



Intravenous Fluid Generation Mini (IVGEN Mini) Summary and Related Research

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NASA/TM-20220012816



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January 2023

Acknowledgments

I would like to express gratitude to my mentor and co-mentor, Tyler Hatch and Nancy Hall, respectively. I could not have undertaken this journey without Tyler and Nancy, who generously provided knowledge and advice throughout the internship. I would also like to thank the IVGEN Mini team and the NASA GRC internship coordinators for their support and assistance. Additionally, this endeavor would not have been possible without the generous support from the Iowa Space Grant Consortium.

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Intravenous Fluid Generation Mini (IVGEN Mini)

Summary and Related Research

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Abstract

This paper assists the ongoing effort to support NASA Glenn’s mission and its Human Research Program (HRP) core competency by investigating a technology demonstration to mitigate human health and performance risks during space exploration. Crew health and performance are critical to successful human exploration beyond low Earth orbit. Four hundred forty-two medical conditions have been identified and may present and require treatment during long-duration space exploration missions. One hundred fifteen out of 442 identified medical conditions would require medical fluid treatment, generating a need for an on-demand or continuous supply of medical fluid. Intravenous Fluid Generation Mini (IVGEN Mini) is a technology demonstration designed to demonstrate a water purification and pharmaceutical mixing system that can make intravenous (IV) fluid in microgravity and builds on the success of the original Intravenous Fluid Generation for Exploration Missions (IVGEN) experiment, which flew on the ISS in March 2010. IVGEN Mini seeks to increase the technology readiness level (TRL) and the overall function of the original IVGEN experiment to reduce the dependence of a needed medical consumable and streamline the size of the device and process to generate IV fluid IVGEN Mini is funded by the Advanced Exploration Systems (AES) directorate via the Exploration Medical Integrated Product Team (XMIPT) as a part of their mission to advance exploration medical technologies to benefit the overall health and safety of crews for beyond low Earth orbit space missions. This paper discusses a collection of related research topics such as microgravity fluid mixing and studying past efforts of IV fluid usage in extreme environments to aid IVGEN Mini project scientists in developing the IVGEN Mini technology.

Nomenclature

ALSP	Advanced Life Support Pack
API	Active Pharmaceutical Ingredient
ASC	Antenna Sterilization Chamber
CONOPS	Concept of Operations
CW	Challenge Water

* Mechanical Engineering Intern from Iowa Space Grant Consortium.

CWC	Contingency Water Container
DACU	Data Acquisition and Control Unit
DC	Direct Current
DI	Deionization
ECLSS	Environmental Control and Life Support System
EU	Endotoxin Units
FAS	Fluid Administration Set
FIST	Flight Infusion System Test
IASC	International Astronomical Search Collaboration
IRD	Intravenous Reconstituting Device
ISS	International Space Station
IV	Intravenous
IVGEN	Intravenous Fluid Generation
IVGEN Mini	Intravenous Fluid Generation Mini
JSC	Johnson Space Center
LVP	Large Volume Parenteral Bags
LAL	Limulus Amebocyte Lysate
MGE	Microgravity Environment
MSG	Microgravity Science Glovebox
NLT	Not Less Than
NMT	Not More Than
NS	Normal Saline
PGSC	Payload and General Support Computer
PW	Product Water
PWR	Potable Water Reservoir
REFLUPS	Resuscitation Fluids Production System
SCD	Sample Containment Device
SWC	Source Water Container
SWI	Sterile Water for Injection
SWIS	Sterile Water for Injection System
TFC	Thin Film Composite
TOC	Total Organic Carbon
TRL	Technology Readiness Level
USAISR	U.S. Army Institute of Surgical Research
USP	United States Pharmacopeia
VEGGIE	Vegetable Production System
WFI	Water for Injection
WPA	Water Processing Assembly
WSC	Wavelength Sterilization Chamber

1.0 Introduction

International Space Station (ISS) resupply missions are critical for the health and vitality of astronauts aboard the ISS. Approximately 31,000 to 37,000 lb of cargo are delivered to the ISS annually through resupply missions (Ref. 1), which is made possible due to the ISS's proximity to the Earth compared to other terrestrial bodies. While this delivery mechanism works well for a body orbiting only 248 miles from the Earth's surface, it is not practical for future long-duration space flight missions to the Moon or Mars (Ref. 2).

Stabilizing and treating patients on exploration missions will depend on access to needed medical consumables. Twenty-five percent of the 400 identified medical conditions that may occur and demand treatment during space missions will require intravenous (IV) fluid treatment, defining IV fluid as an essential consumable to maintain astronaut homeostasis (Ref. 3). The Intravenous Fluid Generation for Exploration Missions (IVGEN and IVGEN Mini) experiments were designed by NASA to demonstrate a water sterilization and pharmaceutical salt mixing system that produces 0.9 percent normal saline IV fluid standardized by the United States Pharmacopeia (USP) and provide a continuous supply of IV fluid without the need for resupply missions. The driving concept for IVGEN Mini is to develop a miniaturized system that produces sterile water from ISS potable water and converts it to Normal Saline (NS) for crews of missions beyond low-Earth orbit, long-duration lunar orbit, lunar surface operations, and missions to Mars. The purpose of this Technology Demonstration is to raise the filtration and mixing technology's technology readiness level (TRL) of the original IVGEN technology to a level, sufficiently tested and verified, that it can be utilized effectively by a crew of astronauts to produce IV fluids when needed with a minimum of either physical resources or technical support. To achieve this goal, IVGEN Mini project scientists plan to focus on reducing the mass and volume of the unit and consumables proportional to that of an equivalent amount of IV fluids flown from Earth.

