distributed along the channel and the WFI passed through the channel before entering the IV bag. Baxter conducted experiments with a dyed concentrate and observed a low degree of mixing, with the heavier, dyed concentrate located on the bottom of the bag in 1-g testing. Baxter felt that bag manipulation by hand produced sufficient mixing, but did not quantify the mixing. No quantitative mixing studies were completed in normal gravity or microgravity.

Our brief analysis of the fluid physics suggests that the concentrate would have been flushed out of the channels almost immediately, with the subsequent fluid nearly pure water, consistent with Baxter's observations. It is felt that the mixing that was subsequently obtained by Baxter was highly dependent on internal waves produced from the density difference between the concentrate and the pure water in a gravity field. This type of mixing will be greatly reduced in microgravity. Experiments were conducted at NASA Glenn specifically to look at mixing using manual squeezing of the bag as recommended by Baxter. Concentrated saline solution was added to a bag filled with distilled water. A fluorescent technique (planar laser-induced fluorescence) was utilized to quantify the mixing inside of the bag similar to what is being used to characterize magnetic stirrer mixing (ref. 4). Mixing was accomplished by manual squeezing of alternate sides of the bag at ~2 Hz while maintaining a horizontal orientation to minimize gravity effects. After 5 min of continuous squeezing, over 50 percent of the bag still had pure, unmixed, distilled water. It was not until the bag was tilted ±45° at 1 Hz for 1 min that mixing was finally achieved. This tilting motion introduces gravity-driven mixing as gravity moves the heavy fluid to alternate sides of the bag as it is tilted. A second experiment with vigorous horizontal oscillation for 5 min achieved similarly incomplete mixing, with over 50 percent still completely unmixed. These experiments demonstrate that it is easy to produce mixing that is gravity-driven, but that these mixing techniques will not function in microgravity.

1.4.4 STS–47 Fluid Therapy System (FTS)

The Spacelab–Japan Module flew on STS–47 during September 1992. One of the experiments was the FTS, testing the equipment and procedures developed thus far for IV generation. The FTS utilized the adsorption filters developed by Sterimatics to produce the WFI, and the IV bags and mixing method developed by Baxter to produce the final solutions. An infusion pump administered a saline solution into a mannequin arm to complete an end-to-end system test. The degree of mixing was not quantified on orbit, nor was the solution frozen or fixed in any fashion to preserve the state of mixing on orbit. While later analysis on Earth showed that the final solution met the tolerance criteria for solution concentration (±5 percent of desired concentration), that determination was only a validation of the amount of solute in the final solution, not a verification of achieving the in-flight mixing requirements because vibrations from landing and handling as well as molecular diffusion would have easily homogenized the sample by the time the ground analysis was performed. Ground testing of the produced WFI concluded that it did not meet the required total organic carbon requirement. It speculated at the time that this was caused by the bags themselves, although NASA Glenn suspects that channeling in the adsorption system is a more likely cause.

Serious bubble problems were observed by Astronaut Mae Jemison during testing on STS–47. The bubbles were sometimes hundreds of very small bubbles in the IV bag, and sometimes many large bubbles. The bubble traps in the system were overloaded and failed on multiple occasions. The IV pump also shut down from error signals generated by the bubbles. It has been hypothesized that these extreme bubble problems were caused by the unique nature of this experiment. The source water was in a pressurized container with a bladder. Part of the container held a pressurized gas, which would collapse the flexible

membrane and force out the liquid. It is possible that sufficient gas diffused through the membrane and saturated the liquid. When the liquid pressure was reduced inside of the IV bag, this solution degassed, forming the bubbles. No followup ground testing was conducted to confirm the hypothesis.

In the 15 years since the hardware was flown, the activated charcoal in ground prototypes exhibited noticeable settling. There was some mention of noticeable settling during the timeframe of operations. This settling suggests that the fluid phenomenon known as channeling may have occurred. Fluid flow in packed beds (containers with loose particles used for chemical reactions) such as employed in the SWIS can rearrange the packing, as a result of hydrodynamic forces, into regions of higher and lower packing densities. Low packing density regions are preferential for fluid flow and result in voids in the filter media that does not filter the water properly. The adsorption material in this region becomes overloaded, while other material remains unused. This situation occurs with greater frequency in microgravity packed beds because there is no gravity force to help maintain the positioning of the packing. For example, there can be no empty space at the top of the reactor in microgravity because in microgravity there is no "top," and this void space is distributed throughout the reactor from hydrodynamic forces that minimize the pressure drop. The result is also a reduction of the treatment effectiveness of the reactor (ref. 5). Special precautions must be taken to avoid these problems, such as elaborate packing procedures or mechanical compressive forces, and it does not appear that such measures were taken. It is possible that channeling is the reason that testing of the flight solutions showed that they did not meet the total organic carbon standards.

1.5   Objectives of This Study

This study focuses on developing the requirements for IV fluids for NASA's missions, presents key issues in developing any IV generation system, introduces potential generation technologies, and offers conclusions on whether generating IV fluids on orbit is preferable to flying prepackaged supplies. The profiles of expected missions, as outlined in the Exploration Systems Architecture Study (ESAS) DRMs, are described and analyzed for potential emergency medical care needs. These missions are still very early in the planning stages, so detailed equipment requirements have not been developed and mission scenarios may change. Many of the expected medical care needs are based on current and past mission requirements, as well as past advanced planning.

Potential medical conditions are analyzed to determine whether IV fluids might be required and the approximate quantity. The analysis is on a layman's level to give a rough estimate of fluids requirements. No detailed fluid treatment regimes are developed. This review is not intended to be an exhaustive medical analysis, but rather a guide to when IV fluids may be required, along with the quantity of such fluids.

Some of the key questions and requirements that an IV generation system must meet are elucidated. Questions include quantities required, production rate and quality requirements, and inspace operation. Some potential technologies are critically described. Conclusions are drawn about whether produced or stored IV fluids are more appropriate for a given DRM. A later paper will include a detailed trade study that compares potential technologies will be made to determine the most appropriate technology for a given DRM. The future trade study would develop a more accurate estimate of the weight, volume, et cetera, required for the recommended system.

2.0   Clinical Need for Additional Fluids

The shelf life of some pharmaceuticals can be improved by lyophilization, or storing them in their freeze-dried form (ref. 6). These drugs may need to be reconstituted with potable or sterile water, prior to oral or parenteral (e.g., intravenous, subcutaneous, and intramuscular) administration, respectively. Other fluids including NS, LR, and colloid solutions are frequently used to treat a variety of illnesses including hypovolemia as a result of blood loss and severe burns, anemia, and dehydration. The following sections discuss some typical fluids used in clinical treatments, the ISS-approved drugs that require these fluids, and the standards for the water used to manufacture them. Furthermore, the major routes of administration

of these fluids are defined and the operational challenges that might arise during the employment of these treatments in microgravity are briefly discussed.

2.1 Methods of Administering Fluids

Often there is a choice of the route by which a therapeutic agent may be given, and knowledge of the advantages and limitations of the various routes of administration becomes important. Some characteristics of the major routes employed for systemic drug effect are compared in table I (ref. 7).

TABLE I.—CHARACTERISTICS OF COMMON DRUG ADMINISTRATION ROUTES

Route	Absorption pattern	Special utility	Limitations and precautions
IV	Absorption circumvented Potentially immediate effects	Valuable for emergency use Permits titration of dosage Usually required for high molecular weight protein and peptide drugs Suitable for large volumes and for irritating substances, when diluted	Increased risk of adverse effects Must inject solutions slowly, as a rule Not suitable for oily solutions or insoluble substances
Subcutaneous	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for some insoluble suspensions and for implantation of solid pellets	Not suitable for large volumes Possible pain or necrosis for irritating substances
Intramuscular	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for moderate volumes, oily vehicles, and some irritating substances	Precluded during anticoagulant medication May interfere with interpretation of certain diagnostic tests (e.g., creatine kinase)
Oral ingestion	Variable	Most convenient and economical Usually more safe	Requires patient cooperation Availability potentially erratic and incomplete for drugs that our poorly soluble, slowly absorbed, unstable or extensively metabolized by the liver and/or gut

2.1.1 Enterally

Enteral routes of drug administration refer to all methods where the drug is able to pass through the lining of the gastrointestinal tract. The water required for this course of administration should meet potable standards, but does not need to meet stricter standards. If the patient is unconscious or cannot swallow for any reason, secondary preference routes may be used such as gastric or duodenal feeding tubes, and rectally via suppository or enema. Since enteral administration does not require sterile water, it will not be further discussed in this paper.

2.1.2 Parenterally

Parenteral drugs are introduced by routes outside of the gastrointestinal tract including subcutaneous, intramuscular, and IV injection. All methods require sterility of both the drug, and any additives (including water) necessary for administration. Problems may occur with this method of administration if an air embolus is injected into the patient's circulatory system, a potentially fatal condition (ref. 8), so air-bubble removal prior to injection is critical. Bubble removal is difficult in microgravity fluid systems; a bubble trap in the injection line may suffice if the total bubble volume is relatively small. In microgravity and partial gravity, the system to administer parenteral drugs must employ a force to drive the solution into the blood vessel rather than the standard gravity-driven devices used in terrestrial applications. Other requirements for all parenteral drugs are the sterility and purity of the injected fluid, as nonsterile injections will cause infection and lack of purity can introduce toxins.

2.2 Medications That Need IV Administration

Though oral drug administration is often the preferred method, parenteral injection of drugs has distinct advantages. In some instances, parenteral administration is necessary for the drug to be absorbed in active form. When given parenterally, the bioavailability of a drug is usually more rapid and more predictable than when a drug is given through the gastrointestinal tract, so the therapeutic dose can be more accurately

selected. In emergency therapy, parenteral administration is particularly useful. If a patient is unconscious, uncooperative, or unable to retain medication given orally, parenteral therapy is required.

The issues involving absorption are avoided by IV injection of drugs in aqueous solution; for example, a drug that is absorbed from the stomach and intestine must first pass through the liver before it reaches the systemic circulation. If the drug is metabolized in the liver or excreted in the bile, some of the drug will be inactivated and diverted before it can reach the general circulation and be distributed to its sites of action. With IV injection, the drug is administered directly into the general circulation, and the desired concentration of a drug in blood is obtained with an accuracy and immediacy not possible by any other procedure. Also, certain irritating solutions can be given only in this manner, since the blood vessel walls are relatively insensitive, and the drug, if injected slowly, is greatly diluted by the blood (ref. 7).

2.2.1   Current ISS Medications

The ISS medical kit includes eight drugs that require intravenous fluid (IVF) administration. Table II describes the use and quantity of drug needed for a full course of treatment, and quantity of IVF required for one dose. The drugs that have no available units on ISS are those that have been approved by the Space Medicine Configuration Control Board (SMCCB) for future ISS missions. Precisely determining how much IVF is required for one full course of treatment for some drugs is difficult because the length of treatment and amount of required fluid changes according to severity of the illness and patient response to the medication.

TABLE II.—SMCCB APPROVED FOR ISS FLIGHTS

Medications that require IV fluid (unit concentration)	Class	Use	No. of units on ISS	Ideal quality for one full treatment course	Amount of base IVF required for each dose
Primaxin (500 mg)	Antibiotic	Lower resp. tract infection; UTI (complicated and uncomplicated); Intra-abdominal infections; gynecologic infections; bacterial septicemia; bone and joint infections; skin and skin structure infections; endocarditis; polymicrobic infections	1	Up to 4 g/day depending on severity of infection	100 mL
Rocephin[a] (1 g)	Antibiotic		1	10 days, 1 to 2 g/day	100 mL
Dilantin IV (50 mg/mL; 2mL)	Antiseizure	Seizures	10	1gm = 1 loading dose slated for removal with Carpuject change	500 mL
Amikacin[a] (250 mg/mL; 2mL)	Antibiotic		4		100 mL
Acyclovir (50 mg/mL IV fluid, 20 mL)	Antiviral	Systemic viral infection (shingles, etc.)	0	Max. 800 mg, 3 times a day for 10 days	For IV infusion, dilute concentrate containing acyclovir 25 or 50 mg/mL with a compatible IV fluid (NS, D5, LR) to a concentration of 7 mg/mL or less
Azithromycin (500 mg for IV use; dry powder for reconstitution in 4.8 mL sterile water)	Antibiotic	Infections above the diaphragm	0	500 mg IV once a day for 2 days (followed by 8 days of oral dosing)	250 mL NS
Procainamide	Antiarrhythmic		0		
Pyridoxine (100 mg/ml, 1 ml vials)	Antidote	Antidote for hydrazine poisoning	0	25 mL of 25 mg/kg	Administer into running IV

[a]Can also be administered intramuscularly.

2.2.2 Potential Lunar/Mars Medications

This report assumed that the list of medications for lunar and Mars missions will be similar to that for the ISS, discussed in Section 2.2.1, though limited storage and mass requirements of the Crew Exploration Vehicle, Orion, may require flight surgeons to truncate the ISS list by choosing only the medications that are applicable to the most likely ailments that might occur for a particular mission. Quantities of each medication should be chosen based on the number of crew in Orion, as well as other factors such as mission length and profile. According to the NASA's 2005 ESAS report, Orion will accommodate four crewmembers for Lunar missions, while being reconfigurable to hold up to six crewmembers for future Mars missions (ref. 1).

2.3 Types of Fluid and Operational Challenges

On average, fluid constitutes 60 percent of the adult human body weight. Body fluid contains water and two types of solutes: electrolytes and nonelectrolytes. Nonelectrolytes are molecules that remain intact in the body and consist of dextrose, creatine, and urea. Electrolytes are molecules that break down into charged particles, or ions, and serve two major functions: By osmotic pressure, they control the allocation of water volume to the intracellular and extracellular compartments of the body, and maintain the proper pH (potential of hydrogen (a measure of acidity)) balance of the body. Parenteral fluids are classified according to the osmolality of the fluid in relation to normal blood plasma, which has an osmolality of 290 mOsm/L (milliosmoles). Fluid that approximates 290 mOsm/L is considered isotonic. IV fluids with an osmolality greater than 340 mOsm/L or less than 240 mOsm/L are generally considered hypertonic and hypotonic, respectively (ref. 9). Injuries such as burns result in fluid loss; similarly, dehydration is caused by fluid loss or electrolyte imbalance. Fluid maintenance in such situations is critical in providing nutrients such as water, electrolytes, dextrose, vitamins, and protein. There are currently 200 types of commercially prepared parenteral fluids available (ref. 9). Sections 2.3.1 to 2.3.6 will focus on a few of the most common types of fluid and the therapies for which they are used to treat illnesses pertinent to Exploration missions.

Aside from fluid in the form of plasma, which includes components other than electrolytes, whole blood contains red and white blood cells, and platelets. The main function of red blood cells is to transport oxygen to all of the tissues and cells of the body. Loss of red blood cells, depending upon how severe, may result in a range of disorders from anemia to tissue necrosis and death. White blood cells, specifically granulocytes, are important in the immune response, are transfused in rare cases when an infection is unresponsive to antibiotics. Platelets are cellular fragments that form in the bone marrow and serve a major role in the clotting cascade. Platelet transfusions are generally given to people with hematological disorders, such as leukemia patients, and for the purposes of this discussion we will assume that a new diagnosis of leukemia or other form of bone marrow disease will be beyond the scope of the mission's medical system. Massive blood loss as a result of trauma may require transfusion therapy in order to restore the circulation of oxygen in the system. Sections 2.3.7 and 2.3.8 discuss blood products and alternatives currently in development, respectively, along with any issues that are apparent in application to Exploration missions.

2.3.1 Terrestrially Available Fluids

Table III compares the storage requirements of IV fluids that are typically required for a broad spectrum of medical treatments. The data do not show any difference in shelf life of the different fluids for a given vendor, but there is a 40 percent shelf life difference between the two vendors, mainly for reasons discussed later in Section 2.3.9. However, even this longer shelf life is insufficient for missions to Mars when loading and launch time are considered. Hence, NASA must either develop the capability to generate these fluids in flight or undertake a program to develop ways to extend the shelf life. Given constraints of spaceflight, the mass required for prepackaged IV fluids may be excessive.

TABLE III.—COMPARATIVE STORAGE REQUIREMENTS FOR COMMON MEDICAL FLUIDS

Treatment	Shelf life		Storage temperature., °C	Various uses/indications, µg specific	Other considerations
	Baxter[a]	B. Braun[b]			
IV fluid					
0.9% sodium chloride	18 mo.	30 mo.	25	Dehydration, burns, blood loss, wound irrigation, drug administration	PVC (Baxter[a] IV bags) degrades when exposed to gamma radiation; chemical alteration of PVC may produce harmful byproducts. PVC also reactions with some drugs
LR	18 mo.	30 mo.	25		
5% dextrose	18 mo.	30 mo.	25		
SWFI	12 mo.	30 mo.	25		
Transfusion therapy					
Whole blood	35 days		4	Blood loss and complications	Use of whole, packed, or frozen red blood cells (RBCs) requires the storage of O-type blood
Packed RBCs	42 days		4		
Frozen RBCs	10 yr		−80		Frozen RBCs must be deglycerolized and resuspended using various fluids
Blood substitutes	Hemopure (Biopure): 3 yr		2 to 30		Still in FDA trials; used as a "bridge" until blood available/regenerated. Due to shorter intravascular half-life than RBCs
	Oxygent (Alliance Pharmaceuticals) >1 yr		5 to 10		
Plasma, fresh frozen	1 yr		−20		
Plasma, lyophilized	N/A		25		Requires reconstitution in SWFIs; reduced clotting rate
Cryoprecipitate	1 yr		−20	N/A	Mainly used in hemophilia patients
Platelets	5 days		20 to 24	N/A	Mainly used in cancer patients

[a]Baxter IV bags are made of Viaflex plasticized polyvinyl chloride (PVC).
[b]B. Braun bags are made of Excel ethylene and polypropylene (latex-, PVC-, and NEHP-free).

2.3.2 WFI

The USP denotes categories of water suitable for parenteral use. WFI is water purified by distillation or other suitable methods that remove chemicals and microorganisms (currently, only distillation and reverse osmosis are approved methods for generating WFI). USP standards for WFI limit endotoxin concentration, which are released when gram-negative bacteria die, to 0.25 USP units/mL. The standards allow WFI to be used for producing parenteral solutions if they are used immediately following production and meet USP solution standards. This includes all parenteral solution discussed in Section 2.0.

Bacteriostatic water for injection (BWI) is produced from WFI with the addition of an antimicrobial agent, typically benzyl alcohol. BWI must contain no more than 0.5 USP endotoxin units (EUs)/mL and is appropriate for parenteral applications provided the antimicrobial agent is compatible with any drugs or other solutes that are added. However, typical crystalloid solutions of NS, dextrose, and LR must contain no antibacterial agents, according to USP standards, and thus cannot utilize BWI.

USP standards for SWFI allow no antimicrobial agents, less than 0.25 USP EUs per mL, and no other added substances. SWI meets all standards of WFI, but must also meet additional standards for sterility, pH, particulates, and trace contaminants. Following USP standards, when generating fluids from packaged water, SWI is the only fluid that can be used to generate all of the intravenous fluids discussed in Sections 2.3.3 through 2.3.8. Additionally, SWI may be used for all other medical applications where lesser grades of water, such as water for injection, or potable water are suitable. In most cases, potable water is suitable only for enteral treatments.

2.3.3 NS Injection

NS is an electrolyte used to replenish intravascular fluid volume and provide hydration and medication delivery. It is a relatively simple composition that has an osmotic pressure close to blood. Matching osmotic pressure is critical because osmotic pressure differential is what drives fluid exchange through cell walls. NS is a 0.9% (w/v) (or in mEq/L: 154 Na^+, 154 Cl^-) aqueous solution of sodium chloride, which has an osmolality of 308 mOs/L. The osmolality of NS is slightly higher than blood plasma, which averages 290 mOsm/L (refs. 9 and 10). NS at 0.9% is also acidic with a pH of 5.6,

compared to normal blood pH of 7.4. Various medications, blood sugar level, and oscillations in plasma osmolality, which can increase due to dehydration, could require alternate solutions for patient treatment including: ½ NS (0.45%NaCl/5% D-glucose); ¼ NS (0.22%NaCl/5% D-glucose); and dextrose (0.18%NaCl/4% D-glucose, 250mOsm/L); and LR as discussed in Section 2.3.4.