The current source of IV fluid on the ISS comes from the Advanced Life Support Pack (ALSP), a divided cloth pack that contains medications, tools, bandaging supplies, bladder catheterization items, IV catheterization, and physical exam hardware (Figure 1). The ALSP pack functions as a nominal preventive health care measure, treatment for minor illness/injury, and has some advanced life support capability. It is designed to support three crew members for a 6-month mission and is resupplied after each crew rotation. The pack also contains IV fluid of 0.5-L bags of dextrose solution and 0.5- and 1-L bags of 0.9 percent NS solution for a total of 4.5 L. Due to shelf-life considerations of the IV fluid and other medical consumables, each of the contents of the ALSP is replaced at least every 18 months. The pack cannot treat a crew member in the case of a life-threatening illness. It is meant to sustain a patient's state of homeostasis until the patient can be evacuated back to Earth. Due to a limited shelf life of 18 months after which time it is unsafe to use the fluid for medical purposes, the need for resupply missions, and restricted medical care capabilities, the ALSP is not a suitable solution for long-duration space flight missions (Ref. 4).



Figure 1.—Advanced Life Support Pack (ALSP). This is a photo taken of the ALSP which contains, medications, tools (wound repair, dental), bandaging supplies, bladder catheterization items, IV catheterization and physical examination hardware.

1.1 Purpose

This document was undertaken to summarize published literature on novel microgravity fluid mixing techniques and IV fluid usage in extreme environments and provide an overview of the IVGEN and IVGEN Mini technology demonstrations. An evaluation of related research, including fluid microgravity mixing techniques, past efforts of IV fluid usage in extreme environments, parenteral pharmaceutical development, and portable pharmaceutical generation devices are discussed to aid IVGEN Mini project scientists in the development of the IVGEN Mini technology and facilitate an increase in the IVGEN Mini TRL.

1.2 Scope

This document describes the IVGEN and IVGEN Mini's primary system functions but does not discuss deployment, operations, support, manufacturing, and verification concepts. Instead, the document serves as a technology risk assessment to compare and analyze current IVGEN Mini systems to similar studies and past IVGEN work. This work only explores the generation of IV fluid and not the administration of IV fluid to a patient.

2.0 IVGEN Design and Documentation

The objective of the IVGEN technology demonstration was to verify the ability to produce Water for Injection (WFI) and mix it with salt to generate 0.9 percent Normal Saline (NS) solution from the ISS potable water supply. IVGEN project scientists set out to achieve five main objectives:

1. Design a compact water purification system to reliably produce Sterile Water for Injection (SWI) in a reduced gravity environment.
2. Integrate production system with reduced gravity pharmaceutical mixing capability. Verify a prototype aboard the ISS in 2010.
3. Prototype size and production rate should be the minimum necessary to meet the Exploration Investigation requirements.
4. Filtering capacity should be easily rescalable to meet exploration requirements and constraints.

The primary components of the system included the accumulator, purifier module, and mixing stand. Diagnostic devices were placed near function critical components to measure hydraulic and purification characteristics and ultimately verify system performance. On-orbit system performance was monitored by cameras, pressure transducers, thermocouples, conductivity sensors, and a flow meter. Solution compliance with USP standards was determined during ground laboratory testing because of the number of tests that the IV solution would have to undergo (Ref. 3).

2.1 Accumulator

The purpose of the accumulator (shown in Figure 2) was to receive potable water from the ISS and pump the water from the bladder supplying the ISS potable water to the device. The accumulator consisted of a polycarbonate housing with a 1.5-L internal bladder. Potable water from the shuttle fuel cells via Contingency Water Containers (CWCs) or the ISS Water Processing Assembly (WPA) was delivered to the bladder using two hoses with custom fitting connections. Gaseous nitrogen provided within the Microgravity Glovebox (MSG) was used to pressurize the accumulator housing and pump water from the bladder. During the late design development stages, the Environmental Control and Life



Figure 2.—IVGEN Accumulator. This is an image taken of the IVGEN accumulator. The accumulator's bladder can be seen through the clear casing.

Support Systems (ECLSS) required a filter added to the IVGEN Accumulator Fill Hose for WPA to prevent back-flow into the WPA. The addition of the filter presented challenges for generating USP NS, such as decreasing the allowable water by introducing a significant amount of air (55 mL) to the system displacing the water that could be added to the saline solution. These problems would later contribute to salt concentration USP specification failure during ground testing.

The final IVGEN configuration was tested before launch. However, only two bags of normal saline were produced due to time constraints. Of the two bags, one bag passed all the USP requirements. The saline concentration of the second bag failed to meet USP standards. The IVGEN team was unaware of the second bag failure until after the hardware had been launched due to prolonged testing and reporting times. A post-flight investigation was undertaken to identify anomalies and system failures that led to this problem which is discussed in Section 2.5 (Ref. 3).

2.2 Purifier

The purifier module (shown in Figure 3) is a core assembly responsible for converting potable water to WFI. The water from the Accumulator Assembly enters the Water Purification Assembly and travels through the flow meter and pressure transducer. The assembly included the Deionization (DI) resin cartridge, air removal filters, and instrumentation. An aluminum box housed the purifier components in two layers. A Coriolis flowmeter measured the mixture's fluid flow rate and density. The density measurement provided a means to determine whether tapped air or liquid was flowing from the accumulator into the purifier. A dual-ring conductivity probe measured the baseline conductivity of incoming baseline water to further measure air detection and salt concentration monitoring. Two pairs of Supor filters made by the Pall Corporation prevented air from entering the DI cartridge. These filters had a polyethersulfone membrane with a pore diameter of 1.2 μm in a 0.7 mL housing. During a blockage due to particulate accumulation, bypass lines to pass each Supor filter could be switched to convert the flow away from the filters.

The DI cartridge removes ionic contaminants from the water through ion exchange. The cartridge was loaded with DI resin from ResinTech. The specific resin used was MBD-10-ULTRA. In a terrestrial environment, the resin had a 5-year shelf life. However, the shelf life may be impacted in space due to radiation. This assessment was beyond the scope of the IVGEN study. Settling of the resin beads was mitigated by periodically compressing the interstitial volume of the cartridge by gently tapping on the beads with a blunt rod.

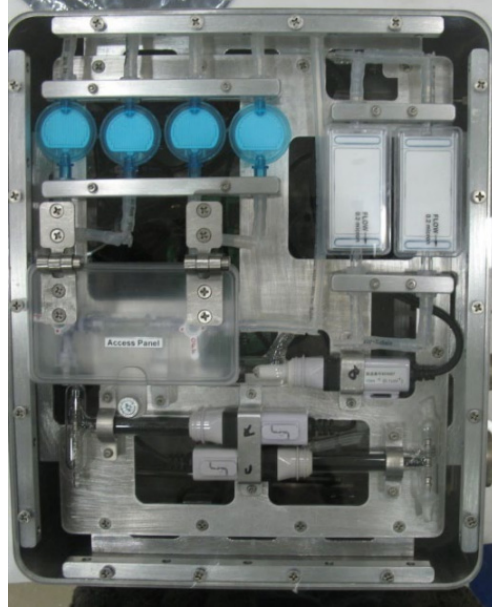


Figure 3.—IVGEN Top level of purifier module
an image taken of the top level of the IVGEN
purifier module.

The purifier's instrumentation included a series of Posidyne ELD filters, a flat plate sensor, and three absolute pressure transducers. The Posidyne ELD filters were used primarily to prevent air from entering the collection or saline bags. The flat plate sensor measured the conductivity of the purified water and indicated the efficiency of the Pall filters in removing air bubbles. The absolute pressure transducers measure the pressure loss across the two types of Pall filters and the DI cartridge and provide a means of determining the density of any gas present within the system (Ref. 4).

2.3 Mixer Assembly

The Mixer assembly (shown in Figure 4) consisted of two flat aluminum plates, a mixer motor and its controller, the saline, and collection bags. The bags were multilayered, manufactured from ethyl vinyl acetate, and could hold 2 L of fluid. Although the bags could hold 2.0 L, the accumulator was designed to only supply 1.5 L of water to the bags to prevent over-pressurization. The bags are equipped with three ports, an inlet, an outlet, and a filling port. The salt and stir bar were fitted into the bag via the filling port. Attached to the inlet and outlet ports were isolation valves used to maintain the integrity of the collection bag contents. A Pall Pediatric IV filter was spliced between the bag and the valves to vent any air entrained in the fluid from the collection bag to the transfer bag. The transfer bags held the final IV solution and were gamma irradiated for sterilization.

The Mixer Assembly's mixing mechanism employed a rotating magnetic field to cause a stir bar to rotate within the ethyl vinyl acetate saline collection bag. The mixer featured two samarium cobalt rare earth magnets on a rotor driven by a direct current (DC) motor. The DC motor was activated and controlled via a dial and switch (Ref. 3). A full system assembly including the accumulator, purifier and mixer is displayed in Figure 5.



Figure 4.—This is an image taken of the IVGEN Mixer Assembly.

4.2 Flight Hardware Description

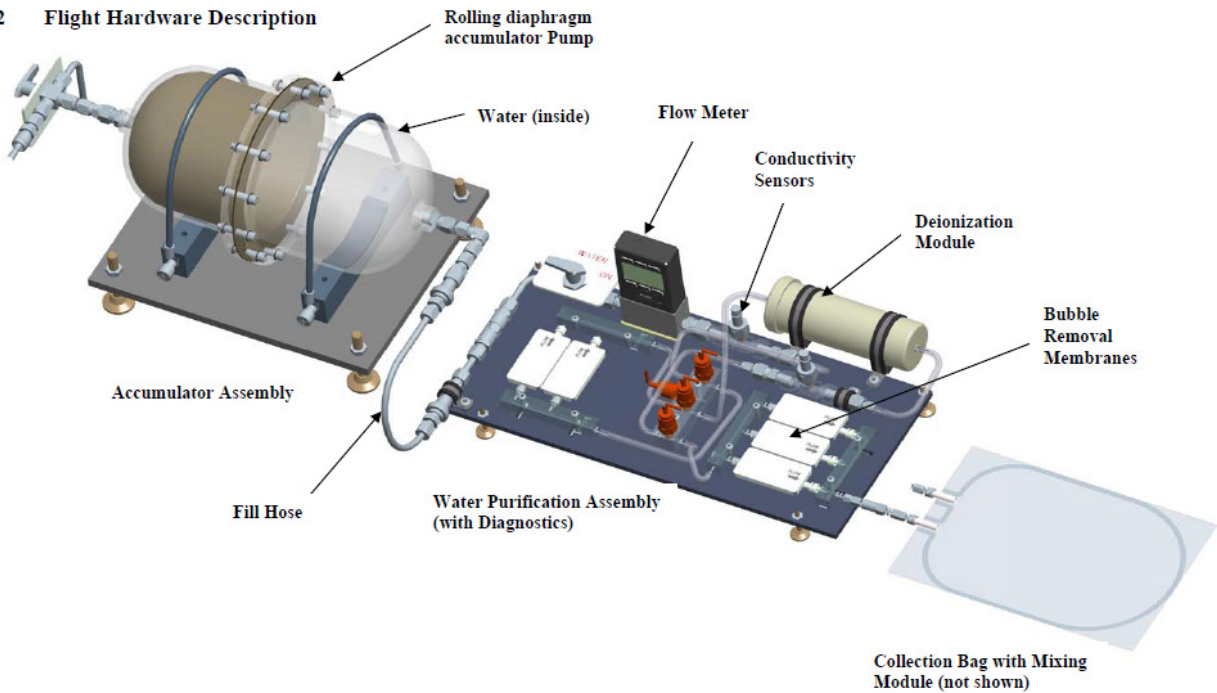


Figure 5.—IVGEN System Layout.