2.3.4   LR Injection

LR injection is an electrolyte with an osmolality of 273 mOsm/L. This fluid is categorized as an alkalizing fluid and is often used to treat or prevent mild acidosis, which is often associated with acute fluid loss such as in the event of a trauma. The solution contains 0.6% NaCl, 0.31% sodium lactate, 0.03% KCl, and 0.02% $CaCl_2$ (or in mEq/L: 130 of Na^+, 109 of Cl^-, 28 of lactate, 4 of K^+, and 3 of Ca^{2+}). The electrolyte concentration of LR closely resembles that of the extracellular fluid, so it may be used to replace fluid loss from burns or as fluid lost as bile and diarrhea (ref. 9). LR is not an appropriate fluid to administer in the same IV line with blood, as it may cause coagulation, though some recent studies concluded that there was no difference in coagulability between NS and LR (refs. 11 and 12).

In spite of the theoretical advantages of LR, evidence in the medical literature does not support the view that it is a superior fluid. According to a National Academies Press metareview, LR and NS are equally effective at maintaining intravascular volume after hemorrhage (ref. 13). Additionally, there was no difference between the two fluids in mortality rate or pulmonary function. While those findings are neutral with respect to fluid choice, the National Academies did note that LR increases neutrophil activity, meaning that this fluid can exacerbate systemic immune response following injury. Such a response can produce acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). Finally, some studies recommended that D-lactate be removed from LR and lower levels of L-lactate be used to reduce potential toxicity of LR (ref. 13).

2.3.5   Dextrose Injection

When glucose is part of parenteral injections, it is usually referred to as "dextrose," a designation by the USP for glucose of required purity. Dextrose is available in concentrations of 2.5, 5, 10, and 20 percent, of which 5 percent dextrose is the only isotonic solution. Dextrose fluids are used in patients with dehydration or electrolyte disturbances (i.e., high potassium or sodium levels), and can also be used as vehicles for drug delivery and nutrition. Dextrose can be mixed with electrolytes in various concentrations when both nutrition and electrolytes need to be replenished, or in certain cases of hypovolemia. Dextrose fluids should not be administered in the same IV line with blood, as it may cause hemolysis and/or agglomeration, as stated on commercial storage containers.

2.3.6   Colloids

When used to treat hypovolemia, crystalloid solutions, such as NS or LR, perfuse into the interstitial and intracellular tissues because of the minute size of the ions in these solutions. After such diffusion, osmotic pressure will draw fluid out of the vasculature and into the interstitial space, and the hypovolemia will only be partially corrected. Typically only 20 to 30 percent of the injected fluid volume will remain in the vascular system after 1 hr. This ratio does increase with large volume injections (ref. 14). In this case, or when blood is not available, some physicians prefer using colloid solutions of large molecules that are unable to pass into the cellular and interstitial regions. These large molecules are able to remain in the intravascular space until they are cleared by the liver, which often takes a matter of days during which the patient is able to replenish their blood supply. Concentrated colloid solutions can even draw fluid from the interstitial space, with a vascular volume increase of greater than 100 percent of the injected volume, although typical concentrations provide a 100 percent vascular volume increase. Common colloid solutions include albumin and synthetics such as Dextran and hetastarchs Hespan and Hextend.

Although albumin has been used for over 50 years, and synthetic colloids seemed to have promise, clinical trials have not conclusively proven the benefits of colloids over crystalloids. They may reduce the fluid volume requirements on Exploration missions, but there could be additional concerns with the effect of radiation on these solutions. While these fluids have theoretical advantages for maintaining vascular volume, metastudies of these fluids found that mortality is not reduced when these fluids are used (ref. 15). A large Australian study found that the mortality rate for albumin and NS was the same in an emergency room setting (ref. 16). Another study found that there were no differences between colloidal and crystalloidal fluids, with the exception of albumin, which was found to increase mortality (ref. 17).

2.3.7   Blood and Blood-Derived Products

Whole blood and its apheresis components have a wide range of shelf lives and various storage temperature requirements (table III). If part of the emergency medical supplies provided for space Exploration missions, whole blood, and packed or frozen red blood cells (RBCs) should be type O-negative in order to be compatible with every crewmember's blood type. Dried blood plasma was used in the military during World War II (ref. 8), while current research is focusing on the development of lyophilized plasma and blood substitutes for both military and commercial use (refs. 18 and 19). One disadvantage of lyophilized plasma is a reduction in clotting rate when compared to fresh plasma, because of a significantly lower fibrinogen concentration (ref. 20).

As is evident from the information presented in table III, blood and its apheresis products are not sufficiently stable for Exploration class missions without refrigeration and/or freezing. Therefore, if appropriate risk reduction for the chosen Exploration architecture requires these fluids, NASA must take steps to ensure that they are available in the proper quantities with appropriate efficacy.

2.3.8   Blood Substitutes

Three types of blood substitutes are currently in advanced clinical trials. Hemopure (hemoglobin-based oxygen carrier (HBOC)–201) by Biopure Corporation (Cambridge, MA), and PolyHeme by Northfield Laboratories Inc. (Evanston, IL), contain chemically modified bovine and human hemoglobin, respectively. Both products are universally compatible. Hemopure is stable for 3 years when stored at 2 to 30 °C, and PolyHeme can be stored at room temperature and has a shelf life of 1 year. However, because these products have a short 24-hr intravascular half-life, the product is best used as an intermediary until blood becomes available or the patient regenerates their own RBCs (refs. 21 and 22). PolyHeme can be stored at room temperature and has a shelf life of 1 year. Oxygent by Alliance Pharmaceutical Corporation (San Diego, CA) is a perfluorodecyl bromide (perflubron)-based oxygen-carrying emulsion. Also universally compatible, this blood substitute is stable for >1 yr at 5 to 10 °C. At 4 days (ref. 23) its half-life is longer than that of Hemopure. While useful as interim measures, none of these therapies last as long as a blood transfusion, since transfused RBCs can persist in circulation for several weeks.

2.3.9   Possible Storage Material Concerns

Two of the major manufacturers of IV fluids include Baxter Healthcare Corporation (Deerfield, IL) and B. Braun Medical Incorporated (Irvine, CA). Baxter provides solutions contained in Viaflex polyvinyl chloride (PVC) bags that typically contain 30 to 40 percent of the plasticizer di-(2-ethylhexyl) phthalate (DEHP). Because DEHP is not chemically bound to PVC, leaching may occur when the material is heated or comes into contact with blood, drugs, or IV fluids (ref. 24), though toxicity in humans has not been well established. The PVC polymer has been shown to produce low acute toxicity (ref. 25) in addition to the fact that vinyl chloride has been recognized as a potential carcinogen (ref. 26). While these PVC effects are known, the effect of ionizing radiation on PVC is unknown. For example, when PVC is exposed to gamma radiation, (~25 kGy (gray) dose) the mechanical, physical, and chemical properties of PVC (refs. 27 and 28) may be changed and harmful byproducts produced. In order to avoid

possible problems with the use of PVC-containing medical devices such as IV bags, using bags made from a different material may be prudent. Possible substitutes include the IV bags manufactured by B. Braun, Inc. Those bags are composed of a proprietary three-layered polymer laminate composed of biologically inert ethylene and polypropylene. As well as having no known interaction with drugs, this material is 28 to 48 percent lighter than PVC (ref. 29) and contains no plasticizers. B. Braun advertises a 30-month shelf life for their IV fluids, in contrast to Baxter's IV fluids, which are quoted to have a 12- to 18-month shelf life (ref. 30). Possible PVC health issues aside, the prolonged shelf life and reduced mass of the B. Braun IV bags make them the best commercial option for Exploration missions.

2.4   IV Fluids Summary

Because so many IV fluids of various compositions and concentrations exist, and because NASA has not yet formulated medical care requirements for Exploration missions, we do not focus on providing fluid for any possible parenteral medication. Instead, a few of the most commonly used fluids for the administration of the drugs selected for Exploration missions, as well as the medical conditions requiring IV fluids most likely to occur during Exploration missions were analyzed. Using the SMCCB drug list, the choice of fluid is generally chosen based on the drug(s) administered (table IV). If necessary, lower concentrations of sodium chloride injections may be formulated by diluting NS. Refrigeration may prolong the viability of these premixed solutions; however, this resource may be unavailable during Exploration missions. The standard IV fluids that will be considered are NS, dextrose, LR, and variations of these. Colloids will be considered, but their storage and efficacy concerns will not be examined. Current mission and hardware concepts will not have the refrigeration capability to safely carry blood or blood-derived products, and blood substitutes are not sufficiently developed at this time to consider.

TABLE IV.—COMPATIBLE IV FLUIDS FOR SMCCB-APPROVED DRUGS

Medications that require IV fluid (unit concentration)	Class	Compatible fluids

Primaxin (500 mg)	Antibiotic	As supplied in single use infusion bottles:
		    0.9% sodium chloride injection
		    5 or 10% dextrose injection
		    5% dextrose and 0.9% sodium chloride injection
		    5% dextrose with 0.225 or 0.45% saline solution
		    5% dextrose with 0.15% potassium chloride solution
		    5 and 10% mannitol
		As supplied in single dose ADD-Vantage vials:
		    0.9% sodium chloride injection
		    5% dextrose injection

Rocephin[a] (1 g)	Antibiotic	5% dextrose injection 0.45 or 0.9% sodium chloride injection 10% invert sugar 5% sodium bicarbonate 5 or 10% mannitol
Dilantin IV (50 mg/mL; 2mL	Antiseizure	0.9% sodium chloride injection LR injection
Amikacin[a] (250 mg/mL; 2mL)	Antibiotic	5% dextrose injection 5% dextrose and 0.2, 0.45, or 0.9% sodium chloride injection LR injection
Acyclovir (50 mg/mL IV fluid, 20 mL)	Antiviral	Do not use biologic or colloidal fluids such as blood products or protein solutions.
Azithromycin (500 mg for IV use; dry powder for reconstitution in 4.8 mL sterile water)	Antibiotic	0.9 or 0.45% sodium chloride injection 5% dextrose LR injection 5% dextrose in 0.45% sodium chloride with 20 mEq potassium chloride 5% dextrose in LR 5% dextrose in 0.3 or 0.45% sodium chloride
Procainamide	Antiarrhythmic	5% dextrose
Pyridoxine (100 mg/ml, 1 ml vials)	Antidote	Compatible fluid information could not be identified.

[a]Can also be administered IM.

Because the effects of radiation on PVC IV bag material during Exploration missions are unknown, it would be prudent to consider using alternate materials such as those discussed in Section 2.3.9. Whatever material is chosen, the compatibility of that material with the SMCCB-approved drugs listed in table IV should also be considered.

3.0   Medical Conditions Requiring Fluid Treatment

The ISS PCDB was mined to determine which potential conditions may require fluid treatment, as semirepresentative of treatable conditions on Exploration missions. The list is not exhaustive, and there are other potential patient conditions as well. Of the 442 listed patient conditions that may be encountered while onboard the ISS, approximately 115 may require IV fluid treatment. These conditions may also occur on other Exploration missions, possibly with a different probability of occurrence. These possible conditions have been grouped into major areas where the reason for fluid treatment is approximately the same. The required treatment is developed only at the top level, following standard medical practices. Individual patient situations and physician preference may change the preferred fluid treatment.

From the point of view of providing WFI for Exploration missions, the most demanding scenario is treating a 100-kg male. While NASA does not have official astronaut weight standards, the maximum height allowed is 76 in., and the maximum Air Force pilot weight at 76-in. height is 102 kg. The main goal in this study is to determine the overall volume of fluids required, and which solutions are generally preferred. These results will be used to define and size an IV fluid generation system. Actual fluid requirements for an operational system will be determined by the Space Medicine Division. A summary of the results can be found in Section 3.6.

3.1   Severe Burn

Serious burns result in increased capillary permeability, causing fluid to shift from the vascular system into the surrounding interstitial space. This shift occurs in thermal burns of second and third degree, as well as severe chemical, electrical, and radiation burns. For thermal burns, fluid treatment is based on the size of the burned surface area. Burn surface area calculations include areas with second- and third-degree burns, but not first-degree burns. Burns covering more than 15 percent total body surface area (TBSA) require fluid treatment to replace the lost intravascular volume. In these cases, prompt fluid treatment is critical to survival. There are many guidelines for fluid treatment, but the most widely recognized is the Parkland formula (ref. 31). Most guidelines recommend fluid treatment for 24 hr, and then lesser treatment for the next 24 to 48 hr, with fluid intake levels approaching normal maintenance requirements.

3.1.1   Standard Fluid Treatment Regimen

The Parkland formula recommends 4 mL/(kg %TBSA) of LR in the first 24 hr, with half of that amount given in the first 8 hr. These times are relative to the moment of injury, and a delay in treatment requires a corresponding increase in fluid delivery rate. Other formulas recommend similar volumes, but sometimes utilize NS and/or small volumes of colloids. The fluid treatment is required to make up the intravascular fluid loss, and cannot be taken orally. Large volumes of fluid can be required with time-critical delivery, and oral administration is insufficient for extensive burns. LR is generally preferred over saline because of the large volumes required and the fact that LR more closely approximates extracellular fluid, especially pH. Dextrose is not given in the initial 24 hr except for in children.

Fluid resuscitation is normally complete after 24 to 30 hr, but many terrestrial guidelines continue IV delivery for up to an additional 48 hr. Larger burns typically require more time for capillary permeability to return to normal. Subsequent treatment can include colloids to replace lost protein, as well as dextrose and other crystalloids for maintenance requirements. The total volume recommended in the second 24 hr ranges from half to nearly the same as the first 24 hr. Colloids of 5 percent albumin are sometimes recommended at

0.3 to 0.5 mL/(kg %BSA) in 24 hr for the second 24 hr, possibly continuing for the third 24 hr. One treatment guideline for the second 24 hr calls for LR at 2 mL/(kg %TBSA), colloids at 2 mL/(kg %TBSA), and 2 L of 5 percent dextrose in water (D5W). Another common terrestrial approach would be 2 L of 5 percent albumin, synthetic colloid, or plasma in the second 24 hr plus any maintenance requirements (~4 L) (ref. 31). Synthetic colloids such as pentastarch and hetastarch are new options that are being investigated. Colloids are not universally utilized for burn treatment, especially in the first 24 hr. Colloid use is more common for burns of greater than 40 percent TBSA because that therapy better maintains blood volume (ref. 32). For Exploration missions, fluids after the first 48 hr may be taken orally if the patient is physically able, but pain medication and ongoing activities may make it more conducive to continue IV delivery.

For this paper, the recommendations contained in The United States Naval Flight Surgeon Handbook, 2nd edition (1998) will be utilized (ref. 33). These guidelines were based on recommendations from Brooke Army Medical Center. The handbook recommends 2 to 4 mL/(kg %TBSA) of LR in the first 24 hr, with half of that amount given in the first 8 hr. Recommendations for the second 24 hr are 0.5 mL/(kg %BSA) of 5 percent albumin in LR (200 cc 25 percent albumin in 800 cc of LR) and D5W at 2 to 4 mL/(kg %TBSA), which is the same fluid hourly infusion rate as the first 24 hr. Albumin is not recommended for inclusion in Exploration missions because of uncertain efficacy, storage life concerns, and radiation concerns (see Section 2.3.8).

A 100-kg male with second- or third-degree burns over 40 percent of his TBSA is considered a worst-case burn scenario. In this situation, there are three risk factors for death. Burn area greater than 40 percent is one of these risk factors, with the other two risk factors being an age of 60 or older and inhalation injury (ref. 34). The mortality rate is 0.3 percent with no risk factors present, 3 percent with one factor, 33 percent with two factors, and 87 percent with three factors. Inhalation injuries are more common with burn victims in closed environments, which will generally be the case during Exploration missions. In applying those numbers to Exploration missions, while the astronauts probably will be younger than 60, any fire scenarios in a closed exploration vehicle are likely to cause inhalation injuries, virtually guaranteeing the presence of two risk factors. Hence, the mortality rate may be 33 percent for a burn injury greater than 40 percent TBSA. The level of care provided during Exploration missions will also not be as high as given in the study, which would increase the mortality rate. In addition, there are also severe constraints on the extra supplies to treat severe burns. Because of these considerations, this document assumes that a 40 percent TBSA burn is an upper bound on what NASA would attempt to treat, thus driving requirements for the production capacity of an IV fluid generation system.

When following recommended medical practices, a 100-kg male with a 40 percent burn surface area would require 16 L of LR in the first 24 hr according to the Parkland and Naval formula (8 to 16 L Naval), with 8 L given in the first 8 hr. The second 24 hr would require 8 to 16 L of D5W and 2 L of 5 percent albumin according to Naval guidelines. As mentioned above, this study does not recommend including albumin for Exploration class missions. The D5W rate is adjusted by monitoring urine output, but these tests may not be available on Exploration missions. Fluid treatment beyond 48 hr would only be required if the patient is physically unable to eat and drink. The maximum total fluid requirements would be 16 L of LR and 16 L of D5W, for a total of 32 L. Additional fluid requirements if the patient is physically unable to eat or drink after the second 24 hr are covered in Section 3.6. Note that the metabolic rate of burn patients can increase by a factor of 2 to 3 (ref. 35).

3.1.2 Alternative Treatments

Crystalloid fluid treatment is considered essential for the first 24 hr of burn treatment. The Parkland formula recommends fluid levels that are on the high end of the many guidelines, although actual hospital use can be significantly greater. The low end of Naval guidelines is 8 L in the first 24 hr for the described scenario. Colloid use is not always recommended, and albumin use and storage raises concerns. Some guidelines recommend greatly reduced or no fluid treatment beyond 24 hr. Fluid treatment for the first 24 hr only would require 8 to 16 L, and would probably incur minimal increased risk assuming the patient is able to eat and drink. A reasonably safe alternative treatment requires 12 L of LR and 12 L of D5W

over 48 hr. The minimum treatment would be 8 L of LR over 24 hr. NS could also be utilized instead of LR. NS is utilized in some hospitals, and reducing the fluid types provided on Exploration missions would have logistical benefits.

3.2 Hemorrhagic Shock

Hemorrhagic shock due to blood loss requires fluid treatment to maintain the intravascular volume. The blood loss can occur from a major laceration, blunt trauma, penetrating trauma, or other causes. Crystalloids are the appropriate treatment for moderate volume loss, but blood transfusions should normally be considered after 2 L of crystalloids. The general terrestrial rule of thumb is 1 unit of blood for every 3 units of crystalloid. Hemoglobin-based oxygen carriers (HBOCs) are a potential alternative for whole blood in cases of severe blood loss, assuming a sufficient supply while the body regenerates the red blood cells. Blood loss of 40 percent or greater (Class IV shock) requires prompt resuscitative measures to avoid patient demise, and therefore should be considered nonsurvivable in our operational environment.

Typical hemoglobin concentration levels are 15 g/dL. Although levels below 7 g/dL are generally felt to require blood transfusion, a study of patients refusing blood transfusions on religious grounds found few deaths attributed to anemia if the concentration remained above 5 g/dL (ref. 36).

3.2.1 Standard Fluid Treatment Regimen

Hemorrhagic shock generally utilizes only 2 L of crystalloids before considering blood or HBOC transfusion, although for the 100-kg male 3 L of crystalloids would provide the same dilution. NS is the most commonly used solution in emergency rooms. If the hemoglobin level is allowed to decrease from 15 to 7 g/dL without oxygen-carrier transfusion, 53 percent of the blood volume could be replaced with fluid. Males have a blood weight fraction of 7.5 percent, while females have a weight fraction of 6.5 percent. Given a blood specific density of 1.06, a 100-kg male has 7.1 L of blood, compared to the typical 70 kg male with 5 L of blood. These volumes do not account for any possible changes due to chronic hypogravity or hypoxic cabin environments.

A 100-kg male could receive 4 L of fluid while maintaining a hemoglobin concentration above 7 g/dL, and 5 L of fluid and maintain a hemoglobin concentration of 5 g/dL (ref. 36). Because crystalloids tend to leave the vascular system and diffuse to the interstitial volume, additional fluid is required to maintain proper intravascular volume while the patient recovers. Assuming a 30 percent intravascular volume loss is acceptable, a maximum 66 percent blood loss to maintain sufficient hemoglobin, and a 20 percent intravascular crystalloid retention, a maximum 12 L of NS would be required for the worst case. A patient would be physically unable to survive without an oxygen-carrier transfusion if the blood loss was more severe. Only 3 to 5 L would be delivered immediately, with the remaining amount delivery as the crystalloid leaves the intravascular volume and blood pressure drops. Infusing 12 L of crystalloid could introduce other serious problems, and should be considered an absolute worst case, to be used only if blood or HBOCs are not available.