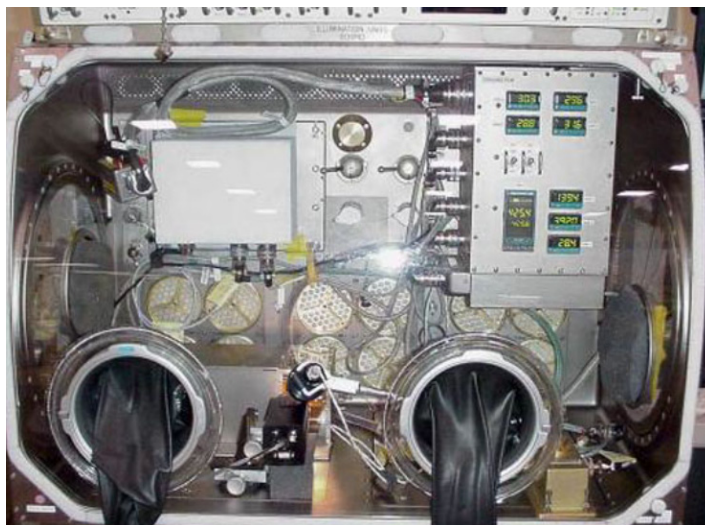


Figure 6.—ISS Microgravity Science Glovebox.

2.4 Operating Procedure

IVGEN was flown and operated aboard the ISS, Increment 23/24, during May 2010. On May 4, IVGEN was installed into the ISS's Microgravity Science Glovebox (MSG) (displayed in Figure 6). The IVGEN system was developed to run autonomously after installation (Figure 5). The purifier, accumulator, and mixer assembly were mounted to the back wall baseplate of the MSG, and the power converter, Data Acquisition and Control Unit (DACU) were installed on the MSG back wall. Power cables and connectors connected the power, command, control functions, and data between the MSG facilities and IVGEN. Fluid hoses were attached to each system subset to connect the individual components. The accumulator was connected to the MSG nitrogen port to act as a pressurant to the accumulator housing and facilitate the flow of the water. Water was supplied from the Water Processing Assembly (WPA), the source of drinking water for astronauts. The potable water was dispensed from the Potable Water Reservoirs (PWR). Back contamination was prevented by a sterilizing filter placed between the receiving container and the PWR. The accumulator disconnected from the MSG baseplate, transported, and filled with potable water via the PWR, and reconnected to the MSG assembly.

Six system purification cycles were conducted in the MSG. Water collection bags containing a premeasured amount of salt were filled with water to test IVGEN mixing capabilities and generate NS solution for the first two cycles. Based on flow meter readings, 500 mL of purified liquid had been generated, and the magnetic stirrer was remotely started via the DACU. Mixing occurred for 20 min after the purification was complete for the first saline bag and 5 min for the second bag.

The last four cycles did not generate NS but tested the capacity of the DI resin cartridge by removing the salt from the collection bag. Two cycles were performed each day for two consecutive days without changing the DI resin cartridge. The crew emptied the collection bags back into the ISS water reservoir. The empty bags and NS bags were returned to Earth for testing. The NS bags were inspected, weighed, and photographed. And shipped to Pace Analytical Services, Inc., Life Sciences, to test for compliance with USP standards (Ref. 3).

2.5 Post Flight Analysis

All six samples were evaluated for the purification effectiveness, but only two samples, NS-1 and NS-2, were evaluated for the uniformity of solution concentration and compliance with USP standards

for sterile NaCl solution for injection. Both bags of product solution passed all tests except for the allowable salt concentration. The first bag, NS-1, salt concentration was over the allowable concentration limit with a concentration of 117 percent of the target value of 0.9 g/L. It was speculated that the cause of the high salt concentration was due to trapped air in the accumulator during the filling process displacing the purified water from the collection bag and not allowing enough water to enter the accumulator. A potential resolution is to place a bubble separator at the accumulator inlet. In the second bag, NS-2, the salt concentration was too low due to an insufficient amount of salt placed into the collection bag during the bag assembly process (Ref. 3).