3.2.2 Alternative Treatments

LR solution can also be used to treat hemorrhagic shock. While LR has a pH and osmolality closer to blood than NS, there are no definitive studies demonstrating superior clinical performance, and ERs generally use NS as a matter of cost and expediency. Colloid solutions can also be used to treat hypovolemia and have intravascular volume retention of 60 to 100 percent versus 20 to 30 percent for crystalloids. Based on the potential reduction in the size of spacecraft volume required for fluid generation capability, synthetic colloids such as hetastarch solutions may be considered. Conversely, those savings may well disappear when the additional resources required for an additional fluid type are considered. Because the medical literature reports little or no improvement of clinical outcome with

colloid use (refs. 14 and 37), at this time colloids are not recommended to treat hemorrhagic shock on Exploration missions.

3.3   Drug Delivery

Certain medications specify delivery by IV fluid. This restriction is often due to the need for a prolonged delivery timeline, and may be avoided in some emergency situations by a time course of injections. The ability to provide drugs by IV does have procedural advantages, eliminating the requirement for multiple injection sites, and providing versatility in controlling the drug introduction rate. Currently four drugs that are on the ISS require some volume of IV fluid for delivery, and four more are under consideration. Longer duration missions with no chance of timely transport will presumably carry more such drugs. There are many conditions in the PCDB that may require IV drug delivery, from severe conditions such as cardiac arrest to less life-threatening conditions such as various forms of infections. To provide a quick method for administering medicines if needed, starting an IV line upon arrival is standard procedure for serious conditions in most terrestrial emergency rooms. NS is often preferred as it avoids any potential problems with excess glucose, and LR cannot be injected at the same site with blood because of interactions with stabilizing chemicals (refs. 11 and 12).

3.3.1   Standard Fluid Treatment Regimen

Many of the drugs requiring IV delivery would be administered in one dose, or given over a relatively short duration. They would require only 1 to 2 L of fluid for injection. Conditions requiring long-term IV drug delivery, such as pain medication, typically require 1 to 2 L per day, with NS as the generally preferred diluent (ref. 14).

3.3.2   Last Resort Treatments

Fluid requirements could be reduced by utilizing higher drug concentrations at lower injection rates. For cases of immediate drug delivery, it may be possible to utilize only 1 L of solution, assuming 1 L increments. This reduces flexibility in changing drug dosages if multiple drugs are required. Terrestrial infection control practices include changeout of the entire fluid administration set every 48 hr, which implies the long-term fluid delivery rate could be as low as 0.5 L per day given appropriate drug concentration. Other fluids such as LR and D5W can also be utilized in most situations, although the use of D5W is more limited.

3.4   Bone Fracture

Fractures of major bones of the body such as the femur, radius, or hip may require fluid treatment. Fluid therapy may also be required for open or multifragmentary fractures of other bones. Major blood vessels could be severed, resulting in blood loss and hemorrhagic shock. In closed fractures, the blood loss is generally internal to the body. Treating severe fractures may require open reduction and realignment; these procedures may be simple enough for consideration on Exploration missions. This minor surgery would entail additional blood loss. A fracture of the femur is more severe, with major arteries subject to severing. A femur fracture can cause internal blood loss as high as 2 to 3 L, with compartment syndrome a major concern (refs. 14 and 38). Compartment syndrome occurs when bleeding within a muscle compartment causes swelling and dramatically increases the pressure within the compartment, producing capillary collapse, which may eventually lead to tissue necrosis. If not treated promptly, compartment syndrome can cause loss of limb or life. Treating of severe cases may require major surgery to avoid loss of life (refs. 14 and 39).

3.4.1   Standard Fluid Treatment Regimen

Fractures of the long bones in the arms and lower legs may cause internal blood loss and sequestration, but generally do not require fluid treatment. A worst-case scenario for these fractures that also includes open reduction may require up to 2 L of NS. Fractures of the femur can be far more severe. If a fasciotomy is not attempted to reduce intracompartmental pressure and avoid tissue necrosis, the treatment fluid volume required is bounded by the need to prevent excessive hemodilution while preserving adequate blood pressure. This internal blood loss limit is lower than that of the external blood loss case discussed in Section 3.2, hemorrhagic shock. An estimate of the maximum amount of fluid required to treat a femur fracture without a fasciotomy is 8 L of NS (ref. 13).

3.4.2   Last Resort Treatments

LR could be utilized instead of NS. In certain conditions, D5W could also be used, but is generally not due to the added potential of a glucose imbalance.

3.5   Fluid Maintenance

Humans require water to replace that which is lost during the day through bodily waste, through the skin as a heat regulation mechanism, and through the lungs because of evaporative losses during breathing. Normally water replacement is ⅔ from drink and ⅓ from food. A patient physically unable to eat or drink must have water, electrolytes, and caloric requirements replaced intravenously. The most common method to calculate requirements is the Holliday-Segar Method. This method is widely accepted, but was developed from pediatric studies in patients up to 70 kg in weight, and has not been verified for hypobaric environments. Hypogravity is known to at least temporally affect body fluid levels, and a low-pressure cabin might affect the fluid loss through respiration. For humans >20 kg, the daily requirements are 1500 kcal + 20 kcal/kg over 20 kg, 1 cc water/kcal, 3 mEq Na/100 cc water, 2 mEq K/100 cc water, and 2 mEq Cl/100 cc water (ref. 40).

A close match to the electrolyte requirements is D5 ¼ NS with an additional 20 mEq KCl/L added. A solution of D5 ½ NS with 20 mEq KCl/L is generally used instead to promote renal function and excretion. This solution only provides 1/6 of the caloric requirements, and is generally not utilized for more than 10 days. Dextrose is not used at the concentration required to provide total nutrition because the resulting osmotic pressure is several times higher than blood. For long-duration use, total parenteral nutrition (TPN) is required. TPN utilizes solutions with dextrose, amino acids, and electrolytes. The total fluid volumes are the same as before, but the solution is still hyperosmotic, and requires additional care and monitoring. The injection site is rotated because of the vein damage that occurs because of wound inflammation, as well as the acidity and osmolality of the solution being infused.

A common terrestrial approach to providing nutrition to patients unable to swallow is tube feeding. Enteral feeding is done by tubes inserted into the stomach (gastric or G-tubes), into the small intestine (jejunostomy or J-tubes) through the nose and into the stomach (nasogastric or NG-tubes) and through the nose and into the small intestine (nasojejunum or NJ-tubes). Special formulations are utilized that have a consistency and viscosity that permits transport through the tubes. The tube is flushed before and after with water to ensure it remains unobstructed. The water provided does not have to meet WFI requirements. This procedure may be considered for long-term nutrition in lunar or Martian gravity, but it has not been proven in microgravity. Tube feeding in terrestrial settings requires that the patient is upright, no less than 30°, during the feeding and for 30 to 60 min after feeding. This is to minimize the risk of regurgitation and aspiration. This also implies that gravity is necessary to prevent the food from traveling up the esophagus. When tube feeding, the lower esophageal sphincter is unable to completely seal against the feeding tube, and the liquid would migrate up the esophagus from capillary forces without gravity to keep it down. NG-tubes are used in a horizontal position in terrestrial emergency settings, such as to avoid spinal movement. Aspiration is a concern and monitored carefully. Often suction is used to

avoid and/or treat aspiration, but may not be available in Exploration missions. The more invasive G-tube, inserted directly into the stomach through the abdomen, would not have the regurgitation problem, but involves minor surgery and an increased risk of infection. G-tube surgery in microgravity is more complicated because of the unknown influence of microgravity on anatomical positions of intra-abdominal organs, the unclear physiological processes due to microgravity or hypogravity, and other factors.

3.5.1 Standard Fluid Treatment Regimen

A 100-kg male would require 3.1 L of fluid per day according to the Holliday-Segar formula. The solution would typically be D5 ½ NS + 20 mEq KCl/L. This should continue for no longer than 10 days before alternative treatments would be required because of the lack of calories and other trace chemicals. Assuming the patient would be treated with fluids only for 14 days, 44 L of fluid would be required. The upper limit is 14 days because beyond that the condition is considered nonsurvivable without TPN or tube feeding. Tube feeding would not require medical water generation, and TPN is not considered as likely on an Exploration mission.

3.5.2 Alternative Treatments

D5 ¼ NS + 20 mEq KCl/L is a commonly utilized treatment that better meets sodium requirements. Because of normal spaceflight restrictions, NASA may elect to specify only one maintenance fluid to be provided onboard. In order to minimize solution types, treatment utilizing 2 to 4 L of D5W to every 1 L of NS supplemented with KCl would provide the appropriate sodium ion, potassium, and chloride ion intake, but with reduced caloric intake. The daily intake of D5W could be increased to raise the caloric intake, resulting in increased urine output.

Short-term treatment could potentially use just D5W and NS without potassium supplements. Potassium is primarily an intracellular ion, with 98 percent of the potassium found inside cells. Despite this, the blood potassium level generally reflects total body potassium. A blood potassium level of 3.5 to 5.0 mEq/L is considered normal, with levels below 2.8 mEq/L causing concern (ref. 41). A healthy person in a terrestrial environment can survive 10 days before the potassium level became dangerously low, if a short-term potassium drop of 20 percent is considered acceptable in an emergency. This is derived from blood potassium levels dropping from 3.5 to 2.8 mEq/L, a normal total body potassium level of 120 g, and a daily requirement of 2.5 g (refs. 40 and 41).

3.6   Medical Treatment Summary

Five different generic patient conditions were described and fluid requirements developed. Terrestrial care facilities employ a wide variety of treatment options, using several different types of crystalloid and colloidal solutions. Little evidence in the medical literature supports one treatment option over the other. Because of the multiple treatment options, and the lack of clear guidance from evidence-based medicine, it is recommended that no more than three types of fluids be provided, and consideration should be given to only providing the option of two fluids during a mission. The three recommended fluids are LR solution, NS, and a dextrose-based solution D5 ¼ NS + 20 mEq KCl/L that will be referred to as D5KS. If only two fluids are provided, D5KS and NS are recommended.

D5KS is a standard maintenance fluid that provides the recommended amounts of sodium and potassium according the Holliday-Segar Method. It also provides the maximum amount of dextrose while still maintaining a near-normal osmotic pressure. D5KS would provide one solution that would be utilized for both maintenance requirements and burn treatment. Electrolytes are sometimes avoided in burn treatment during the second 24 hr (where D5W treatment is common), but some treatment regimens include electrolytes (ref. 31). The saline level is low enough in D5KS that concerns of excessive sodium levels would be minimal. D5KS also contains the appropriate levels of potassium, which would reduce

concerns if long-term maintenance is required. The recommended fluid treatment for these generic patient conditions is given in table V. The medical community may develop their own set of recommendations, but it is expected they would be similar to these, especially with respect to the maximum volume required.

TABLE V.—FLUID REQUIREMENTS FOR GENERIC
PATIENT CONDITION TREATMENT

Condition	Fluid treatment	Discussion
40% TBSA burn	16 L LR; 16 L D5KS	Section 3.1
Hemorrhagic shock	12 L NS	Section 3.2
Drug delivery	2 L NS initially, 2 L NS/day	Section 3.3
Fracture	8 L NS	Section 3.4
Maintenance fluids	3.1 L D5KS/day	Section 3.5

LR and NS are nearly interchangeable solutions, with usage often based on historical or clinician preference. LR is considered to be closer to physiological normal, but there is little evidence of benefits over NS in most clinical or emergency settings. LR is generally preferred during surgeries, with some evidence of its benefits over NS (ref. 42). However, major surgeries are not being planned for in Exploration missions. LR is the preferred solution for burn treatment, but there have been no major studies comparing LR to NS in burn patients. NS is quite common in emergency room settings, and even large dosages do not cause problems, especially in initially healthy adults (ref. 14). Carrying one type of electrolyte solution would reduce logistics, as well as potentially providing better emergency response. Because the two fluids are nearly interchangeable, recommendations for fluid generating capacity will be given for three cases: LR and NS not interchangeable, LR and NS completely interchangeable, and NS only.

4.0   Exploration Mission Fluid Requirements

NASA is currently considering and planning a wide variety of missions that vary in duration from several days to many months in the case of a Martian voyage. The missions also differ from one another by the ease with which a patient can be returned to Earth. These two factors, duration and ease of return, dictate different fluid generation and mixing requirements for each mission, even for the same set of patient conditions. There will also be considerable differences in the mass allotted for medical supplies to treat patient conditions. In this section we outline treatment timelines and fluid needs for four different missions, one to ISS, a Lunar visit, a Lunar habitat, and a trip to Mars.

4.1   ISS

The ISS currently has a crew of three, with a planned increase to six crewmembers in the future. There will be some major physical activities during the ISS construction stage, and occasionally during maintenance. During operations, the ISS will be continually manned, with crews serving for 6-month missions.

4.1.1   Treatment Timeline

The long-duration nature of the mission allows for some flexibility in the treatment timeline. The time, space, and potentially the supplies required are available to treat the patient in situ. Patients could be allowed to stabilize after major injury prior to transport to Earth. The transport time would be a matter of hours, but loading time may be extended because of issues of moving the patient. For a worst-case condition, the patient could be stabilized for up to 2 weeks prior to transport.

4.1.2   Critical Fluid Patient Conditions

The critical fluid patient conditions for an ISS mission are severe burns, hemorrhagic shock, major fractures, and IV maintenance. It is expected that most medical events would involve only one patient, but

a major fire could encompass multiple crewmembers. The potentially long stabilization time makes maintenance the largest potential fluid requirements event.

Femur fractures and hemorrhagic shock would likely be encountered by only one patient, and would require a maximum of 12 L of NS, and possibly 3 days of maintenance requiring 9 L of D5KS. An infection or other minor illness or trauma requiring medication delivery or maintenance fluid may arise in one patient. It is envisioned that such treatment would not extend beyond 7 days for a patient requiring only drug delivery, or 3 days for a patient requiring maintenance. In these cases the fluid volume requirements would be 16 L of NS (2 L/day + 2 L initially) and 4 L NS + 9 L D5KS (initial treatment + maintenance), respectively. A major fire could involve more than one crewmember. For planning purposes, this document assumes one 100-kg crewmember with 40 percent TBSA full-thickness burns, and a second 100-kg crewmember with 20 percent TBSA full-thickness burns. There would be a combined requirement of 24 L of LR and 24 L of D5KS in the first 48 hr of treatment.

The fluid maintenance requirement would be in addition to any treatment for the condition that caused the debilitation. The worst-case scenario for IV fluid requirements would be for maintenance treatment subsequent to a burn. The assumption will be that one crewmember will require maintenance for 12 days beyond the initial treatment, and the second 5 days beyond the initial treatment. This would require a total of 53 L of D5KS in addition to that required in the first 48 hr. The fluid requirements for the described events are given in table VI.

TABLE VI.—FLUID REQUIREMENTS TO TREAT TWO CREWMEMBERS
WITH MAJOR INJURIES/ILLNESSES ON THE ISS

Burn	Major long bone fracture	Trauma with hemorrhagic shock	Illness will drug delivery	Trauma or illness with maintenance
24 L LR 77 L D5KS	8 L NS	12 L NS 9 L D5KS	16 L NS	4 L NS 9 L D5KS

4.1.3   Overall Fluid Requirements

The events described can be broken into two categories: major events that would most likely result in an evacuation and termination of the mission, and minor conditions that might be treated without evacuation. The capability should exist to handle any major event after the occurrence of a minor event if evacuation does not take place or supplies are not replenished. Prior to Orion availability, if the ISS crew complement expands to six, a partial evacuation could be conducted if the envisioned two Soyuz lifeboats are present. Partial evacuation could not take place if the only lifeboat was one Orion capsule. In all likelihood, any burn serious enough to require fluid treatment (>15 percent TBSA) would require evacuation, as well as any major fracture where bone mending in microgravity would be a concern. These two patient conditions would be considered major events. An infection or other minor illness requiring medication delivery or maintenance would be considered a minor event. A combination of these minor events or a chronic minor event could require more fluid than a mission-terminating major event. A severe hemorrhagic shock event may or may not require mission termination, but will be considered as both a major and minor event as it results in a larger fluid volume requirement.

Table VII gives the fluid requirements to handle missions with varying combinations of medical situations. The volume requirements are based on handling multiple events prior to restocking the supplies, and include missions with any one event, any one minor event and any one major event, and any two minor events and any one major event. The volumes listed are dependent on whether LR or NS are considered interchangeable and if only NS is provided (see Section 3.6). Based on these volume requirements and the near-complete interchangeability of LR and NS, it is our recommendation that while LR and NS may be considered interchangeable during emergencies, and both fluids should be provided onboard. This reduces the volume requirements and allows some flexibility for unique situations. It is not anticipated that the production of LR will be substantially different than NS, but this recommendation is subject to change dependent on findings of the relative suitability for production. The total volume required for any one minor event and any one major event would be 126 L as 20 L LR, 20 L NS, and

86 L D5KS. The total volume required for any two minor events and any one major event would be 151 L as 28 L LR, 28 L NS, and 95 L D5KS.

Given the nature of emergent events and the length of time that may be required to stabilize the situation and begin to operate water generation equipment, enough fluid should be on hand to treat any emergency situations for 8 hr prior to producing more solutions. Femur fractures and hemorrhagic shock would likely be encountered by only one patient, and would require a maximum of 12 L of NS in a short timeframe. Medication delivery and maintenance requirements would consume substantially less fluid in the first 8 hr. The major fire scenario would have a combined requirement for both patients of 12 L of LR in the first 8 hr. It is recommended that 2 L of D5KS be immediately available for other minor treatments that require a dextrose solution. Note that with the recommendation to treat LR and NS as interchangeable, the 8-hr contingency requirement of 12 L of crystalloid to treat either a severe burn or a hemorrhagic shock event is the same as a 2-hr contingency requirement of crystalloid to treat a hemorrhagic shock event. The water production system should have the ability to produce an additional 22 L of D5KS over 24 hr to satisfy the burn requirement, and a long-term production rate of 6.2 L/day over 14 days maximum to satisfy the maintenance requirement assuming 2 crewmembers require support. The system would have to be able to produce 12 L of LR or NS over 16 hr to satisfy the burn scenario.

TABLE VII.—OPTIONS FOR FLUID TYPES AND AMOUNTS NEEDED ON THE ISS

Event	LR and NS not interchangeable	LR and NS interchangeable[a]	NS only
Any one event	24 L LR 16 L NS 77 L D5KS 117 L total	12 L LR 12 L NS 77 L D5KS 101 L total	24 L NS 77 L D5KS 101 L total
Any one minor event and any one major event	24 L LR 28 L NS 86 L D5KS 138 L total	20 L LR 20 L NS 86 L D5KS 126 L total	40 L NS 86 L D5KS 126 L total
Any two minor events and any one major event	24 L LR 44 L NS 95 L D5KS 163 L total	28 L LR 28 L NS 95 L D5KS 151 L total	56 L NS 95 L D5KS 151 L total
8-hr contingency fluid storage	12 L LR 12 L NS 2 L D5KS 26 L total	6 L LR 6 L NS 2 L D5KS 14 L total	12 L NS 2 L D5KS 14 L total

[a]Interchangeable means that while both fluid types should be available, and one may be preferentially used, substitutions are envisioned.

4.2   Lunar Sortie

A lunar sortie mission will include four crewmembers for up to 7 days on the surface. EVAs will be accomplished in pairs, with potentially all four members on the surface at once. The crew will be conducting many EVAs during the mission, with an increased potential for physical injury when compared to the ISS. The low gravity and normal bone mass (for short-duration missions) will tend to mitigate physical injuries from personal events such as minor falls. The unique operating environment and mission parameters may make major events such as a low-speed motor vehicle accident or landslide more probable than operation on Earth because of the lack of knowledge and experience. Orion and the lunar lander will operate with a low-pressure, high-oxygen-level atmosphere, which increases the risk of fire. EVA suits will operate at similar conditions or lower pressures with even higher oxygen levels.

4.2.1   Treatment Timeline

The short duration of the mission limits the potential time for patient stabilization prior to Earth return. It also lessens the chance of multiple events during the mission. A maximum of 7 days can be spent on the surface, and transport back to Earth can occur from any site at any time in 5 days or less.

Medical events that happen during the initial transit to the Moon can utilize the free-return abort mode as in Apollo 13, limiting the maximum total treatment time to 6 days for an event in the early stages of the mission when a direct-return is not possible. The limited supplies in these missions will restrict the time allowed for stabilization prior to starting return. Requirements in this document assume that transport will begin 24 hr after any major incident.