3.0 IVGEN Mini Design and Documentation

The Intravenous Fluid Generation Mini (IVGEN Mini) is a follow on to the initial IVGEN system and is being developed to generate IV injectable fluids from the ISS potable water supply to demonstrate an ISS exploration system maturation. The objective of the IVGEN Mini system is to miniaturize the previously flown IVGEN system while maintaining functionality, including generating safe and effective IV fluid, minimizing ISS crew time and resources, and having long-term storage capabilities. Although the IVGEN spaceflight experiment was mostly successful, final verification testing of the down massed IVGEN generated IV fluid showed the IV fluid failed to meet the required USP saline concentration standard. For this reason, a significant amount of work should be completed concerning the testing and design of the operating system, which is to be addressed by the IVGEN Mini technology demonstration. After the completion of the IVGEN project, a claim for future development was made by Mike Giannone, “The proposed design of the IVGEN hardware for exploration missions is compact. Except for the accumulator, which plugs into the potable water supply to get the source water, everything else could fit inside a small laptop computer. It would be about 1.5 in. thick with a footprint of around 8 by 11 in., making it a real option for solving the problem of saline supplies in space.” (Ref. 5)

3.1 Fluid Generation Module

The following information was derived from the “Intravenous Fluids Generation, Miniaturized (IVGEN Mini) Concept of Operations (CONOPS) Document.” by Zin Technologies Inc. There are two fluid intake inlets on IVGEN Mini. The first inlet connects to a VEGGIE transfer bag which hold 2.5 L of potable water. The second inlet connects to a syringe containing 26 percent concentrated saline solution; a value high enough to prevent bacterial contamination but below the complete saturation limit. The fluid generation module (FGM) contains two peristaltic pumps: one for each inlet. The two pumps are Boxer 9QQ Miniature Peristaltic Pumps. The pumps are designed for a Tap Water Feedstock (conductivity $\sim 275 \mu\text{S}/\text{cm}$) and maintain a flow rate of ~ 17 to $25 \text{ mL}/\text{min}$. Both pumps can provide a volumetric measurement based on time, the number of pump rotations, and a known volume moved by each rotation. After leaving the pumps, Supor[®] AEF2NT Intravenous Filter air elimination filters reduce inadvertent particulate debris and eliminate entrained air found in the intravenous solution for a maximum of 24 hr. Next, the ISS potable water supply flows through a DI cartridge. The DI cartridge deionizes the ISS supply bag water. The cartridge contains a mixed bed of cation and anion beads that deionize the water passing through them. A pressure transducer measures the fluid pressure of the mixed water and saline concentrate. Each pump will be set at a specified volumetric flow rate such that when the potable water and concentrated saline combine at the t-connector, the fluids are mixed, and the final normal saline concentration of 0.9 percent is met. A conductivity sensor is installed at the outlet of the mixing-t to measure the conductivity of the normal saline solution and ensure it is of the right concentration. The full configuration of the IVGEN Mini system is shown in Figure 7 (Ref. 6).

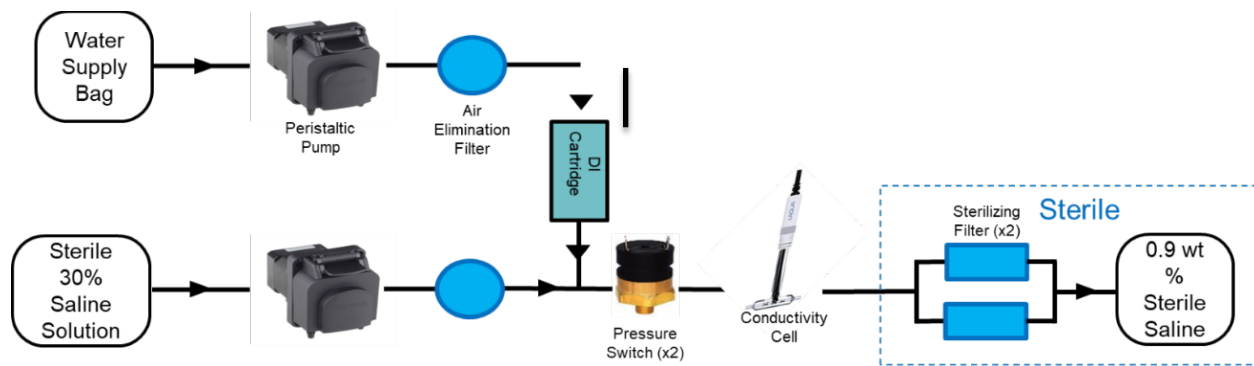


Figure 7.—IVGEN Mini System Layout.

3.2 Saline Concentrate Syringe

Concentrated saline solution will be prefilled into syringes and inserted into the input of the IVGEN Mini system. A certain amount of concentrate will be administered into the device and mixed with potable water. The current target concentration of the concentrated saline solution is 26 percent which is a value high enough to prevent bacterial contamination but below the complete saturation limit.

3.3 “VEGGIE” Bag (Water Transfer to MSG)

A dedicated Vegetable Production System (VEGGIE) transfer Bag is filled with ISS potable water by a crew member and used for water transport. VEGGIE, developed by Orbital Technologies Corp (now Sierra Nevada Corporation), is a deployable plant growing facility capable of producing vegetables when installed on ISS in 2014. VEGGIE is a simple, easily stowed, low-power system used to grow fresh, nutritious food for astronauts to supplement their diet and use as a tool to support recreational activities. The VEGGIE bags are an on-orbit ISS resource or are already stored on the ISS for another ISS mission. The VEGGIE bags can hold up to 3 L of fluid upon request.

3.4 Filter Box Assembly

The filter box assembly contains the filter module and is the main mechanism for fluid sterilization. To prevent sterilization complications within the complex arrangement of the fluid generation module, sterilization is left until the end of the IV fluid generation process to ensure IV fluid entering the IV bag is sterile. Components upstream of the sterilization filters are “clean” but not sterile, allowing nonsterile components to be reusable. The filter box assembly contains all the sterile components of the IVGEN Mini assembly. Individual filter box assembly components that do not come in sterile packaging will be sterilized via an autoclave. The system will be assembled in a cleanroom to guarantee complete sterilization before launch.