4.2.2   Critical Fluid Patient Conditions

The critical fluid patient conditions are burns, hemorrhagic shock, and major fracture. Total maintenance fluid requirements are lower than for the ISS mission because of the fewer days of treatment (6 versus 14). Severe illness or infections that would require long-term drug delivery are not considered likely on these short-duration missions if astronauts are effectively prescreened for health conditions.

A major fire could affect more than one crewmember, but such a large fire has a strong potential to damage the spacecraft enough to prevent return. The requirements in this document will assume a fire in the spacecraft or spacesuit involving one 100-kg crewmember with a 40 percent TBSA full-thickness burn. This scenario would require 16 L LR and 16 L D5KS for treatment in the first 48 hr. If return transport begins 24 hr after the fire, a treatment duration of 6 days is required, with an additional 12 L of D5KS over the last 4 days of treatment in this worst-case scenario. EVA contingency planning may handle accidents where an astronaut sustains fractures or lacerations. A suit breach may occur and require patching as well. However, medical treatment could not occur until the astronaut is back in the lander, increasing the blood loss when compared to a terrestrial setting. A hemorrhagic shock event could require up to 12 L of NS + 9 L D5KS over 3 days for treatment, while a fracture could require up to 8 L of NS. A minor event that may occur such as space motion sickness (SMS) could require initial drug treatment and maintenance over 2 days, requiring an initial 2 L NS and 6 L D5KS maintenance fluid. The fluid requirements for the described events are given in table VIII.

TABLE VIII.—FLUID REQUIREMENTS TO TREAT TWO
CREWMEMBERS ON THE LUNAR SORTIE

Type of injury or illness	Fluid needed
Burn (1 patient)	16 L LR 28 L D5KS
Major long bone fracture	8 L NS
Trauma with hemorrhagic shock	12 L NS 9 L D5KS
Trauma or illness with maintenance	2 L NS 6 L D5KS

4.2.3   Overall Fluid Requirements

Medical events for lunar sorties can also be categorized as major events that terminate the mission immediately, and minor events that allow the mission to continue. For a lunar sortie, only a full-thickness burn with TBSA greater than 15 percent and a severe hemorrhagic shock event are considered major. Bone mending would not be a concern for the short-duration mission, although incapacitation of part of the crew may require mission termination. A fracture and an illness are considered minor events. Because of the relatively short nature of the mission, only scenarios involving up to two events are considered.

Table IX gives the fluid requirements for a lunar sortie mission. It is recommended that only NS be provided as a crystalloid to reduce mass, volume, and inventory. If only one fluid is provided, a total of 44 L of fluid would be required to treat any one event. Also, 52 L of fluid would be required to treat any one minor event and any one major event. The 8-hr contingency storage is 14 L. Note that with LR and NS considered interchangeable, the 8-hr contingency requirement is the same as a 2-hr contingency requirement for one medical event, driven by the hemorrhagic shock requirement. The water production system should have the ability to produce approximately 0.5 L/hr for 40 hr to satisfy the burn treatment requirement, and 3.1 L/day to satisfy maintenance requirements for one crewmember.

TABLE IX.—OPTIONS FOR FLUID TYPES AND AMOUNTS NEEDED TO TREAT CONDITIONS ON
THE LUNAR SORTIE WITH VARYING LEVELS OF SEVERITY

Conditions	Fluid type		
	LR and NS not interchangeable	LR and NS interchangeable[a]	NS only
Any one event	16 L LR 12 L NS 28 L D5KS 56 L total	8 L LR 8 L NS 28 L D5KS 44 L total	16 L NS 28 L D5KS 44 L total
Any one minor event and any one major event	16 L LR 14 L NS 37 L D5KS 67 L total	12 L LR 12 L NS 37 L D5KS 61 L total	24 L NS 37 L D5KS 61 L total
8-hr contingency fluid storage	8 L LR 12 L NS 2 L D5KS 22 L total	6 L LR 6 L NS 2 L D5KS 14 L total	12 L NS 2 L D5KS 14 L total

[a]Interchangeable means that while both fluid types should be available, and while one may be preferentially used, substitutions are envisioned.

4.3   Lunar Habitat

The lunar habitat missions currently envisioned will require a crew of four occupying an outpost for up to 6 months. A continuous human presence on the Moon will be accomplished by crew rotation. The supplies available for medical treatment may well be increased over the short-duration missions, but exact parameters have not been established. The vehicles developed for the lunar sortie will be used for crew rotation. This implies a maximum 5 days from return decision to touchdown. One of the purposes of this class of missions is validating technologies required for Martian exploration, including medical capabilities. These missions are the best opportunities for evaluating medical technologies and procedures for Mars missions when no return will be possible.

4.3.1   Treatment Timeline

This study assumes that the treatment timeline is similar to that outlined for the ISS. The facilities available will allow time for patient stabilization prior to transport if that is the best course of action. Because of the relatively long transportation time with limited facilities, in situ treatment may produce better outcomes than evacuation. Requirements in this document envision that a patient could be stabilized for up to 14 days prior to a 5-day evacuation. Not considered are potential mission scenarios with an extended-duration rover away from the habitat for several days.

4.3.2   Critical Fluid Patient Conditions

The envisioned scenarios are assumed to be similar to that described for the ISS, albeit with a potentially longer treatment timeline. The likelihood of a particular incident may be different. Femur fractures or hemorrhagic shock for a single patient could require a maximum of 12 L of NS, and 3 days of maintenance with 9 L of D5KS. An infection or other minor illness or trauma requiring medication delivery or maintenance fluid may arise in one patient. Requirements presented in this document presume that such treatment would not extend beyond 7 days for drug delivery, or 3 days for maintenance. The fluid volume requirements would be 16 L of NS (2 L/day + 2 L initially) and 4 L NS + 9 L D5KS (initial treatment + maintenance), respectively. A major fire could involve more than one crewmember; this document will assume one 100-kg crewmember with 40 percent TBSA full-thickness burns, and a second 100-kg crewmember with 20 percent TBSA full-thickness burns. The combined requirement would be 24 L of LR and 24 L of D5KS in the first 48 hr of treatment.

The fluid maintenance requirement for any condition would be in addition to any treatment that caused the debilitation. The worst-case scenario requires maintenance fluids after a burn event. The assumption is that one crewmember will require maintenance for 12 days beyond the initial treatment plus

5 days treatment during transport, with the second crewmember requiring 5 days maintenance beyond the initial treatment. The total fluid requirement is then 68 L of D5KS in addition to that required in the first 48 hr. The fluid requirements for the described events are given in table X.

TABLE X.—FLUID REQUIREMENTS TO TREAT TWO
CREWMEMBERS DURING A LUNAR HABITAT MISSION

Condition	Required fluid
Burn (two patients)	24 L LR
	92 L D5KS
Major long bone fracture	8 L NS
Trauma with hemorrhagic shock	12 L NS
	9 L D5KS
Illness with drug delivery	16 L NS
Trauma or illness with maintenance	4 L NS
	9 L D5KS

4.3.3   Overall Fluid Requirements

The events described can be broken into major events that would most likely result in an evacuation and termination of the mission and minor conditions may potentially be treated without evacuation, as was done with the ISS events. The system should still have the capability to handle any major event after a minor event occurs, even if evacuation does not occur. Burns and long bone fractures will be considered major events; drug delivery and maintenance will be considered minor events. An episode of severe hemorrhagic shock will be considered as both a major and a minor event as it results in a larger fluid volume requirement.

Table XI gives the fluid requirements to handle missions with varying combinations of medical situations. While LR and NS are interchangeable in many situations, this document contains requirements for both fluids due to the slight advantage LR has in fluid resuscitation for 40 percent full thickness burns.

TABLE XI.—OPTIONS FOR FLUID TYPES AND AMOUNTS NEEDED TO TREAT CONDITIONS
DURING A LUNAR HABITAT MISSION WITH VARYING LEVELS OF SEVERITY

	LR and NS not interchangeable	LR and NS interchangeable[a]	NS only
Any one event	24 L LR	12 L LR	24 L NS
	16 L NS	12 L NS	92 L D5KS
	92 L D5KS	92 L D5KS	
	132 L total	116 L total	116 L total
Any one minor event and any one major event	24 L LR	20 L LR	40 L NS
	28 L NS	20 L NS	101 L D5KS
	101 L D5KS	101 L D5KS	
	153 L total	141 L total	141 L total
Any one minor event and any one major event	24 L LR	28 L LR	56 L NS
	44 L NS	28 L NS	110 L D5KS
	110 L D5KS	110 L D5KS	
	178 L total	166 L total	166 L total
Any one minor event and any one major event	12 L LR	6 L LR	12 L NS
	12 L NS	6 L NS	2 L D5KS
	2 L D5KS	2 L D5KS	
	26 L total	14 L total	14 L total

[a]Interchangeable means that while both fluid types should be available, and one may be preferentially used, substitutions are envisioned.

Treating any one minor event and any one major event would require 141 L as 20 L LR, 20 L NS, and 101 L D5KS. Treating any two minor events and any one major event would require 166 L as 28 L LR, 28 L NS, and 110 L D5KS. The 8-hr contingency requirement is 14 L as 6 L LR, 6 L NS, and 2 L D5KS. Again, with LR and NS considered interchangeable, the 8-hr contingency requirement is the same as a 2-hr contingency requirement. The water production system should have the ability to produce approximately 1 L/hr for 40 hr to satisfy the burn treatment requirement, and 6.2 L/day to satisfy maintenance requirements for two injured crewmembers.

4.4   Mars Exploration

Mars Exploration is planned as a conjunction-class mission, with a 6-month transit to and from Mars, and an 18-month stay. A crew of six will be included on this 2.5-year mission. No early return is possible in the case of an emergency. All medical conditions must be treated onsite with available resources. This mission will include extended time in both microgravity and 0.38g. A predeployed surface habitat, and a predeployed Mars lander will precede crew launch. Separate medical equipment may well be provided for the transfer vehicle and the habitat.

4.4.1   Treatment Timeline

The inability to transport injured crew to Earth facilities requires that all medical conditions, except those at the very beginning or end, must be treated to recovery, supply exhaustion, or death of the patient. The total mission length is equivalent to the combination of two continuous ISS expeditions in microgravity and three continuous lunar habitat expeditions in partial gravity. The medical conditions that may be encountered on the Martian surface are similar to those for the lunar habitat. The microgravity transit will presumably not include any construction activities like on ISS, but may include repair EVAs.

4.4.2   Critical Fluid Patient Conditions

The medical conditions that may be encountered on the Martian surface are similar to those for the lunar habitat. The microgravity transit will presumably not include any construction activities as on ISS, but may include repair EVAs. The fluid requirements for a Mars mission could be either greater or less than that for a lunar habitat mission depending on basic assumptions. For instance, while saving a patient with 40 percent TBSA full-thickness burns may be possible in the short term, carrying the supplies to treat the patient for the complete time required for recovery may be impractical. While the decision to treat such a chronic condition will affect the total amount of medical water required, requirements for other medical supplies may be so great that the condition will not be treated. In that case, the additional medical water will not be needed. To develop an appropriate envelope for fluid requirements, this report will assume that treatment is attempted in such patients. The increased crew size, long duration, and extreme environment all increase the probability of more severe medical conditions. As a result, the fluid requirements will reflect the potential for increased treatment duration.

The largest fluid requirement again results from a fire, which may injure multiple crewmembers because of the closed environment. Such a fire may not damage the equipment beyond crew survival. Requirements in this document assume that one patient suffers a 40 percent TBSA full-thickness burn, and requires 28 days of maintenance fluids, and a second patient suffers a 20 percent TBSA full-thickness burn, requiring 12 days of maintenance fluids. This scenario would require 24 L of LR and 148 L of D5KS. A total treatment time of 30 days maximum is chosen because of a low probability of survival beyond that point on maintenance fluids alone. Maintenance fluid treatment provides only 1/6 of the calories and none of the trace elements required for nutrition. Treatment beyond 30 days would require nutrition from tube feeding or total parenteral nutrition. Such treatment would generally begin after 1 to 2 weeks if available, and 30 days is considered an upper limit on survival on IV fluids alone. An incident resulting in a femur fracture could require 8 L of NS for treatment. A trauma that also includes hemorrhagic shock could require 12 L of NS and 16 L of D5KS for 5 days of maintenance. An illness requiring drug treatment for 10 days would require 22 L of NS (2 L initially + 2 L/day). A trauma or illness that requires fluid maintenance for 5 days would require 4 L NS and 16 L D5KS. The fluid requirements for the described events are given in table XII.

TABLE XII.—FLUID REQUIREMENTS TO TREAT TWO CREWMEMBERS
WITH MAJOR INJURIES/ILLNESSES DURING A MARS MISSION

	Type of incident				
	Burn (tow patients)	Major long bone fracture	Trauma with hemorrhagic shock	Illness with drug delivery	Trauma or illness with maintenance
Fluid required	24 L LR 148 L D5KS	8 L NS	12 L NS 16 L D5KS	22 L NS	4 L NS 16 L D5KS

4.4.3 Overall Fluid Requirements

All medical situations arising on a Mars mission must be treated until resolution because of the inability to transport for further care. As with other mission scenarios, a serious fire produces the largest need for medical fluids. Driven by the possibility of long-term fluid maintenance requirements, fluid requirements are developed that consider one fire event in combination with other events.

Table XIII gives the fluid requirements to handle missions with varying combinations of medical situations. A mission with up to three medical events is analyzed because of the extreme duration of the mission. The question of whether LR and NS are interchangeable has less relevance because of the grouping of event types. A burn is the only situation where LR is medically preferred. Including LR results in no difference in total fluid requirements when compared to multiple events where burns are not treated. Therefore, this document requires both LR and NS be provided onboard at the volumes recommended with LR and NS not considered interchangeable. This changes only the relative amount of LR and NS (increasing NS) and does not increase the total volume. Nevertheless, as is common in most emergency rooms, the 8-hr contingency requirement should be met by assuming the LR and NS are interchangeable, to reduce the requirement by 50 percent. The total volume required to treat any two minor events and a major burn event would be 248 L as 24 L LR, 44 L NS, and 180 L D5KS. The total volume required to treat any three minor events and a major burn event would be 286 L as 24 L LR, 66 L NS, and 196 L D5KS. The 8-hr contingency recommendation is 14 L as 6 L LR, 6 L NS, and 2 L D5KS. As in the other DRMs, the 8-hr contingency requirement with LR and NS considered interchangeable, at least in the short term, is the same as a 2-hr contingency requirement. The water production system should have the ability to produce approximately 1 L/hr for 40 hr to satisfy the burn treatment requirement, and 6.2 L/day to satisfy maintenance requirements for twocrewmembers.

TABLE XIII.—OPTIONS FOR FLUID TYPES AND AMOUNTS NEEDED TO
TREAT CONDITIONS (VARYING LEVELS OF SEVERITY) DURING A MARS MISSION

Scenario	LR and NS not interchangeable	LR and NS interchangeable[a]	NS only
Any one event	24 L LR 22 L NS 148 L D5KS 194 L total	12 L LR 12 L NS 148 L D5KS 172 L total	24 L NS 148 L D5KS 172 L total
Any one minor event and one burn event	24 L LR 22 L NS 164 L D5KS 210 L total	23 L LR 23 L NS 164 L D5KS 210 L total	46 L NS 164 L D5KS 210 L total
Any two minor events and one burn event	24 L LR 44 L NS 180 L D5KS 248 L total	34 L LR 34 L NS 180 L D5KS 248 L total	68 L NS 180 L D5KS 248 L total
Any three minor events and one burn event	24 L LR 66 L NS 196 L D5KS 286 L total	45 L LR 45 L NS 196 L D5KS 286 L total	90 L NS 196 L D5KS 286 L total
8-hr contingency fluid storage	12 L LR 12 L NS 2 L D5KS 26 L total	6 L LR 6 L NS 2 L D5KS 14 L total	12 L NS 2 L D5KS 14 L total

[a]Interchangeable means that while both fluid types should be available, and one may be preferentially used, substitutions are envisioned.

4.5   Fluid Requirements Summary

Potential medical conditions were hypothesized for Exploration missions, and the fluid treatment requirements developed. Total mission fluid requirements were developed based on treating various combinations of medical events. It is recommended that LR and NS be considered nearly interchangeable electrolytes to reduce the overall volume requirements (as discussed in Section 3.6).

Table XIV gives the final recommended volumes for the various missions. The longer duration missions include fluid to treat multiple medical events. Mass constraints may limit the fluid provided on missions, so a minimum fluid recommendation is also included. NS, whether premixed or mixed on-board during an emergency, is the only electrolyte included in the minimum recommendations. The ISS minimum recommendation would be sufficient to treat any one medical event excluding maintenance fluids (dextrose is carried to meet the 48-hr fluid requirement for burns). The lunar sortie minimum recommendation would cover any one event except a burn event, and excluding maintenance fluids. It would provide the minimum volume recommendations for a 100-kg patient with 30 percent burns, although not the caloric intake provided by D5KS and not any fluids beyond the first 48 hr. The lunar habitat minimum recommendation would treat any one event, excluding maintenance requirements. The minimum recommended for a Mars mission is more generous. It would cover the initial fluid requirements of the burn event with two patients, and the initial requirements of any other one event. Maintenance fluids for a total of 15 days are also included to treat the 3 potential patients.

TABLE XIV.—FLUID VOLUME RECOMMENDATIONS FOR EXPLORATION MISSIONS

Mission	Recommended event coverage	Fluid volume recommendation	Minimum fluid recommendation
ISS	Any one minor event and any one major event	20 L LR 20 L NS 86 L D5KS 126 L total	24 L NS 24 L D5KS 48 L total
Lunar Sortie	Any one event	8 L LR 8 L NS 28 L D5KS 44 L total	12 L NS 12 L total
Lunar Habitat	Any one minor event and any one major event	20 L LR 20 L NS 101 L D5KS 141 L total	24 L NS 24 L D5KS 48 L total
Mars Exploration	Any two minor events and one burn event	34 L LR 34 L NS 180 L D5KS 248 L total	36 L NS 69 L D5KS 105 L total

5.0   Considerations For Creating Water for Injection

There are many questions that need to be answered when developing a WFI production system for NASA's Exploration missions. The unique operational environment raises additional challenges not encountered when developing a ground-based system, which will require special consideration. In addition, the initial water source supplied to the system may have important differences from the water that ground-based systems typically employ. The gravity level, radiation level, and sealed environment all raise concerns about microbial contamination and how to maintain sterility of the system in conditions not previously encountered by WFI systems. These concerns are in addition to the normal NASA concerns on weight, volume, power, and reliability.

5.1   Water Quality Requirements

The requirements for WFI and SWFI are set out in the United States Pharmacopeia–National Formulary (USP–NF), currently USP 29–NF 24 issued in 2006. That document contains specific requirements that must be met, as well as general requirements that can be difficult to quantify. The general, unquantified requirements could be problematic with a unique system specific to NASA's needs.

For example, USP standards for WFI, covered in Section 5.1.4, require distillation, reverse osmosis (RO), or a system that provides equivalent or better performance. A more stringent reading of the USP standard might lead to the conclusion that only distillation and RO are approved methods for producing WFI, limiting the technology choices but perhaps making validation easier.

NASA's needs may be better met by a new type of system, but defining equivalent performance of existing systems could be a challenge. As an example, the USP standard requires that source water meet Environmental Protection Agency (EPA) potable water standards. The EPA does not have standards on all possible contaminates, such as iodine and silver because biocides are not normally a problem with public water systems. Biocides are not allowed in water for injection and must be removed. Silver is used by the Russians as a biocide and remains in the potable water at 0.50 mg/L, while iodine is used as NASA's biocide and is removed at the point of use. The EPA does not have a primary standard for silver, but does have a secondary, nonenforceable guideline of 0.10 mg/L. NASA's ISS MORD (Medical Operations Requirement Document) has a requirement of 0.50 mg/L for silver and 0.05 mg/L for iodine at point of use. The Food and Drug Administration (FDA) recommended daily allowance for iodine is 0.150 mg. The USP standards for the solutions of interest indicate that no antimicrobial agents are allowed, but were written assuming processing that starts with public water sources. Iodine and silver are present in groundwater at low levels. The USP standards require iodine and silver removal equivalent to distillation or RO. This may require determining a proven USP WFI production system performance for silver and/or iodine removal. The Exploration Life Support group is currently looking at alternative biocides that could remain in the potable water, with silver high on the list, and a WFI system would have to be designed to remove those as well with performance equivalent to that of distillation and/or RO.

5.1.1 FDA Medical Standards

The USP is a not-for-profit private organization founded in 1820. The Federal Food, Drug, and Cosmetics Act recognizes the USP–NF as the official compendia for medicines marketed in the United States. The FDA supervises the development of new drugs, while the USP–NF provides the standards for production and distribution. The standards in the USP–NF are legally enforceable. The current standards for IV fluids are given in USP 29–NF 24 (ref. 49). Packaged parenteral solutions require water meeting WFI standards as outlined in the Official Monographs and then rendered sterile. Alternatively, the parenteral solution can use water meeting SWFI standards if protected from subsequent microbial contamination. WFI is prepared from water meeting EPA regulations or comparable regulations of the European Union or Japan. It contains no added substance. There are specific requirements that WFI and SWFI must meet, as well as the requirements for the parenteral solution. Sodium chloride injection and dextrose injection must include no less than 95 percent and no more than 105 percent of the labeled amount of solute. LR injection has similar requirements on the individual solutes, although the tolerance is ±10 percent for most solutes in LR.

USP–29 provides inconsistent direction on whether a technology other than distillation or RO is permitted for WFI production. The Official Monograph for WFI begins by stating, "Water for Injection is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms." This statement clearly allows for alternative technologies to be used in WFI production. However, in Chapter 1231, "Water for Pharmaceutical Purposes," there is a contradictory statement that WFI water that "is finally subjected to distillation or RO. A later sentence in the chapter states "Other technologies such as ultrafiltration may be suitable in the production of Water for Injection, but at this time, experience with this process is not widespread." The best conclusion is that other technologies are permitted in WFI production, but must have performance equivalent to or better than distillation.

Nevertheless, distillation cannot stand alone to produce WFI. As noted elsewhere in the USP, "For distillation, due consideration must be given to prior removal of hardness and silica impurities that may foul or corrode the heat transfer surfaces as well as prior removal of those impurities that could volatize and condense along with the water vapor…In spite of general perceptions, even the best distillation

process cannot afford absolute removal of contaminating ions and endotoxin. Most stills are recognized as being able to accomplish at least a 3 to 4 log reduction in these impurity concentrations." Hence, even if distillation were to be chosen for a spaceflight system, additional filtration elements would be required to produce WFI, just as is the case in terrestrial settings.

5.1.2 EPA Potable Water Standards

The EPA regulates the quality of drinking water in the United States. Water meeting USP standards must be prepared from water meeting the EPA National Primary Drinking Water Regulations (NPDWRs or primary standards). The primary standards regulate the levels of microorganisms, disinfectants, disinfection byproducts, inorganic chemicals, organic chemicals, and radionuclide contaminants that can be found in drinking water. The primary standards apply to public water systems and are legally enforceable. There are also National Secondary Drinking Water Regulations (NSDWRs or secondary standards) that are nonenforceable guidelines regulating contaminants. These secondary standards cover contaminants that may cause cosmetic effects (such as skin or tooth discoloration) or aesthetic effects (such as taste, odor, or color) in drinking water. Individual states may adapt the secondary standards as legally enforceable. A list of both primary and secondary standards may be found in EPA 816–F–03–016 (ref. 43). The EPA also maintains the contaminant candidate list (CCL) as prescribed by the Safe Drinking Water Act. The CCL contains 51 contaminants that are under investigation for possible regulation. Aluminum and many solvents, potential NASA contaminates, are included in the CCL. The complete list is found in EPA 815–F–05–001 (ref. 43).

5.1.3 NASA Potable Water Standards

NASA has developed its own standards for potable water contaminants. These standards reflect the unique contaminates possibly present in spacecraft systems. The EPA standards are primarily concerned with contaminants potentially found in ground water used by public water systems. First-use potable water in NASA missions would be produced from terrestrial ground water as well, although stored and used in systems different from terrestrial systems. Long-duration missions, however, would produce potable water from wastewater. The wastewater is composed of condensate recovered from the air, hygiene water, and urine. These water sources have vastly different contaminates than those covered by EPA standards. An ersatz formulation of wastewater expected on a Mars transit mission (based on ISS data) includes significant amounts of sodium, chloride, ammonium, sulfate, and potassium (ref. 45). Of these contaminants, only chloride and sulfate are covered under EPA secondary standards, and none by EPA primary standards. NASA's potable water standards cover all except sodium. NASA's standards for ISS potable water are covered in Space Shuttle Program (SSP) 41000 (ref. 46), and can also be found in JSC–38571C (ref. 46) and SSP–50260 (ISS MORD) (ref. 47). These standards also include acceptable microbial levels.

NASA potable water does not necessarily meet EPA primary standards. Water that does not meet EPA standards requires acceptance testing or qualification testing (ref. 49). If available water does not meet EPA standards, treatment prior to making WFI is required. Alternatively, the produced WFI would have to demonstrate equivalent or better removal performance on those unmet initial conditions than a qualified distillation or RO-system-fed water meeting EPA standards. This alternative interpretation is not covered in the USP standards or FDA guidance.

5.1.4 WFI Versus SWFI

There has been confusion in past work on whether SWFI or WFI is needed for a medical water system. Descriptions of SWFI and WFI are given in USP 29–NF 24 under the official monographs and under the general information chapter Water for Pharmaceutical Purposes 1231. WFI is "intended for use in preparation of parenteral solutions" and "an excipient in the production of injections" (ref. 50). SWFI is "prepared from water for injection that is sterilized and suitably packaged" and "intended for

extemporaneous prescription compounding and is distributed in sterile units" (ref. 50). Official monographs for sodium chloride injection, Ringer's injection, Ringer's lactate injection, dextrose injection, et cetera, all state that they are "a sterile solution of <solute> in water for injection" (ref. 50). The conclusion is that only WFI is needed for immediate production of solutions such as sodium chloride. SWFI may be used for immediate production of these solutions as well, but is required if using prepackaged water. The decision to produce WFI or SWFI depends on if there are other potential uses of the Medical Water System. SWFI is only required if it is to be stored in unmixed form for later use.

SWFI has many additional requirements beyond those of WFI. Some of these requirements are similar to those for the final solutions, but others are not. These additional requirements for SWFI include limits on pH, particulate matter, ammonia, calcium, carbon dioxide, chloride, sulfate, and oxidizable substances.

Finally, WFI "produced on site for use in manufacturing" does not have to meet a bacterial endotoxins test, but the final solution does have to meet the bacterial endotoxins test associated with the fluid produced. As an example, the maximum bacterial endotoxin level for packaged WFI is 0.25 EU/mL, while for 0.9 percent sodium chloride and 5 percent dextrose it is 0.5 EU/mL. The complete requirements for the solutions and their solid components are found in table XV.

TABLE XV.—REQUIREMENTS FOR SOLUTIONS FROM USP 29–NF 24

Contaminants	Requirements							
	WFI	SWFI	0.9% saline	5.0% dextrose	LR	9.0 g NaCl	50.0 g dextrose	LR components
Bacterial endotoxins	≤0.25 EU/mL (packaged only)	≤0.25 EU/mL	≤0.50 EU/mL	≤0.50 EU/mL	≤0.50 EU/mL			≤0.50 EU/mL
Total organic carbon	≤0.50 mg/L	≤0.50 mg/L (produced from WFI)						
Water conductivity	≤1.3 µS/cm	≤1.3 µS/cm (produced from WFI)						
Sterility		Passes test	Passes test	Passes test	Passes test			Passes test
pH		5.0 to 7.0 with buffer solution	4.5 to 7.0	3.2 to 6.5 with buffer solution	6.0 to 7.5			6.0 to 7.5
Particulate matter (light obscuration test)		≥10 µm: ≤25/mL ≥25 µm: ≤3/mL	≥10 µm: ≤25/mL ≥25 µm: ≤3/mL	≥10 µm: ≤25/mL ≥25 µm: ≤3/mL				
Ammonia		≤0.3 mg/L						
Calcium (derived from USP 21)		≤0.5 mg/L						54.5 mg
Carbon dioxide (derived from USP 21)		≤4.0 mg/L						
Chloride (derived from USP 21)		≤0.5 mg/L				5.46 g	≤9 mg	3.88 g
Sulfate (derived from USP 21)		≤0.5 mg/L						
Oxidizable substances		Passes Test						
Iron			≤2.0 mg/L			≤0.018 mg		
Heavy metals			≤0.09 mg/L as Pb	≤0.25 mg/L as Pb	≤0.3 mg/L as Pb	≤0.045 mg as Pb	≤0.25 mg as Pb	≤0.066 mg/L as Pb
5-(hydroxymethyl) furfural and related substances (284 nm light absorbance)				Passes test				
Antimicrobial agents	None allowed	None allowed	None allowed	None allowed	None allowed	None allowed	None allowed	None allowed

5.2 Water Sources

While using potable water as the source to generate WFI is obvious, other potential sources exist. Short-duration missions may use a fuel cell as does the shuttle, with the resulting high-purity water a potential source. Moderate-duration missions may use water to produce cabin oxygen using electrolysis. The oxygen generation water is usually potable water with an additional deionizing bed to remove the iodine biocide. This water may also provide a starting source to generate WFI. A generic emergency water source to be used for oxygen generation, medical emergencies, or replenishing potable water stores may be a viable option for moderate to long-duration missions. Water obtained from in situ resource utilization would presumably go through processing to bring quality up to potable water standards.

5.2.1 Potable Water

Potable water on the ISS is used for drinking and hygiene. NASA potable water must meet requirements as set out in SSP 41000, which is different than EPA standards. There is some overlap in the two standards, but NASA's standards cover contaminants specific to spacecraft water, and do not have requirements to eliminate contaminants commonly found in public water systems. Overlapping contaminant standards are generally stricter in NASA's requirements, but this is not true for all substances.

Potable water contaminants are specific to the water source. From 2003 to 2006, most of the water on ISS was transported via Russian Progress cargo ships. Therefore, the water meets Russian standards. Russian water is mineralized for taste, and uses silver as a biocide. Prior to that time, the main source of ISS water was usually shuttle deliveries of fuel cell water, NASA potable water for drinking, and water for the oxygen generation system. NASA potable water uses iodine as a biocide and does not contain added minerals. The European Space Agency Automated Transfer Vehicle is capable of delivering both Russian and NASA potable water and is scheduled for its inaugural launch in 2008.

ISS water is also recovered and processed in the Russian condensate recovery system, delivered through a system separate than the transported water system. NASA is also planning to launch the water recovery system (WRS) within the next few years, which will recover water from hygiene water, condensate, and urine. The WRS will produce water meeting NASA requirements, but will have contaminant levels different than those from fuel cell, transported potable, or condensate water.

5.2.2 Oxygen Generation Water

Oxygen production requires higher purity water than NASA potable water. The oxygen generation system (OGS) flight hardware generates oxygen via electrolysis and was flown to ISS on STS–121 this year. This system is designed to utilize NASA potable water provided by the WRS. An internal deionizing bed removes the iodine biocide, as well as other ions (ref. 51). This treated water remains internal to the OGS, and is not normally available for other uses. There is an internal system designed to reject this treated water if gas is present. This system is currently finished, flight qualified, and on station. It will not become operational until 2007 because station modifications are required for it to operate in the new location in the Destiny lab module instead of its design location in Node 3. Modifications in orbit to allow for access to the deionized water are unlikely. Nevertheless, the system could potentially be modified with new software and an additional outlet so that water could be generated in an emergency. On the other hand, integration and operational challenges may preclude this as an efficient source for generating WFI precursor water for ISS use.

5.2.3 Fuel Cell Water

At the time of generation, fuel cell water has high purity, and shuttle fuel cell water is used directly on ISS. Fuel cells are generally only used on short-duration missions such as Shuttle. No fuel cells are present on ISS. The ESAS study recommended solar panels over fuel cells for Orion electrical production because of the 6-month quiescent state required during ISS and lunar outpost missions. Fuel cells are being investigated as potential replacements for batteries to store energy over the day/night solar cycle and as backup power. Such

fuel cells are closed systems, with the water recycled internally. Fuel cell water is a possible source on NASA missions to the Moon and Mars, though in long-duration, closed-loop systems, the water quality is unknown at this time.

5.3   Production Timeline

The choice of a system to produce WFI is critically tied with the timeline over which water would be available. Systems that produce water more slowly must have some sort of stored capacity to meet potential requirements for an initial bolus in the case of an emergency. Such a contingency may be at odds with the general WFI philosophy to eliminate the mass of stored water. Production timelines for various systems are described below.

5.3.1   Instant On-Demand

An on-demand system would require a high production rate in order to meet the initial needs, on the order on 4 L/hr. This high production rate may preclude certain technologies from consideration. For instance, a distillation system would most likely be unreasonably large for an on-demand system. In addition, producing the fluids immediately would heighten the crew workload, which would not be desirable during an emergency. Nevertheless, such a system would eliminate or greatly reduce fluid storage requirements.

5.3.2   Limited Stores

Stowing limited supplies on the order of 2 to 10 L to handle the initial needs, and then producing fluids at a moderate rate to keep the supplies replenished is an alternative to a large capacity on demand system. Typical IV fluid maintenance rates are 4 L/day, although certain conditions could require more fluids in the short term. There is a tradeoff between production rate and the amount of stores required to handle the initial needs. If the WFI system is used to replace the stores as they expire, sterility may be an issue.

5.3.3   Always-Available Production

An online system available for production at any time, or a limited use system that produces a fixed quantity of fluid before requiring consumable replacements is another option. Typical lab systems such as RO or distillation are always available and may require consumable replacements after months and/or thousands of gallons of production. Similar to the system outlined in Section 5.3.2, online systems will require monitoring and maintenance to ensure the sterility of the system.

5.3.4   One-Time Use

Cartridge-type systems use consumables to remove and store the contaminants. Cartridge systems typically treat limited quantities of fluid, on the order of 10 L. Such systems could be developed for one-time use, where a cartridge is rated for a certain volume of fluid for a limited time duration. At least one cartridge would be used per emergency, and potentially several if an astronaut suffers a severe injury or multiple astronauts require fluid simultaneously. The cartridge and all associated hardware could be sterilized and sealed prelaunch, eliminating maintenance during the mission. There may be increased mass and/or volume requirements with a cartridge-type system.

5.4   Solution Production

5.4.1   Constituent Form

The final product for ultimate use will be a medical solution. This requires adding and mixing the constituents, such as sodium chloride, glucose, or other pharmaceuticals. The physical state of the constituents directly affects the mixing method and indirectly affects the water production method. Powders weigh less and

generally have a longer shelf life than concentrated liquids. However, powders take longer to dissolve and mix and are more difficult to handle in microgravity. Liquid concentrates take much less time to mix and are potentially easier to add to WFI, but weigh more and have a limited shelf life. Liquid concentrates may be required for unique technologies such as forward osmosis (FO).

5.4.2 Mixing Method

The mixing time also influences the delivery timeline. Time to treatment can be critical in an emergency. To fit within a therapeutic window, longer mixing times reduce the time available for WFI production. A long mixing time may require a large-capacity production system to decrease the WFI production time. Mixing time is less critical for a system with emergency stores.

The method appropriate for mixing the solution to final form is the subject of an ongoing project at NASA Glenn. The initial trade study that evaluated potential technologies is available in NASA/TM—2007-215000 (ref. 52). Two methods were chosen for further study, a vibrating wall method and a magnetic stirrer bar method. The magnetic stirrer bar was ultimately chosen as the preferred solution and is undergoing further testing and qualification. Normal-gravity experiments to quantify and correlate the degree of mixing with time, stir bar dimensions, and rotation rate are ongoing. Microgravity testing in drop towers and aircraft will evaluate the effect of microgravity on mixing time and the effect of bubbles in the system.

5.5 Hypogravity Production Challenges

Microgravity poses operational challenges for any fluid system. Potential problems in an IV system arise in all phases of operation, from production to storage to handling. There are also potentially unique sterility issues arising from microgravity operation. Addressing challenges induced by hypogravity issues should be tackled early in the design phase, rather than attempting to add ad hoc solutions later in the development process. Design challenges due to altered gravity are frequently of such magnitude that they can only be effectively addressed in the design phase. In general, partial gravity systems are somewhat easier to design and test, but still require careful analysis.

5.5.1 Production

Many of the microgravity fluids issues arise when a liquid-vapor interface is present. The interface may be present by design, or as an off-nominal condition. All production methods are potentially affected by the presence of bubbles in the system. The location of bubbles in microgravity is much more difficult to predict because, unlike normal gravity, the system has no top. Thus, mitigating bubble problems is harder in microgravity. Bubbles can cause pump problems such as loss of prime, which may be mitigated by less susceptible positive displacement pumps. Adsorbent media such as charcoal filters or ion-exchange resins are only effective when water is able to pass through them. Such media are rendered ineffective when dry because the gas bubbles effectively channel the flow around a volume, resulting in a stagnant flow, which can then become a bacterial breeding ground. Filters and membranes can be rendered ineffective for similar reasons.

Priming systems for operation in microgravity are fundamentally different than in normal gravity. One cannot rely on trapped air rising upward to an outlet from gravity. Priming in microgravity is dominated by capillary forces, and can be enhanced by proper design. Poor priming will result in large volumes of trapped air with many significant problems as described. Proper priming will be more critical in replaceable cartridge-type systems, which must be primed after each replacement.

Distillation, the standard for terrestrial production of WFI, is also probably the technique most affected by microgravity. Distillation systems boil the incoming water and condense the resulting steam, leaving many nonvolatile contaminants behind. The boiling process itself is fundamentally different in microgravity and not completely understood at this time. In normal gravity, vapor bubbles form on the heated surface, and once the bubbles reach a certain size, buoyant forces detach the bubble and it rises to the surface. The steam then travels through a vapor space, usually at the top of the apparatus, and into a condensing coil. The vapor is condensed

and the condensate drains to the bottom of a recovery container. Phase separation occurs at both the bubble detachment and the liquid condensate drainage and explicitly depends on a gravitational field. Bubble detachment in microgravity is particularly problematic and not well understood. The simple distillation systems used in laboratories will not physically work in microgravity, and no simple addition will allow them to function in microgravity.

Distillation units have been conceived that work in microgravity for advanced life support, and they rely on rotating machinery to produce a centrifugal force that substitutes for gravity in the critical components (refs. 53 and 54). Alternatively, the lower production rates required for WFI could allow a capillary action distillation system to be developed. For either method, a microgravity distillation system could be developed, but might be substantially more complex than typical units. While these constraints may seem to eliminate distillation systems from consideration, distillation (in addition to RO) is one of only two methods proven and accepted in WFI production per the USP standards.

5.5.2 Storage

Many ground-based systems, and some proposed microgravity systems have a storage vessel for limited WFI storage. Storage may not be required for an on-demand system, but a system designed for gradual replacement may perform better by storing small volumes of WFI prior to filling IV bags. Filling, venting, and removal from containers in microgravity is complicated by ensuring the proper location of the liquid and vapor present. Capillary devices are often used for liquid management.

Capillary liquid management devices often use narrow channels or sharp acute corners to induce liquid flow, and screens to trap bubbles. Such devices will function in a WFI system, but raises sterility concerns. A general rule of thumb for WFI systems is to maintain smooth surfaces and avoid regions of low flow velocity. Smooth surfaces eliminate attachment points for microbial growth as well as eliminating small regions of low wall shear stress. The liquid shear stress prevents buildup and growth of biofilm in stagnation regions. Acute corners and narrow channels have low velocities as well as surface properties conducive for microbial attachment. Screens also break both of these design rules by having a low relative velocity through them and providing many attachment points for biofilms. Such concerns can be mitigated, but they must be considered.

Another means of providing positive gas and liquid separation is to utilize a collapsible reservoir, either a flexible bag-like reservoir or a bellows-type reservoir. The reservoir is completely liquid filled, and the volume of the device passively changes to accommodate the required liquid volume. Such a reservoir is simple and effective in normal operation. A collapsible reservoir, or bladder, is often used for one-time or limited-duration use. Water is transferred from shuttle to ISS using collapsible reservoirs. However, long duration use for WFI raises issues. The bladder material must remain flexible, inert, and sealed for the entire mission duration. Another concern is that certain sections of the bag may have relatively stagnant flow that also may provide an optimal location for bacterial growth.

Unanticipated bubbles are another potential concern. A bladder can act as a bubble trap, containing these bubbles for a time, but may potentially release a large bubble later when unexpected and overwhelm a bubble trap countermeasure located downstream.