3.5 End to End Ground Testing

Before launch, an End-to-End terrestrial test is planned for IVGEN Mini to ensure the system functions properly. IVGEN Mini prelaunch testing plans to demonstrate in the lab setting creating 10 L of IV fluid as it will be done in orbit. There are a couple of expendable components within IVGEN Mini including two sets of Pall filters and the deionization column. The Pall filters remove the air and endotoxins from the fluid stream but are only functional for 24 hr after being wetted, the filters must be replaced after every time that they are functionally tested. One deionization column will be used for all

functional tests and replaced with a fresh, dry unit just before launch. During testing, an Inflight system configuration will be replicated. Once IVGEN Mini is connected to a power source and powered on, a previously programmed “Purged” run will be performed. Simulated ISS potable water will be used as the challenge water for the End-to-End tests. The challenged water will be transported via a dedicated VEGGIE Bag as it would in orbit. Operations testing will be performed as described in the IVGEN Mini CONOPS (IVGEN Mini-CONOPS-001). ZIN technologies MSG simulator simulates a downlink pathway and will be used for commanding, control, and data acquisition during the test. A simulated “crew” and remote commanding will be used to run the test (Ref. 7).

3.6 Operating Procedure

The operation test procedure is as follows; Once the main modules have been properly positioned, they can be electrically connected. Once the IVGEN Mini system is electrically ready for use, the potable water for the first units must be drawn. IVGEN Mini has elected to use 2.5 L of potable water collected and stored in “VEGGIE” transfer bags. The bags will be fitted with a connector and connected to the “water supply bag” inlet. After that, the syringe containing the concentrated saline solution will be connected to the Saline Inlet port. To prevent air from entering the IV bag that will contain the final NS product, the Filter Module will include a small (50 to 100 mL) purging capture bag on its outlet. Once assembly is complete, the system will be “purged” by filling with water and purging the air using the Pall filters in the Filter Module. Once this action has been completed, the Purging bag will be removed, one of the IVGEN Mini IV Bags will be attached to the outlet, and the system will be ready to use. When activated, the system will accurately pump the potable water through the deionizing packed bed and combine it with the pumped saline from the syringe or the Concentrated Saline Bag and combine the two flows (Ref. 6).

4.0 USP Standards for IVGEN and IVGEN Mini

The United States Pharmacopeia (USP) is the authoritative source for medicine and healthcare product standards. USP is a not-for-profit, nongovernmental organization that sets quality, purity, strength, and identity standards for medicines, food ingredients, and dietary supplements. IVGEN and IVGEN Mini follow the guidance of USP-standardized NaCl injection. USP defines NaCl Injection as a sterile solution of NaCl in Water for Injection. It contains no antimicrobial agents, not less than (NLT) 95.0 percent, and not more than (NMT) 105.0 percent of the labeled amount of NaCl. USP details each standard for NaCl Injection in the form of a monograph which can include process-oriented descriptions, sterility requirements, usage, and final product packaging. Not all standards for NaCl Injection are exactly specified in USP documentation. For example, three major water processing steps are required before NaCl Injection can be manufactured. These steps include generating or sourcing drinking water, purified water, and water for injection (WFI). The USP standard for purified water requires that source water meet Environmental Protection Agency (EPA) National Primary Drinking Water Regulations (NPDWR). To meet USP requirements for WFI distillation, reverse osmosis, or an equivalent or superior process is acceptable; however, there are no quantifiable values for assessment.

Eights tests were conducted on the IVGEN-generated IV fluid before and after flight. The IV solution was tested for Sterile NaCl for Injection concentration, endotoxin concentration, heavy metal concentration, identification of sodium and chloride, the concentration of iron, particulate matter analysis, sterility, and pH testing. IVGEN Mini plans to test for all these items and test for total organic carbon (TOC) concentration. Table I includes each test name, test procedure, specification, and USP general chapter (USP Ch).

TABLE I.—TEST NAME, TEST PROCEDURE, SPECIFICATION AND USP GENERAL CHAPTER FOR TOC TESTING

Test	Specification	USP Chapter
Sterile NaCl for Injection	Contains NLT 95.0% and NMT 105.0% of the labeled amount of NaCl (Ref: for 0.9% Saline: NLT 0.855% and NMT 0.945% NaCl by mass.)	USP NS Monograph
Endotoxin Concentration	NMT 0.5 USP EU/mL where the labeled amount of NaCl in the injection is between 0.5 and 0.9%, and NMT 3.6 USP EU/mL where the labeled amount of NaCl in the injection is between 3.0 and 24.3%	<85>
Heavy Metals by USP	NMT 0.001%	<231>
Identification Na by USP	Sample responds to tests for sodium	<191>
Identification Cl by USP	Sample responds to tests for chloride	<191>
Fe by USP	NMT 2 ppm	<241>
Particulate Analysis by USP	≤25 particles per mL larger than 10 μm ≤3 particles per mL larger than 25 μm	<788>
Sterility by USP	No growth	<1>,<71>
pH Testing by USP	4.5 to 7.0	<791>
TOC	**The solution should be prepared to an accuracy of ± 0.005 mg/L of C	<643>

4.1 Water Purification Processes

The USP specifies distillation and Reverse Osmosis (RO) are the “acceptable” methods to produce Sterile Water for Injection (SWI); however, provisions are included that other processes may be utilized, provided that these processes deliver water of equivalent quality. Common water purification processes and their descriptions include:

Distillation.—The process of separating substances from water by a phase change using selective boiling and condensation collection.

Reverse Osmosis.—A filtration process that involves using a semipermeable membrane to remove ions, molecules, and larger particles from water. A solvent diffuses across the membrane from a region of low concentration to a region of higher concentration

Absorption.—Impurities are chemically absorbed onto a packing material.

Ultrafiltration.—Water is forced through a semipermeable membrane with very small pore diameters that physically block the passage of impurities.

Deionization.—Cation and anion resin beads exchange unwanted ions with pure hydrogen and hydroxide molecules to form pure water. The ion-exchange resin binds with unwanted mineral salts such as sodium, potassium, chloride, fluoride, etc.

5.0 Formulation Development of Parenteral Products

This section will provide an overview of the development of injectable or parenteral drug products with a focus in the development and delivery of intravenous fluids. Intravenous injection is a common route of drug administration. The injection occurs into a vein either by bolus (directly into a vein) or infusion (diluted in a bag of saline or dextrose and slowly administered over time).

5.1 Specifications

Injectable drug products must meet certain specifications to be released for sale to the public. Due to these products having a streamlined bypass to the body's natural defenses against microorganisms,

Injectable drug products have additional standards compared to oral drugs (tablets, capsules, etc.). The United States Pharmacopeia (USP) is the authoritative source for medicine and healthcare product standards and has standards to ensure the product's quality and safety. Mandatory USP defined characteristics of injectable drug products include sterility (free of bacteria, viruses, molds, yeast, etc.), particle-free (free of particles of a specific size), and endotoxin-free (highly toxic molecule derived from the cell wall of dead gram-negative bacteria). Additional specifications dependent on the product include appearance, pH, potency, purity, and tonicity.

5.2 Formulation Development

The injectable drug formulation development process can be broken down into six distinct phases represented in order as a flow chart in Figure 8.

The preformulation assessment is the information gathering and research process stage. This stage ensures that all the required information is in place to begin preformulation development studies. Required research topics and information for parenteral drug development include thermal stability, oxidization potential, light stability, bulk drug preparation, polymorph existence, and PKa or pl (acid dissociation constant for small molecules or the isoelectric point for proteins).

Preformulation development is the process to find the conditions in which the drug molecule is most stable. The goal after ideal stabilization is found is to achieve those conditions during the production process. The solubility and degradation profile of the molecule are two major topics studied during the Preformulation development stage. Solubility can be a challenge for drug development scientists in the case where bulk drug floats on the surface of the solution used to dissolve it. In this case, solubility studies must be conducted.

The next step in the preformulation assessment is determining the drug's degradation profile. The purpose of a degradation profile is to determine the intrinsic stability of a drug substance in the formulation. An important aspect of determining a degradation profile is the thermal stability of a bulk drug because the thermal stability is closely related to the shelf-life of pharmaceutical products. Thermal stability is achieved when no change occurs in a material's structure and properties when submitted to higher temperatures. Thermogravimetry, a method of thermal analysis in which the mass of a sample is measured over time as the temperature changes, is often used on drug products to collect thermal stability data (Ref. 8).

After completing the preformulation development studies, formulation development can begin. The goal of the formulation development stage is to establish the optimal conditions determined in the prior product development stages. Additional information, including the drug dosage, route of administration, and solution concentration, must be determined to start formulation development. If precisely controlling product stability or solubility is a concern, buffers, antioxidants, stabilizers, and bulking agents can be added to stabilize unstable products. A buffer system has the property to resist pH changes despite additions of acid or base. The system works neutralizing any added acid (H⁺ ions) or base (OH⁻ ions) to maintain a moderate pH by the addition and combination of a weak acid and its conjugate salt. Antioxidants are molecules capable of decreasing or preventing the oxidation of other molecules and are used if a drug is shown to be susceptible to damage from oxygen.

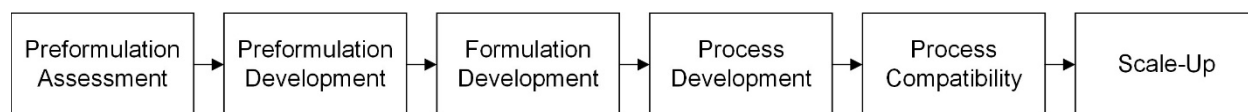


Figure 8.—Parenteral product development flow chart.

Once the final formulation has been developed, the manufacturing, packaging, and transportation of the drug product are developed to ensure the product can be made without flaws and meet the same time release specifications established during the development studies (Ref. 9).

6.0 IVGEN Design Risks

Forty-nine risks were identified throughout the duration of the design process for IVGEN. Eleven of the 49 risks were labeled “Accepted” instead of “Mitigated” before launch implying a that the risk could still present during flight despite mitigation tactics taken. A summary of risks identified by IVGEN project scientists is examined in this section. The detailed risks were selectively chosen from the list of 49 risks applicable to IVGEN Mini.

6.1 Conductivity Sensor Reading With Air Bubble

At the low flow rates that IVGEN uses, bubbles can get trapped by sensors extending into the flow stream. In the case that air becomes entrapped in the fluid line, an air bubble may remain suspended by the conductivity sensor and provide a false reading and loss of scientific data. As a mitigation tactic, IVGEN scientists designed the conductivity sensor assemblies to minimize trapped volumes of air and a unique housing to minimize bubble collection at electrodes.

6.2 Water Channeling

Channeling is a wetting problem, particularly for the low flow rate at which the IVGEN operates. If the cross-sectional area of the flow path is too large, the water will not distribute well in the purification medium; rather, it will channel through a path of least resistance. Under the possibility that channeling occurs through the filtration system, sufficient contact with the resin in the filter will not occur, and the water will not be fully deionized, causing a breakthrough of contaminants to the product stream. IVGEN scientists conducted tests to find the optimal flow rate through the resin bed to prevent channeling. The optimal flow rates were identified as 25 and 17 mL/min from testing. The DI cartridge IVGEN used was specifically manufactured for IVGEN. It was machined from medical-grade polycarbonate into a hollow cylinder with an outer diameter of 21.3 mm and an inner diameter of 15.9 mm with a length of approximately 170 mm. The cartridge was loaded with DI resin MBD-10- ULTRA from ResinTech.