5.5.3 Handling

Microgravity handling challenges arise from potential bubbles in the system. Devices may be required at various stages to trap and remove the bubbles. Bubble traps may be required to remove inlet bubbles from source water prior to entering the WFI production system, prior to any storage container, the mixing device, and prior to actual use. These traps may require constant use, such as the inlet trap, be required only during a priming operation, or require monitoring and action if the closed system is breached and a bubble enters the system. Some production methods, such as distillation, may require more rigorous bubble control methods.

The relatively low flow rates in a WFI system tend to favor passive bubble traps. Screens are simple bubble traps that prevent passage, but they do not remove the bubbles from the system. Screen or membrane traps generally have long-term sterility difficulties as noted above.

There may also be microgravity-handling issues with particulates in the system. The filter-based technologies may have particulates released from the media that may be more readily transported in microgravity, depending on filter orientation. Particulate handling also varies with the size of the particles. Fine particles may be trapped in different locations in microgravity, or overload filters designed to remove them. When released from packed beds, fine particulates have been an issue in microgravity systems; one spaceflight water recovery system test failed because of an unexpectedly large release of fine particulates (ref. 55).

5.5.4 Sterility

Maintaining sterility of a medical water generation system is critical to its ultimate performance. This task is challenging under normal gravity, and presents some unknown issues in microgravity. The environmental effects of microgravity and increased radiation may cause differences in microbial growth, as well as potentially increase mutation. Cell culture experiments on shuttle and ISS have shown measurable differences in microgravity, but operational experience on Mir and ISS has not shown noticeable microbial differences with gravity level. It is not expected that microgravity operation will present any additional sterility challenges, but it is possible.

Recent papers describing ISS potable water test results have described the presence of microorganisms (refs. 56 to 59). While no microorganisms found to date were unusual, the microgravity environment did not prevent growth. The ISS water source SRV–K has a pasteurization unit at 82 to 85 °C designed to destroy bacteria, and a potable water outlet (SRV–K/HOT) at ~80 °C. Water from this outlet has had measurable microbial content, although at lower levels than other sources (ref. 58). This result is not unexpected given the relatively low pasteurization temperature. There is evidence that some microorganisms found on the ISS enter a viable but nonculturable state when exposed to the iodine levels used on ISS for disinfection (ref. 60). Once the iodine is removed, these microorganisms can grow, although the rate is slower than what would be expected for a culture that had not been exposed to iodine. Hence, results from the standard 48-hr test can be misleading.

Experiments have been conducted on microorganism growth in microgravity. Pseudomonas aeruginosa, an opportunistic pathogen of humans, was successfully cultured on STS–95 from October 29 to November 7, 1998. No discernible differences in the morphology of the microgravity-grown biofilms were seen when compared to those formed under conditions of normal gravity (ref. 61).

Microgravity produces a different fluid environment that may inhibit bacterial growth in seldom-used systems. Microorganisms in terrestrial water purification systems tend to grow in regions with low shear stress, which allows formation of a biofilm on a surface. Such regions are usually in corners and fluid motion dead zones such as rarely used outlets. A biofilm must still have some transport of nutrients for growth, which can be provided by internal natural convection. Because buoyancy is driven by density differences within a gravitational field or other accelerating system, microgravity will nearly eliminate fluid flow due to buoyancy. Nevertheless, spacecraft vibrations will still produce some convective transport in the system. Buoyancy-driven convective transport can also be fairly low in 1-g systems with confined geometry such as piping without flow. Species transport will also be present from molecular diffusion, albeit at much lower levels than caused by convection. Microbial growth occurs on the order of hours to days, while typical diffusive transport is probably on the order of days in microgravity (ref. 62). Hence, the microbial growth rate is probably reduced in microgravity, but not eliminated. Adherent microorganisms that prefer to grow attached to surface may have a reduced opportunity to contact a surface and begin colonization because reduced transport will present a reduced probability of coming into contact with a wall within the vessel. However, ground-based systems often experience biofilm growth on upper surfaces despite the settling tendency of microbes and associated reduced probability to contact those surfaces.

6.0 Potential Production Technologies

There are a variety of commercially available technologies for purifying water, some of which may be suitable for producing water for injection for Exploration missions. Additionally, there are some new water

purification techniques that are still in the research stage that should be considered by NASA. These technologies are described in the following Sections 6.1 to 6.9 and are summarized in table XVI at the end of this chapter.

6.1   Distillation

Distillation is a process widely used by industry to remove nearly any contaminant from water. The water is first heated to drive off components that boil at a lower temperature, and then is itself boiled and recondensed leaving behind salts, solids, bacteria, and bacterial endotoxins. This process produces ultrapure water that is suitable for injection. The latter (and most common) part of the process is illustrated simplistically in figure 1.

Normally distillation requires a significant amount of energy to produce pure water due to the needs of the boiling process, but if heat recapture is employed the amount of energy needed can be reduced. As an example, the latent heat of water is 2260 kJ/kg at 100 °C, which is approximately 2260 kJ/L (ref. 63). A new distillation unit producing 25 gal/hr (much more than would be needed for WFI applications) does so using a proprietary process for about 50 kJ/L (ref. 64).

Commercial distillation units use gravity to separate the vapor and liquid phases, as shown in figure 1, rendering them inoperable in microgravity. There has been some research, however, into the use of centrifugal separators in distillation units for reclaiming water on spacecraft (ref. 65). Such a separator requires more power and moving parts, which would add complication to the device for producing WFI. Starting with urine or similar fluids, 97 percent of the minerals and microbes can be removed, which is not yet good enough for WFI, but it is likely that the starting fluid would be purer. In summary, despite distillation being the method of choice for producing WFI in normal gravity, challenges in terms of energy use and separation make it difficult to apply in microgravity and further development is needed.
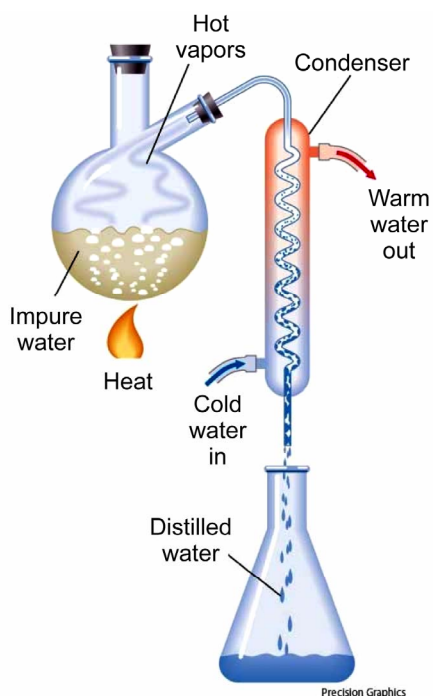

Figure 1.—Distillation process to purify water.
Copyright © 2006 by Houghton Mifflin Company.
Reproduced by permission from The American
Heritage Dictionary of the English Language,
Fourth Edition.

6.1.1 Vendors Working in the Field

GreenShift Corporation
535 West 34th Street, Suite 203
New York, NY 10001
Phone: 888–895–3585
Fax: 646–792–2636
E-mail: info@greenshift.com
http://www.greenshift.com/news.php?id=86

HyClone
925 West 1800 South
Logan, UT 84321
Phone: 1–800–HYCLONE (492–5663)
Domestic: 435–792–8000
Fax: 435–792–8001
E-mail: info@hyclone.com
http://www.hyclone.com/media/wfi_system.htm

Mediatech, Inc.
13884 Park Center Road
Herndon, VA 20171
Phone: (800)CELLGRO
E-mail: custserv@cellgro.com
http://www.cellgro.com/shop/customer/home.php?cat=363

6.2 Reverse Osmosis

To better understand the applicability of reverse osmosis (RO) to generating medical water, the physical process of osmosis will first be described. Osmosis is the diffusion of fluid through a semipermeable membrane from an area of high water concentration to an area of low water concentration until the concentration is the same on both sides of the membrane. The membrane stops particles and large molecules, while allowing water and smaller molecules to pass through. Osmosis generates a pressure differential across the membrane, with the higher pressure on the side into which the water flowed.

In RO the pressure is increased on one side of the membrane to the point where the diffusive flow is stopped and reversed, so that the water actually flows from the lower water concentration side to the higher side (see fig. 2). In this case, sufficient pressure on the salt water side will drive pure water to the fresh water side. The same behavior is obtained regardless of the solute, so that all impurities that cannot pass through the membrane are effectively removed.

RO is commonly used in home water purifiers to remove salts, chlorine, and other compounds from drinking water. Units of varying sizes are commercially available. The FDA also approves RO for producing water for injection if two units are used in series (ref. 66). Often the water needs to go through processing prior to RO, such as filtering or pH balancing, depending on the source. Bacteria have been shown to grow in RO water, so some effort is required to keep the downstream tubing and valves clean. Periodic disinfection is required, but that may not be an issue for short-term emergency use. RO membranes are sensitive to chemical degradation and fouling. Long-term terrestrial use requires chemical pretreatment to protect the membrane. This treatment may or may not be required for NASA use, depending on how long the membrane would be chemically exposed. RO systems also require a wastestream of the contaminant-concentrated water. The wastewater could be stored or retreated in the main water recovery system in Exploration missions.
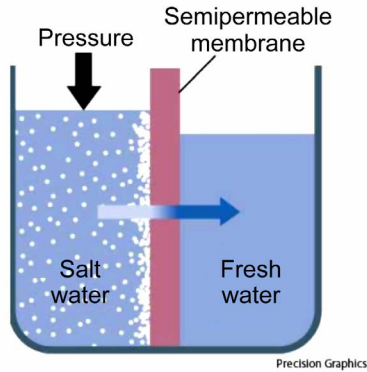
Figure 2.—Reverse osmosis, wherein pressure forces the water to migrate to a region of higher water concentration. Copyright © 2006 by Houghton Mifflin Company. Reproduced by permission from The American Heritage Dictionary of the English Language, Fourth Edition.

In 1999, a project at NASA Kennedy Space Center (KSC) investigated the possibility of using RO to create SWFI (ref. 67). The project, called FLUID (filtering liquids for use in IV devices), sought to demonstrate that RO could purify gray water to the point where IV bags could be safely filled on orbit, thereby eliminating the need for taking prefilled IV bags into space. The system worked by pulling water first through a 10-µm chlorine filter, then into an electric water pump, through the RO membrane, through a 0.5-µm filter, and finally through another 0.5-µm polishing filter.

Shower water using the actual soap used on the ISS formed the gray water. The researchers measured the microbial content, pH, chloride content, chemical composition, conductivity, and endotoxin levels of both the source and the RO product. Bacteria, endotoxin, chloride content, and pH levels met USP standards using the system they tested. Conductivity did not fall within USP standards, which investigators attributed to a low pump pressure (120 psi rather than the 220 psi desired). They did not describe why the lower pressure produced higher conductivity values.

NASA KSC is currently involved in Project Clearwater, a new collaborative effort to produce a RO-based WFI system. The current version has three separate loops, each of which can treat 200 L of water to USP grade sterile water. The separate loops are advantageous in that each loop remains sterile until activated. The system also has adsorption filters in the system and is designed to have no reject water.

6.2.1 Vendors Working in the Field

US Filter
800–875–7873 ext. 5000

Dialysis:
http://www.usfilter.com/en/Product+Lines/High_Purity_Water_Products/High_Purity_Water_Products/hipurity_Hemodialysis_prd_MED_RO_RX.htm

Ultra pure for medical lab use:
http://www.usfilter.com/en/Product+Lines/High_Purity_Water_Products/High_Purity_Water_Products/PURELAB_Ultra_Laboratory_Water_Purification_System.htm

US Filter was the only vendor located that mentioned medical use of their RO water, but there are many vendors working in the drinking water arena.

6.3   Adsorption

Adsorption systems utilize chemical or ionic affinity to remove contaminants from the water feed stream. The contaminants are trapped inside a cartridge that is later disposed. Activated carbon is a common adsorbent that removes many types of chemicals. Ions typically require a different adsorbent. Multiple adsorbents are commonly employed together to remove all desired contaminants. The adsorbents generally have a high surface-area-to-volume ratio to enable efficient removal. A low flow rate in the cartridge is utilized to ensure a high residence time in the system, which allows for efficient contaminant removal. Cartridge lifetime is limited by the maximum amount of contaminant it was designed to adsorb.

Adsorption systems are simple devices, requiring only low pressures to drive the fluid through the media (see fig. 3 for an example). There are no moving parts or electronics required. They generally have a limited lifetime, but some systems can be renewed by flushing with cleaning chemicals. Adsorption systems have several advantages for medical water generation for NASA's missions. They can be a simple, self-contained system that remains sterile prior to use. There are limited shelf-life concerns, and no special storage is required. The WFI volume required is relatively low for some missions, so the limited useful life may not be a concern. Adsorption systems are not suited for large-volume production because of the consumable mass.

The SWIS tested in STS–47 (see Section 1.4.2) was primarily an adsorption system, with additional filters to remove particulates. Prismedical has developed a filter/adsorption-based system that produces 3 L of USP Sterile Purified Water from highly contaminated water in a 0.5-kg package. It has not been approved for parenteral administration, but does meet the endotoxin requirement. It is a purely passive system, relying on gravity feed to provide a flow rate of 75 mL/min; in microgravity a pump would obviously be required. Potential problems with the filter media are particle fine generation and flow channeling in microgravity.

Figure 3.—Prismedical USP Sterile Purified Water
adsorption filter.

6.3.1   Vendors Working in the Field

Prismedical
118 Dodd Court
American Canyon, CA 94503
Phone: 707–556–5000
E-mail: info@prismedical.com
http://www.prismedical.com/sterile/index.html

6.4   Filter

An example of a filter for purifying water is given in figure 4. Filters operate by forcing the water through a sieve with many small holes or past bundles of very small fibers that prevent the passage of contaminants while allowing the water to pass through. Filters normally operate on a mechanical basis by limiting the size of a particle or molecule able to pass through, though there may be some chemical affinity for certain species that cause them to adhere to the filter (see previous section). Filters are normally combined with an adsorbent media to remove molecular-scale impurities to produce high-purity water.

Filters have the advantage of not having moving parts or electrical power requirements themselves, though they do need a source of pressurized water, and therefore power for a pump. This power can be supplied by a person, as in the case of water filters designed for backpackers to purify drinking water. As an example, a filter over-pressure of about 5 psi is needed to obtain a flow of 0.7 L/m through a medium capsule filter described below.

Filters come in a variety of sizes. By using fiber packing or pleated membranes, a large surface area can be packaged in a small volume. Depending on the circumstances, the option of considering the filter disposable could be advantageous. For short-duration missions it may be best to have several small filters in hermetically sealed packages and open one as needed. This avoids the need to sterilize the filter since it will not be reused, though that can be achieved through chemical or heat treatment if necessary.

A disadvantage to filters is that they cannot remove all water-borne contaminants. The better filters can generally remove all bacteria, endotoxins, solids, and some other chemicals. Depending on the type of filter, molecular-scale impurities and smaller viruses may be able to pass through. The total amount of water that can be treated by a filter depends on the contaminant loading in the feed water and would need to be tested for various water sources considered for use on the Orion.

As an example of a filter appropriate for creating WFI, consider the FiberFlo filter described in language taken from their brochure (ref. 68): "FiberFlo ultrapure water filters are manufactured using a unique, patented, Polyphen polysulfone hollow fiber providing high flow rates, low extractables and a wide range of chemical compatibility. The asymmetric hollow fiber provides absolute micron removal ratings. FiberFlo water filters are available in 0.05-, 0.1-, and 0.2-μm pore sizes and a variety of inlet and

Figure 4.—Examples of water filters.

outlet connections and system sizing. FiberFlo capsule filters have easy-to-use, dual upstream vents (whose operation in microgravity would need to be proven) that allow sanitization of the filter using Minncare Cold Sterilant.

FiberFlo water filters are designed and manufactured in accordance with an ISO 9000 Quality Management System. For easy identification and traceability each capsule is labeled with a lot number, catalog number, pore size, and serial number. FiberFlo capsule vent filters are 100 percent integrity tested during the manufacturing process. All FiberFlo filter devices are manufactured and tested nonpyrogenic by limulus amebolysate (LAL).

6.4.1   Vendors Working in the Field

Minntech Filtration Technologies Group
14605 28th Avenue North
Minneapolis, MN 55447
Phone: 800–328–3345
E-mail: ftginfo@minntech.com
http://www.minntech.com

6.5   Forward Osmosis

Forward osmosis (FO) for water purification is used by at least one manufacturer (ref. 69) of outdoor equipment for soldiers and hunters. In this process, a filter with pore sizes of 3 to 5 angstroms (0.3 to 0.5 nm) separates the contaminated water from clean water that has a sport drink or other solute at high concentration dissolved in it (ref. 70). The osmotic pressure alone (see figs. 2 and 5) drives water from the contaminated side to the side with the desired solute. For the flow to occur, the solute side must have a higher concentration of particles (labeled "nutrients" in fig. 5) than the contaminated side. Thus, the method is not useful to produce totally pure water, but is appropriate for creating IV fluids starting from a sterile IV concentrate.

The company has various products meant for producing drinks; the maximum rate is 1 L/hr of drink. The osmotic pressure of NS is on the order of 57 psi, whereas the pressure for sports drinks is approximately 70 psi. Using a simple ratio predicts generating NS at the rate of 0.8 L/hr. While that is too slow to produce IV fluid in an emergency situation, it is sufficient to generate fluids for long-term IV maintenance therapy. The surface area could be increased to increase the production rate, and fluid
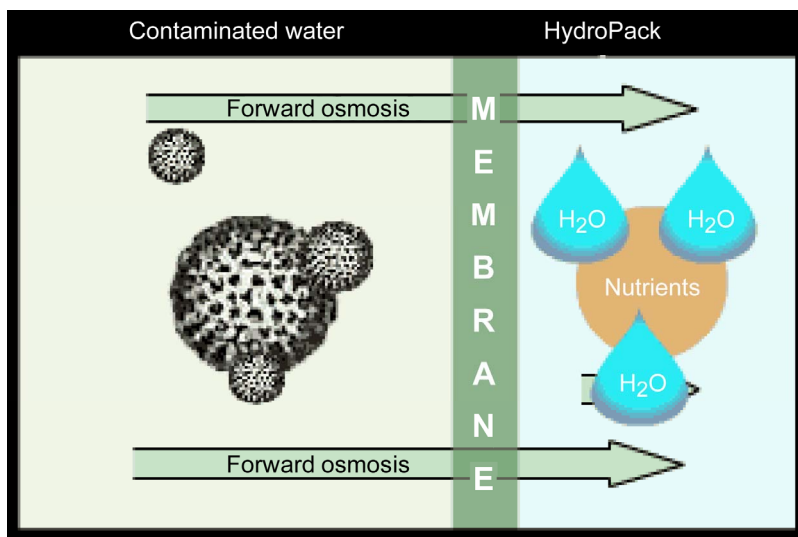

Figure 5.—Forward osmosis to produce a high concentration solution.

mixing on the product side would also increase the production rate by maintaining a higher concentration gradient at the membrane. Most medical fluids such as Ringer's Lactate and dextrose have similar osmotic pressures and are chosen to be compatible with blood osmotic pressure.

Hydration Technologies is currently working with NASA Ames on a potential emergency water purification system for use in lunar missions. There has already been testing on the removal efficiency of the membrane, and other membranes are also being investigated at NASA Ames.

6.5.1   Vendors Working in the Field

Hydration Technologies, Inc.
2484 Ferry St SW
Albany, OR 97322–7801
P.O. Box 1027
Albany, OR 97321
Phone: 541–917–3335
Fax: 541–917–3345
Product inquiries: b.schmieg@hydrationtech.com
http://www.hydrationtech.com/

6.6   Membrane Distillation

A conceptual schematic of the membrane distillation process is shown in figure 6. The use of membrane distillation for large-scale salt-water desalination is a current research topic, though small-scale applications such as personal drinking water generation appear not to be widely pursued. Hot (not necessarily boiling) water gives off vapor that is selectively allowed through a membrane driven by diffusion and the vapor is condensed on the other side. In the absence of gravity, a method to collect and remove the liquid condensate is needed, perhaps with a capillary flow effect. Depending on the geometry, some of the heat given off during condensation could be recaptured and used to heat the incoming water. The system is relatively simple, removes nearly all contaminants, and is not subject to fouling like a traditional filter. The technology has been proposed by at least one company under a currently funded NASA Small Business Innovation Research (SBIR) grant to generate medical grade water for IV fluids in space (ref. 71).
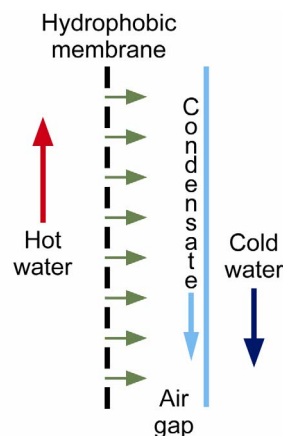

Figure 6.—Membrane distillation.

6.6.1 Vendors Working in the Field

T3 Scientific LLC
1839 Noble Road
Arden Hills, MN 55112–7834
Phone: 612–378–4985
E-mail: Andy.Tsai@t3sci.com

6.7 Osmotic Distillation

Rather than using concentration gradients as a driving force as is done in FO in the liquid phase, osmotic distillation uses the differences in vapor pressures of the contacting liquid phases. This is illustrated in figure 7. Water moves across the osmotic distillation (OD) membrane by evaporating, diffusing through the pores, and condensing on the other side of the pores. The pore sizes of the membrane are designed so that capillary forces prevent liquids from entering the membrane. Design factors include surface tension, contact angle, capillary pressure, and pore radius. The heat of vaporization is supplied by conduction or convection from the upstream liquid through the membrane. The temperature gradient across the membrane is typically less than 2 °C making the process nearly isothermal (refs. 72 and 73).

As in FO, the side to which the water is diffusing must contain a solute. The technique cannot be used to generate pure water. However, forming NS, Ringer's Lactate, or Dextrose solutions from a concentrate is possible. A two-stage system using osmotic distillation with an RO system can be used to produce pure water (ref. 74). A big advantage is that the RO membrane only sees an osmotic fluid chosen for chemical compatibility, typically sodium chloride, and does not have fouling concerns. This type of system is being developed as a potential space water recovery system, and has the potential to be very lightweight.

6.7.1 Vendors Working in the Field

Dr. Tzahi Cath at the University of Nevada in cooperation with Sherwin Gormly at the National Space Grant Foundation, and Michael Flynn at NASA Ames Research Center are vendors working in the field.
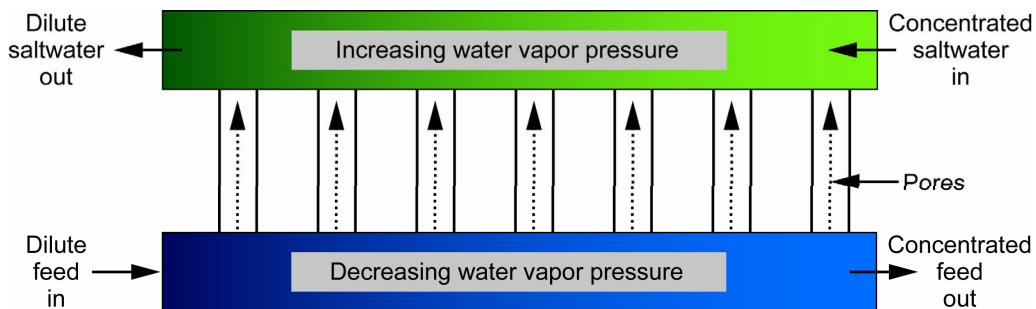

Figure 7.—Schematic of osmotic distillation.

6.8   Nanofiltration

Nanofiltration is a new experimental technique of removing contaminants from fluids being developed for artificial kidneys and other specialized applications (ref. 75). The filter is fabricated on silicon or a similar substrate using lithography processes developed for making integrated circuits. An array of slit channels is cut into the silicon that only allows particles or molecules of a certain size to pass through. The control of channel size afforded by lithography is greater than that offered by other techniques and filters types such as packed fibers. This particular filter is also much thinner than membrane or other filters at 1 μm thick versus 30 μm for a membrane filter. The reduced thickness greatly reduces the pressure drop across the filter.

The small channels on the current device are about 4 nm across and 50 μm long, with 50 nm of separation between channels using the best lithography processes (fig. 8). By making a multitude of channels and packing the wafers together the pressure drop is kept low across a larger device. The prediction for a 300 ml size device indicates a flow rate of 30 ml/min with a 1 psi pressure drop. This flow rate may not be sufficient to make water in an actual emergency, but it is sufficient if the recommended contingency stores are also carried as provided in Section 5.0.

For the artificial kidney application the channels are coated with various materials to reject proteins, which carry a slightly negative charge. For water purification, such coatings could be used to attract or repel certain species in the water to remove them. The filter would operate both mechanically by excluding larger particles or molecules, and chemically by removing smaller ones.

The disadvantage of the nanofilter is that the current generation has a 50 percent probability of fracture, though a new design promises to lower that to 10^{-4}. The filter is also not yet readily available and more research needs to be conducted, but the technology could potentially be available within the next 2 years.

6.8.1   Vendors Working in the Field

Dr. Shuvo Roy of the Lerner Research Institute at the Cleveland Clinic Foundation in Cleveland, Ohio is developing the technology mentioned in this section.
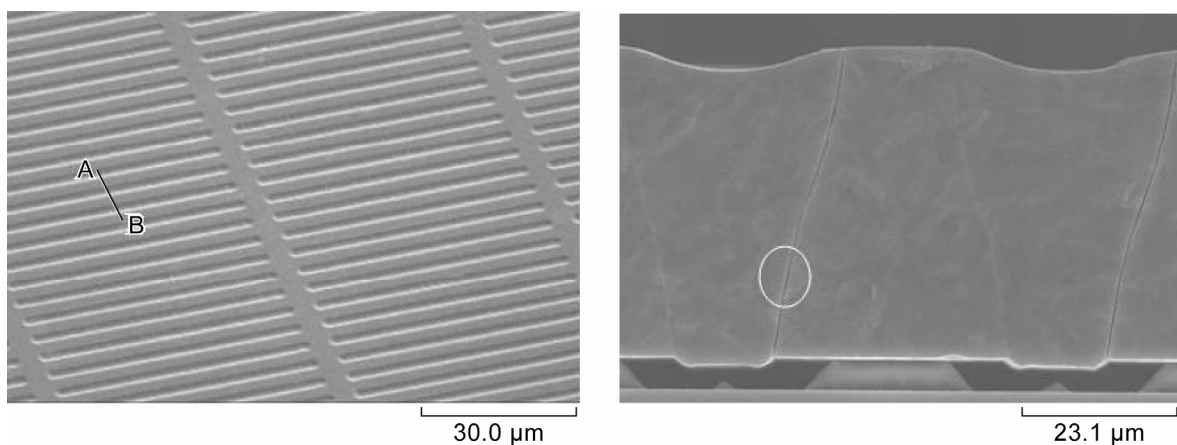

Figure 8.—Scanning electron micrographs (SEMs) of a first generation nanofilter (dimensions in the SEMs may not match text exactly). Left figure shows the large channels that carry fluid to the small channels in the right figure.

6.9   SBIR Research on Medical Water Generation

NASA funded a Phase I SBIR to create IV fluids in space using membrane distillation (see Section 6.6). A second SBIR award, this to the Umpqua Research Company, is currently investigating using microwaves to generate medical grade water (ref. 76). As described in the summary:

"An innovative microwave system is proposed for the continuous production of medical grade water. This system will utilize direct absorption of microwave radiation to rapidly heat potable water well above normal autoclave conditions, achieving equivalent microbial lethality in much shorter times. High thermal efficiencies will be gained by placement of the microwave antennae directly in the flowing water stream allowing very efficient volumetric coupling of microwaves. The sterilized water stream will then pass through a regenerable endotoxin filter to achieve WFI purity standards. This filter will remove endotoxins by selective adsorption. The combined system will enable the energy efficient and practical production of WFI aboard spacecraft or planetary habitats under microgravity or hypogravity conditions with a low equivalent system mass (ESM). In the Phase I research, sterilization chambers and endotoxin filters will be designed, assembled, and tested. The Phase II program will deliver a fully instrumented, computer-controlled system with a low ESM whose performance is well documented. This technology will form the basis for multiple applications in commercial sterilization markets."

During Phase I, Umpqua invented and demonstrated a microwave antenna sterilization system that meets most of the constraints of Exploration missions. This system will be further developed and demonstrated, as Umpqua has recently been awarded a Phase II contract.

6.10   Multipurpose: Drinking, Experimental, WFI

Developing an integrated system that provides water meeting several different specifications is possible. When properly integrated, such a system can have an overall lower mass than the total for separate systems. ISS originally considered a system that would produce both hygiene water and potable water, but this concept was not implemented. Some laboratory-sized water treatment systems have both high-purity and medium-purity outputs. Such systems are commonly dual-pass RO systems, with the medium-purity water passing through only one RO membrane and the high-purity water passing through both RO membranes. Equivalent systems produce high-purity water by passing the medium purity water through additional deionizing beds, membranes, UV sterilizers, or similar treatments.

There is potentially little need for water of intermediate quality between potable and WFI in future NASA missions. The ISS will have far fewer experiments than originally planned, lowering the potential need for experimental water. The experiments most affected by the change in mission, including cell-, plant-, and animal-science experiments, were the biggest potential users of experimental grade water. Other disciplines are less likely to consume water, and if such water were needed, it would have to be well characterized. Future lunar and Martian missions are also not likely to need experimental water. While there is the possibility of in situ clinical laboratory testing, procedures are either evolving away from wet testing, or using much smaller fluid volumes. Most of the testing could also be completed on Earth by transporting relatively small samples.

The remaining question is whether there are benefits to producing a combined potable-WFI system. Since the volume of WFI required is much less than potable water, the requirements of potable water would drive the design of the main purification system. WFI production would be an addition to the main system. There are benefits in have the WFI system collocated with the potable water system. Some technologies, such as RO, do not treat the entire water stream and the waste stream could be handled by a combined wastewater system. Given the relatively small water volume requirements for WFI, this benefit is relatively small. There are potential plumbing benefits, but any WFI system could be located along the plumbing path of other water users. The IV mixing and distribution would also have to be integrated into the combined system. Drawbacks include the extra engineering effort to integrate the systems, as well testing and verification complications. Combined systems also present potential difficulties in technology insertion to upgrade one or the other system.

6.11   Water Purification Technology Summary

Table XVI gives a summary of the technologies discussed that could be used to generate WFI during an emergency and for subsequent maintenance needs (note that the SBIR-level technologies are not included in the table and the reader is referred to Section 6.9 for those). Only two technologies are currently approved for WFI, distillation, and RO. Unfortunately, both suffer from disadvantages that make them difficult to adapt to spacecraft use. Distillation requires a large amount of energy, a cooling surface, and gravity or other means of separating the gas from the liquid. RO, meanwhile needs a relatively high-pressure water source, and faces sterilization issues for repeated use.

TABLE XVI.—EFFICACY OF VARIOUS METHODS OF PURIFICATION

Water generation method	Method characteristics					
	Contaminants removed	In use now for WFI	Rate of generation	Energy needed for generation	Sterilization	Other needs or limitations
Distillation	Essentially everything	Yes	High; many gallons per hour	13 Wh/L	May need to sterilize cold lines	Need a cool surface for condensation. Conventional separation requires gravity to work
Reverse osmosis	Bacteria, endotoxins, viruses, large molecules, solids, salts to some extent	Yes; also was tested by KSC for space use and met most USP standards	Several gallons/day	Need pressurized water (120 psi or more)	Need to sterilize membrane and whole system periodically	
Adsorption	Most contaminants can be removed, but adsorber(s) must be chosen for specific contaminants	No	Depends on size of cartridge; 4.5 L/hr is available	Need low pressure water of a couple psi	Cartridge can be stored sterile, but only used once	Current cartridge can treat 3 L, then dispose
Filtration	Bacteria, endotoxins, solids	No	Varies with filter; 0.7 L/m for 5 psi	Need pressurized water source	Chemical treatment or disposal	
Forward osmosis	Same as reverse osmosis	No	0.8 L/hr	None	Use once, then dispose	Cannot produce pure water, only concentrated solutions
Membrane distillation	Essentially everything, but still under development	No	Not yet tested	Lower than traditional distillation	Not yet tested	Need a cool surface for condensation
Osmotic distillation	Essentially everything	No	N/A, but likely slow	Low	Not yet tested	No high pressure as in RO; cannot produce pure water, only solutions
Nanofiltration	Still in the experimental phase; actually being developed to cleanse blood	No	N/A, but similar to kidney function	Low-pressure fluid needed	N/A; probably need to dispose	No large-scale device ever made

Currently the technology next closest to meeting USP standards is a combination of filtration (to remove larger contaminants) and adsorption to remove specific molecular and living species (i.e., viruses). While not yet approved for parenteral use, vendors are making improvements that may allow this use in the future. FO could likely be approved for parenteral use, given that RO is approved, but is limited to producing concentrated solutions and not nearly as flexible as technologies that produce pure water from which the desired solution can be made. FO may find a niche application in WFI. The remaining three technologies, membrane distillation, osmotic distillation (which, like FO, can only produce concentrated solutions), and nanofiltration offer some potential advantages of weight and power, but are still in the development stage and would require more extensive work to produce WFI in space.

A future trade study is planned to identify, evaluate in more detail, and draw conclusions about these potential WFI production methods. The trade study will select the method most appropriate for the

various DRMs, and provide estimates of expected performance. Other technologies may be identified during the trade study and included as well. The potential technologies will be quantitatively evaluated to present a nonbiased ranking. The selection criteria will include parameters such as production rate, sterility, mass, consumables, hypogravity confidence, operations, and development ease.

7.0   Discussion and Recommendations

NASA's Vision for Space Exploration has initiated new efforts to determine what technologies will be required for exploration of the Moon and Mars, and to define how these technologies will be developed and validated. Medical requirements and capabilities are being developed as part of this process. In particular, the necessity and required volumes for medical IV fluids are developed in this report. A similar effort was conducted in the late 1980s when the ISS planning was in its preliminary stages. A need for in situ IV fluid production was foreseen, and a development effort commenced. The SWIS was developed and tested on STS–47 in 1992 as part of the Spacelab-Japan Mission. This previous work still has relevance today, especially in systems involving adsorption and filtration. However, it must be remembered that the solutions produced on STS–47 did not meet total organic carbon requirements, had serious bubble issues in microgravity that may or may not be understood. The authors of this work have serious concerns about the mixing method proposed.

Terrestrial hospitals have a wide variety of fluids for medical use, but the mass and storage requirements limit what NASA may carry. In particular, human blood or blood products cannot be provided on Exploration missions as stored products because of limited storage life and refrigeration capabilities. HBOCs are under development as a substitute, but have not reached sufficient maturity to be included in NASA's planning at this time. Colloids are also commonly used for terrestrial medical treatment, but recent research questions the efficacy of colloids over crystalloids. It is recommended that three types of fluids be available for use in NASA's Exploration missions: LR (LR); NS (0.9%) (NS); and 5% dextrose with ¼ NS and 20 mEq KCl (D5KS). These are the most common fluids used for burns, trauma, and medication and maintenance requirements, respectively. LR and NS are often considered nearly interchangeable during treatment, and it is recommended that they be considered fully interchangeable for high-volume, medical fluid treatments during Exploration missions to reduce the overall volume requirements. It is also recommended that the medical community evaluate whether the LR and NS requirements can be met by one electrolyte to further reduce the logistics requirements.

The requirements for medical fluids were developed by evaluating the patient conditions in the PCDB. Five generic situations were identified to quantify fluid requirements, rather than develop fluid requirements for each specific condition. These five conditions were second- and third-degree skin burns, hemorrhagic shock, drug delivery, major bone fracture, and fluid maintenance. A major bone fracture is actually a subset of hemorrhagic shock, but its potential severity justified a separate examination. Actual medical events can require fluid treatment for several of these generic conditions. Table V in Section 3.6 summarizes the maximum fluid requirements for these generic conditions.

Typical medical events were postulated and analyzed to determine fluid requirements for the various Exploration missions. The maximum fluid requirement scenario for each mission was always a major fire, possibly injuring two crewmembers, requiring fluid treatment followed by maintenance fluids as the patient(s) recover(s). This scenario is often considered as either the driver for fluid volume requirements, or so severe as to preclude any treatment beyond the most basic. Space exploration has already had several fire or explosion events (Apollo 1, Apollo 13, and Mir NASA–3) and prudence dictates planning for the possibility. Additionally, the planned low-pressure, oxygen-rich environment in the new spacecraft increases the fire hazard over ISS, and surface exploration is EVA intensive in a pure-oxygen spacesuit environment (ref. 77).

The recommended fluid volumes are detailed in table XIV in Section 4.5. These recommendations should be considered as an upper bound of what would be required. Mission constraints may limit the supplies provided onboard, while accepting the subsequent increase in risk. The requirements are similar for the ISS and lunar habitat missions, with somewhat increased requirements for a Mars mission. The

lunar sortie requirements are substantially less and may require a different type of fluid production system if fluids are provided.

7.1   Fluid System Requirements

It is recommended that a system capable of generating 130 L of fluid for two time-separated events should be developed for ISS and lunar habitat missions. The water generation system should have the capability of generating 100 L of medical water at a rate of at least 1 L/hr, at any time after one minor event, or have the capability to produce and store sufficient solutions immediately after the first event. Concentrate or powder and associated supplies should be available to produce 15 L LR, 15 L NS, and 100 D5KS. An 8-hr contingency supply of 6 L LR, 6 L NS, and 2 L D5KS should be carried as stores. Note that when LR and NS are considered nearly interchangeable as recommended, the 8-hr contingency supply is the same as a 2-hr contingency supply for all of the DRMs. The system would preferably have the ability to produce new contingency stores with a shelf life of 6 months after a minor medical event occurs, otherwise new stores will have to be shipped to ensure a sufficient supply. The least mass a system could have, based on powder mass and 50 g/bag, is 12 kg, exclusive of the 12 L of contingency stores. The KSC IVF system currently weighs ~25 kg with three circuits producing 200 L each. A rough estimate of a refined, scaled system with two circuits producing 100 L each would be 10 kg. Adding 1 kg for a lightweight mixer, and the total weight would be approximately 23 versus 139 kg for stored fluids. A current trade study looking at various optimized systems indicates the mass may be less than 10 kg. Such a system may also be capable of further development to meet the Mars mission as well, possibly as two systems with one on the transit vehicle and one in the prepositioned surface habitat. A Mars fluid system would have the additional requirement of being capable of generating replacement contingency stores with at least a 6-month shelf life.

The lunar sortie has a much reduced volume requirement, and less concern with long-term sterility. It is probably not realistic to carry an 8-hr contingency supply, so a 1-hr supply of 4 L NS is recommended. The ability to produce 40 L of solution as 8 L LR, 4 L NS, and 28 L D5KS to handle any one event is recommended. Such a system may or may not utilize similar technology as the ISS and Habitat system. A filter/adsorption-based system could potentially be developed that masses 10 kg or less inclusive of supplies to produce this 40 L. The least a system could mass, based on powder mass and 50 g/bag, is 3.5 kg, exclusive of the 4 L of stores. A commercial adsorption-based device to produce purified water from stream water weighs 0.5 kg to produce 3 L of water. Assuming a similar system could produce 5 L from potable water, the weight of a complete system would be approximately 8.5 versus 43 kg for stored fluids.

Exploration missions will be highly mass sensitive, and the mass allocated to medical supplies may dictate a smaller volume than discussed above. The minimum recommendations are detailed in Section 4.5. The lunar sortie is the most mass sensitive, especially since the ISS and lunar habitat are considered technology testbeds for Mars missions. A lightweight contingency fluids recommendation for the lunar sorties would be for a system capable of producing 12 L of NS, with no fluid stores. This fluid volume could cover most trauma situations, and provide a reasonable chance for survival of a patient with burns up to 30 percent. NS can also be utilized as a maintenance fluid for limited durations where the caloric intake of D5 is not critical. It may be possible to develop such a system in the 3 to 5 kg mass range.

The solutions produced should meet USP standards to ensure the best possible medical care is being provided. The details of these requirements are discussed in Section 5.1.1. There is some concern because the USP standards are defined mainly from the process used to produce WFI rather than quantitative measurements of the final product. This becomes a problem because the standard processes will have problems meeting NASA's mass requirements. There is an additional complication because NASA potable water specifications do not match the EPA potable water specifications that are assumed to be the initial source water. Detailed specifications will have to be developed to ensure the medical water system and the final produced solutions meet the spirit of the regulations if not the specific process regulations.

There are many potential technologies that can be utilized to produce the purified water. Many of these technologies are commercially used to purify liquids in industry, or are being developed in advanced systems for potable water production. Only distillation and reverse osmosis are currently utilized to produce WFI, and the USP WFI standards are written with these processes in mind. NASA's intended usage is significantly different than standard, with production required only occasionally and not continuously. Maintaining sterility is more of a concern with occasional production, and the production system may be altered to include components that are utilized only for limited durations to prevent contamination. NASA's requirements are also unique in that WFI is not required as the final product. This requirement may allow utilizing technologies in a unique fashion to directly produce a solution while bypassing intermediate steps. A future trade study will evaluate the potential technologies, incorporating the results of small breadboard studies, and recommend the type of system that should be developed for NASA's Exploration missions.

50

Appendix A–Acronyms

ARDS   acute respiratory distress syndrome
BWI   bacteriostatic water for injection
CCL   contaminant candidate list
D5KS   5% dextrose/0.225% saline/20 mEq potassium chloride/L
D5W   5% dextrose in water
DEHP   di-(2-ethylhexyl) phthalate
DRM   design reference missions
EPA   Environmental Protection Agency
ESAS   Exploration Systems Architecture Study
ESM   equivalent system mass
EU   endotoxin unit
EVA   extravehicular activity
FDA   Food and Drug Administration
FLUID   filtering liquids for use in intravenous devices
FO   forward osmosis
FTS   fluid therapy system
Gy   gray
HBOC   hemoglobin-based oxygen carrier
ISS   International Space Station
IV   intravenous
IVF   intravenous fluid
KSC   NASA Kennedy Space Center
L   liter
LAL   limulus amebolysate
LR   Lactated Ringer's
MODS   multiple organ dysfunction syndrome
MORD   Medical Operations Requirements Document
mOsm   milliosmoles
NASA   National Aeronautics and Space Administration
NF   National Formulary
NPDWR   National Primary Drinking Water Regulations
NS   normal saline
NSDWR   National Secondary Drinking Water Regulations
OD   osmotic distillation
OGS   oxygen generation system
PCDB   patient condition database
pH   potential of hydrogen (a measure of acidity)
PVC   polyvinyl chloride
RBC   red blood cell
RO   reverse osmosis
SBIR   Small Business Innovation Research
SMCCB   Space Medicine Configuration Control Board
SMS   space motion sickness
SSP   Space Shuttle Program
STS   space transportation system
SWFI   sterile water for injection
SWIS   sterile water for injection system
TBSA   total body surface area
TPN   total parenteral nutrition

USP	United States Pharmacopeia
WFI	water for injection
WRS	water recovery system

References

1. NASA's Exploration Systems Architecture Study; Final Report. NASA/TM—2005-214062, 2005. Available from the NASA Center for AeroSpace Information.
2. Creager, G.: An Evaluation of IV Fluids Requirements for the Space Station Freedom Health Maintenance Facility Assuming a 10-Day Therapeutic Stay. Krug Life Sciences, 1991.
3. Space Station LVP Mixing System, Interim Report #2, J. Ogle, M. Finley, and J. Kipp, Baxter Healthcare, June 1989.
4. Barlow, Karen L.: Intravenous Fluid Mixing Times Quantified Using Planar Laser-Induced Fluorescence. M.S. Thesis, Case Western Reserve Univ., 2007.
5. Chiaramonte, Francis P.; and Joshi, Jitendra A.: Workshop on Critical Issues in Microgravity Fluids, Transport, and Reaction Processes in Advanced Human Support Technology; Final Report. NASA/TM—2004-212940, 2004.
6. Waterman, K.C.; and Adami, R.C.: Accelerated Aging: Prediction of Chemical Stability of Pharmaceuticals. Int. J. Pharm., vol. 293, nos. 1–2, 2005, pp. 101–125.
7. Benet, Leslie Z.; Kroetz, Deanna L.; and Sheiner, Lewis B.: Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination. Goodman & Gilman's the Pharmacological Basis of Therapeutics, Joel G. Hardman and Lee E. Limbird, eds., 9th ed., McGraw-Hill, New York, NY, 1996, pp. 3–27.
8. Bajanowski, T.; West, A.; and Brinkmann, B.: Proof of Fatal Air Embolism. Intl. J. Legal Med., vol. 111, no. 4, 1998, pp. 208–211.
9. Weinstein, Sharon M.: Principles of Parenteral Fluid Administration. Plumer's Principles and Practice of Intravenous Therapy, 8th ed., Lippincott Williams & Wilkins, Philadelphia, PA, 2007, pp. 124–150.
10. Guyton, Arthur C.; and Hall, John E.: The Body Fluid Compartments: Extracellular and Intracellular Fluids; Interstitial Fluid and Edema. Textbook of Medical Physiology, 9th ed., W.B. Saunders, Philadelphia, PA, 1996, pp. 297–313.
11. Lorenzo, M., et al.: Can Ringer's Lactate Be Used Safely With Blood Transfusions? Am. J. Surg., vol. 175, no. 4, 1998, pp. 308–310.
12. Boldt J., et al.: Are Lactated Ringer's Solution and Normal Saline Solution Equal With Regard to Coagulation? Anesth. Anal., vol. 94, no. 2, 2002, pp. 378–384.
13. Pope, Andrew; French, Geoffrey; and Longnecker, David E.: Fluid Resuscitation: State of the Science for Treating Combat Casualties and Civilian Injuries. Committee on Fluid Resuscitation for Combat Casualties, Institute of Medicine, National Academy Press, Washington, DC, 1999.
14. Phelan, M.: Cleveland Clinic Foundation, private communication, 2006.
15. Roberts, I., et al.: Colloids Versus Crystalloids for Fluid Resuscitation in Critically Ill Patients. Cochrane Database of Systematic Reviews 2004, Issue 3, Art. No.: CD000567. DOI: 10.1002/14651858.CD000567.pub2.
16. Finfer, S.R.; Boyce, N.W.; and Norton, R.N.: The SAFE Study: A Landmark Trial of the Safety of Albumin in Intensive Care. Med. J. Aust., vol. 181, no. 5, 2004, pp. 237–238.
17. Bunn, F.; Alderson, P.; and Hawkins, V.: Colloid Solutions for Resuscitation. Cochrane Database of Systematic Reviews 2003, Issue 1, Art. No.: CD001319. DOI: 10.1002/14651858.CD001319.
18. Kendrick Douglas B.: Blood Program in World War II. Office of the Surgeon General, Dept. of the Army, Washington, DC, 1989.
19. Army RDT&E Budget Item Justification. Project 840, Combat Injury Management, 2005.
20. Jensen T., et al.: Influence of Freeze-Drying on the Clotting Properties of Fibrinogen in Plasma. Thromb. Res., vol. 105, no. 6, 2002, pp. 499–502.
21. Jacobs E.E.; Gawryl, M.S.; and Pearce, L.B.: Use of Hemoglobin Based Oxygen Carrier-201 When Blood is Not Available or Not Acceptable. TRANA, vol. 40, no. 10, 2000, p. 41S.

22. Sehgal Lakshman R., et al.: Acellular Red Blood Cell Substitute. U.S. Patent 6,914,127 B2, July 5, 2005.

23. Lowe K.C.: Fluorinated Blood Substitutes and Oxygen Carriers. J. Fluorine Chem., vol. 109, no. 1, 2001, pp. 59−65.

24. Rock G.; Labow, R.S.; and Tocchi, M.: Distribution of di(2-ethylhexyl) Phthalate and Products in Blood and Blood Components. Env. Health Persp., vol. 65, 1986, pp. 309−316.

25. Van Dooren A.A.: PVC as Pharmaceutical Packaging Material—A Literature Survey With Special Emphasis on Plasticized PVC Bags. Pharm. Weekbl. Sci., vol. 13, no. 3, 1991, pp. 109−118.

26. Maltoni, C., et al.: Two Cases of Liver Angiosarcoma Among Polyvinyl Cholride (PVC) Extruders of an Italian Factory Producing PVC Bags and Other Containers. Am. J. Ind. Med., vol. 5, no. 4, 1984, pp. 297−302.

27. Naimian, F.; Katbab A.A.; and Nazokdast, H.: Post-Irradiation Stability of Polyvinyl Chloride at Sterilizing Doses. Radiat. Phys. Chem., vol. 44, no. 6, 1994, pp. 567−572.

28. Esposti, G.D., et al.: Characterization of the Ageing Process of Gamma-Irradiated PVC Samples Using TSDC Measurements. Radiat. Phys. Chem., vol. 54, no. 2, 1999, pp. 203−205.

29. Excel™ IV Containers Made of Eastman's Ecdel Elastomer Reduce Toxic Emissions and Produce Less Medical Waste. Eastman Chemical Company, ECCPR130 press release, 2005.

30. Crum-Skaracky, N.: Baxter Corporation, personal communication, 2006.

31. Yowler, C.J.; and Fratianne, R.B.: Current Status of Burn Resuscitation. Clin. Plast. Surg., vol. 27, no. 1, 2000, pp. 1−10.

32. Oliver, Robert; and Spain, David: Burns, Resuscitation and Early Management. eMedicine, 2005. http://www.emedicine.com/plastic/topic159.htm Accessed Sept. 27, 2007.

33. United States Naval Flight Surgeon Handbook. Society of U.S. Naval Flight Surgeons; Virtual Naval Hospital, 1998.

34. Ryan, C.M.: Objective Estimates of the Probability of Death From Burn Injuries. N. Eng. J. Med., vol. 338, no. 6, 1998, pp. 362−366.

35. Fleming, R.Y.D., et al.: Effect of Recombinant Human Growth-Hormone on Catabolic Hormones and Free Fatty-Acids Following Thermal-Injury. J. Trauma, vol. 32, no. 6, 1992, pp. 698−703.

36. Viele, M.K.; and Weiskopf, R.B.: What Can We Learn About the Need for Transfusion From Patients Who Refuse Blood? The Experience With Jehovah Witnesses. TRANA., vol. 34, no. 5, 1994, pp. 396−401.

37. Roberts, I.: Human Albumin Administration in Critically Ill Patients: Systematic Review of Randomised Controlled Trials. Cochrane Injuries Group Albumin Reviewers, Brit. Med. J., vol. 317, vol. 7153, 1998, pp. 235−240.

38. Keany, James E.: Fractures, Femur. eMedicine, 2005. http://www.emedicine.com/emerg/topic193.htm Accessed Sept. 27, 2007.

39. Wallace, Stephen; Goodman, Stuart; and Smith, Douglas G.: Compartment Syndrome, Lower Extremity. eMedicine, 2004. http://www.emedicine.com/orthoped/topic596.htm Accessed Sept. 27, 2007.

40. Holliday, M.A.; and Segar, W.E.: The Maintenance Need for Water in Parenteral Fluid Therapy. Pedia., vol. 19, no. 5, 1957, pp. 823−832.

41. Garth, David: Hypokalemia. eMedicine, 2005. http://www.emedicine.com/emerg/topic273.htm Accessed Sept. 27, 2007.

42. Waters, J.H., et al.: Normal Saline Versus Lactated Ringer's Solution for Intraoperative Fluid Management in Patients Undergoing Abdominal Aortic Aneurysm Repair: An Outcome Study. Anesth. Analg., vol. 93, no. 4, 2001, pp. 817−822.

43. National Primary and Secondary Water Drinking Standards, EPA, 2003.

44. Fact Sheet: The Drinking Water Contaminant Candidate List—The Source of Priority Contaminants for the Drinking Water Program, EPA 815−F−05−001, 2005.

45. Verostko, Charles; Carrier, Chris; and Finger, Barry: Ersatz Wastewater Formulations for Testing Water Recovery Systems. SAE Technical Paper 2004−01−2448, 2004.
46. Wilkerson, Kent; Bollmann, Karl; and Stecklein, Jonette: System Specification for the International Space Station (ISS), NASA SSP−41000, 2002.
47. Advanced Life Support Requirements Document. NASA JSC−38571C, CTSD−ADV−245C. 2003.
48. International Space Station Medical Operations Requirements Document (ISS MORD). NASA SSP−50260, 2006.
49. ITG Subject: Water for Pharmaceutical Use. FDA no. 46, 1986.
50. The United States Pharmacopeia. USP 29, The National Formulary, NF 24, United States Pharmacopoeia Convention Meeting, Washington, DC, 2005.
51. Bagdigian, Robert M.; Cloud, Dale; and Bedard, John: Status of the Regenerative ECLSS Water Recovery Oxygen Generation System. SAE Technical Paper 2006−01−2057, 2006.
52. Niederhaus, C.E, and Miller, F.J.: Intravenous Fluid Mixing in Normal Gravity, Partial Gravity, and Microgravity: Down-Selection of Mixing Methods, NASA/TM—2007-215000, 2007.
53. Hutchens, Cindy; and Graves, Rex: Results of the Vapor Compression Distillation Flight Experiment (VCD−FE). SAE Technical Paper 2004−01−2450, 2004.
54. Flynn, Michael T.: The Development of the Vapor Phase Catalytic Ammonia Removal (VPCAR) Engineering Development Unit. SAE Technical Paper 2004−01−2495, 2004.
55. Holder, Donald W., et al.: Investigation Into the Performance of Membrane Separator Technologies Used in the International Space Station Regenerative Life Support Systems: Results and Lessons Learned. SAE Technical Paper 2001−01−2354, 2001.
56. La Duc, Myron T., et al.: Evidence of Pathogenic Microbes in the International Space Station Drinking Water: Reason For Concern? Habitation, vol. 10, no. 1, 2004, 39–48.
57. Newcombe, David, et al.: Q−PCR Based Bioburden Assessment of Drinking Water Throughout Treatment and Delivery to the International Space Station. SAE Technical Paper 2005−01−2932, 2005.
58. Rebekah Jean Bruce, et al.: Microbial Surveillance of Potable Water Sources of the International Space Station. SAE Technical Paper 2005−01−2886, 2005.
59. Straub II, John E.; Plumlee, Debrah K.; and Schultz, John R.: Chemical Analysis of ISS Potable Water From Expeditions 8 and 9. SAE Technical Paper 2005−01−2885, 2005.
60. Stuecker, Tara, et al.: Implications of the VBNC State of B. Cepacia and S. Maltophilia on Bioreduction and Microbial Monitoring of ISS Potable Waters. SAE Technical Paper 2005−01−2933, 2005.
61. McLean, R.J.C., et al.: Bacterial Biofilm Formation Under Microgravity Conditions. FEMS Microbiol. Lett., vol. 195, no. 2, 2001, pp. 115–119.
62. Diffusion in Liquids. Skylab, Classroom in Space, L.B. Summerlin, ed., NASA SP−401, part III, ch. 12, 1977. http://history.nasa.gov/SP-401/ch12.htm Accessed Oct. 4, 2007.
63. Lide, David R.: CRC Handbook of Chemistry and Physics: A Ready-Reference Book of Chemical and Physical Data. 84th ed., CRC Press, Boca Raton, FL, 2003.
64. GreenShift Portfolio Company Ovation Products Reports Successful Testing of New Production Version of Water Purification Technology. GSHF News, GreenShift, New York, NY, Nov. 23, 2005. http://www.greenshift.com/news.php?id=86 Accessed Oct. 3, 2007.
65. Hutchens, Cindy F.: Vapor Compression Distillation (VCD) Flight Experiment. NASA Fact Sheet FS−2002−06−114−MSFC, 2002. http://www.nasa.gov/centers/marshall/news/background/facts/vcd.html Accessed Oct. 4, 2007.
66. ITG Subject: Reverse Osmosis. U.S. Food and Drug Administration, no. 36, Oct. 21, 1980. http://www.fda.gov/ora/inspect_ref/itg/itg36.html Accessed Oct. 4, 2007.
67. Pounds, Jedadiah D., et al.: Filtering Water Sources for Use in Hydrating Intravenous Fluids (IV) Onboard Space Shuttle and International Space Station (ISS). Kennedy Space Center, FL. http://aeromedical.org/Articles/SLSTPF1.html Accessed Oct. 4, 2007. Unable to open Web site

68. Medical applications: Water filtration. Industries and Applications, Minnitech, Little Falls, NJ. http://www.minntech.com.
69. HTI: Anywater, Anywhere. Hydration Technologies, Inc., Albany, OR. http://www.hydrationtech.com Accessed Oct. 4, 2007.
70. Salter, Robert J.: Forward Osmosis. Water Conditioning & Purification, vol. 48, no. 4, 2006, pp. 36−38.
71. Tsai, Chung-Yi: Novel Foul-Resistant Nano-Pervaporation Membrane for Medical Grade Water Generation. Autonomous Medical Care, Proposal 05 X11.03−8109, NASA SBIR 2005 Solicitation, 2005. http://sbir.nasa.gov/SBIR/abstracts/05/sbir/phase1/SBIR-05-1-X11.03-8109.html?solicitationId=SBIR_05_P1 Accessed Oct. 4, 2007.
72. Osmotic Distillation. The Chemical Engineers' Resource Page, Midlothian, VA, 2004. http://www.cheresources.com/osdistzz.shtml Accessed Oct. 4, 2007.
73. Hogan, P.A., et al.: A New Option: Osmotic Distillation. Chem. Engng. Prog., vol. 94, no. 7, 1998, pp. 49−61. http://www.liqui-cel.com/uploads/documents/Osmotic%20Distillation%20using%20Liqui-Cel.pdf#search=%22A%20New%20Option%3A%20Osmotic%20Distillation%22 Accessed Oct. 4, 2007.
74. Cath, Tzahi Y., et al.: New Concepts and Performance of the Direct Osmotic Concentration Process for Wastewater Recovery in Advanced Life Support Systems. SAE Technical Paper 2006−01−2086, 2006.
75. Fissell IV, William H., et al.: Ultrafiltration Membrane, Device, Bioartificial Organ, and Methods. U.S. Patent 7048856, 2006.
76. Akse, James R., et al.: Microwave Powered Gravitationally Independent Medical Grade Water Generation. Autonomous Medical Care, Proposal NNC06CA77C, NASA SBIR 2005 Solicitation, 2005. http://sbir.gsfc.nasa.gov/SBIR/abstracts/05/sbir/phase2/SBIR-05-2-X11.03-9545.html Accessed Oct. 4, 2007.
77. Friedman, Robert: Fire Safety in Extraterrestrial Environments. NASA/TM—1998-207417, 1998.

REPORT DOCUMENTATION PAGE

1. REPORT DATE *(DD-MM-YYYY)* 01-05-2008	2. REPORT TYPE Technical Memorandum	3. DATES COVERED *(From - To)*

4. TITLE AND SUBTITLE
Medical Grade Water Generation for Intravenous Fluid Production on Exploration Missions

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Niederhaus, Charles; Barlow, Karen; Griffin, DeVon; Miller, Fletcher

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER
WBS 444543.01.02.01

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
National Aeronautics and Space Administration
John H. Glenn Research Center at Lewis Field
Cleveland, Ohio 44135-3191

8. PERFORMING ORGANIZATION REPORT NUMBER
E-16207

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
National Aeronautics and Space Administration
Washington, DC 20546-0001

10. SPONSORING/MONITORS ACRONYM(S)
NASA

11. SPONSORING/MONITORING REPORT NUMBER
NASA/TM-2008-214999

12. DISTRIBUTION/AVAILABILITY STATEMENT
Unclassified-Unlimited
Subject Category: 52
Available electronically at http://gltrs.grc.nasa.gov
This publication is available from the NASA Center for AeroSpace Information, 301-621-0390

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This document describes the intravenous (IV) fluids requirements for medical care during NASA's future Exploration class missions. It further discusses potential methods for generating such fluids and the challenges associated with different fluid generation technologies. The current Exploration baseline mission profiles are introduced, potential medical conditions described and evaluated for fluidic needs, and operational issues assessed. Conclusions on the fluid volume requirements are presented, and the feasibility of various fluid generation options are discussed. A separate report will document a more complete trade study on the options to provide the required fluids. At the time this document was developed, NASA had not yet determined requirements for medical care during Exploration missions. As a result, this study was based on the current requirements for care onboard the International Space Station (ISS). While we expect that medical requirements will be different for Exploration missions, this document will provide a useful baseline for not only developing hardware to generate medical water for injection (WFI), but as a foundation for meeting future requirements. As a final note, we expect WFI requirements for Exploration will be higher than for ISS care, and system capacity may well need to be higher than currently specified.

15. SUBJECT TERMS
Fluid filters; Aerospace medicine; Microgravity applications

16. SECURITY CLASSIFICATION OF:

a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
U	U	U	UU	61	STI Help Desk (email:help@sti.nasa.gov)

19a. NAME OF RESPONSIBLE PERSON
STI Help Desk (email:help@sti.nasa.gov)

19b. TELEPHONE NUMBER *(include area code)*
301-621-0390