6.3 Return to Earth and IV Bag Leakage in Storage

Due to the prolonged time that elapses between IV fluid generation on-orbit and retrieval on the ground of the IV fluid samples, the IV fluid’s properties may degrade and fail USP testing despite meeting USP standards on orbit. IVGEN MINI scientists mitigated this risk using three methods which were the use of refrigeration, early sample retrieval, and the use of conductivity sensors. Another risk that could arise due to the storage time before return to the ground is that the IV fluid samples could be stowed with a small leak that would allow a release of the required IV fluid before recovery by the ground team. Redundant IV fluid samples were generated, and the bags were double bagged to ensure scientific data were not lost.

6.4 Radiation Event and Single Event Upset

The following discusses the combined risks of a radiation event and a single event upset. Given a Single Event Upset, there is a possibility that the system will fail. Another risk identified and categorized as a single event upset is a radiation blast. If the IVGEN system were to experience a radiation blast, there

is a possibility that there would be a total system failure due to the degradation of components. A radiation blast would at least cause a single experiment failure, perhaps destroying the system. This risk was ultimately accepted due to the low probability of occurrence.

6.5 Materials Usage

Material selection considerations must be taken for space flight and medical usage. Materials must be compatible with medical water processes, and there is a possibility that not all of the materials are rated in terms of suitability for space flight. There may not be materials available for all system components on the commercial market that are compatible with the project's water purification aspect and the space flight suitability aspect. IVGEN MINI team members decided to mitigate this risk by selecting as many "A" rated materials as possible for the final system configuration.

7.0 IVGEN Mini Design Risks

Several risks have been identified by the IVGEN Mini team that have the potential to cause a total or partial system failure. Solutions and mitigation tactics must be developed before in-flight testing to ensure the project's success and increase the systems TRL. Risks will be candidates for closure once a mitigation strategy is identified for that risk and captured in the design and CONOPS. The current method for defining the severity of a risk is a five-by-five square grid with the likelihood of risk occurrence on the y-axis and severity of risk consequence on the x-axis, with one representing the lowest chance occurrence and lowest risk severity.

7.1 Pump Head Tubing

Failure of the system's pump head tubing due to a rip or tear is an identified project risk. The severity of the risk is defined as a level three likelihood and a level four severity of consequence and is visually represented in Figure 9. Concern for this risk developed from a prior Plant Water Management project (PWM), experiment VEG-01 of the vegetable production system (VEGGIE) project. VEGGIE is a small plant growth chamber with a passive wicking design consisting of a reservoir that wicks to substrate-filled pouches or plant pillows. At the initiation of test VEG-01, one of the flight pillows could not be hydrated due to a blocked or damaged pillow quick disconnect or internal tube (Ref. 10). Given the tubing ripped on the VEGGIE system of a similar design, the pump tubing of the IVGEN Mini system could break, causing complete failure in pump operation. Undamaged spare tubing was swapped with the old, damaged tubing to continue VEGGIE experiments and served as the primary mitigation strategy for tubing failure. Likewise, the current mitigation strategy for the IVGEN Mini project is to supply extra tubing for replacement and a written repair guide in the case of tubing failure.

7.2 Meeting USP Standards With ISS Generated Fluid

Given that USP standards certify the process of generating IV fluid rather than the IV fluid solution, there may be issues with fluid generated on ISS meeting USP standards, thus generating the need to assess not meeting USP standards with ISS generated fluid as a risk (Figure 10). IVGEN Mini's predecessor's, IVGEN, on-orbit results indicated that all the experimental success criteria were met except for the salt concentration of the IV fluid, further supporting the need for risk assessment. A fluid validation test plan is being developed to alleviate this risk's concerns, to test the generated IV fluid on the ground, and validate the system's ability to produce USP grade IV fluid. The risk will be a candidate for closure once the PDR review and validation plan review have been finished.

7.3 Bubble Occlusion

Under terrestrial conditions, liquids normally position under gases due to the buoyancy effects of Earth’s gravity. As a result, gas occlusions or bubbles entrained in a liquid will migrate towards the top of the container and escape the fluid. Buoyancy forces are not present in a microgravity environment; thus, the bubbles remain encased in the bulk fluid. Bubble occlusion, which can lead to air embolism in patients, is a common health hazard in terrestrial IV fluid usage. Bubble occlusions occurring on the ISS may prevent meeting the requirement of generating IV fluid usable for intravenous injection and thus poses as a risk (Figure 11). The current IVGEN Mini design has a filter to trap and remove bubbles, but it does not prevent the existence of bubbles. The identified maximum allowable air content is 50 mL per 1 L of fluid. One way to minimize the dissolved air in water is the more dissolved air, the higher the likelihood for bubbles to come out of the solution upon a slight change in pressure. IVGEN Mini project scientists are researching how this constraint will impact the design.

7.4 Unknown pH of Source Water

The pH of the ISS potable water supply can vary below the acceptable limit. Potable water dispensed on the ISS has a pH of 5.5 to 5.6. The EPA recommends but does not require that the municipal water supply be kept between a pH of 6.5 to 8.5. According to USP general chapter <791>, the pH of NaCl injection must fall between 4.5 to 7.0. However, the USP standard for purified water requires that source or potable water meet EPA standards (Figure 12).

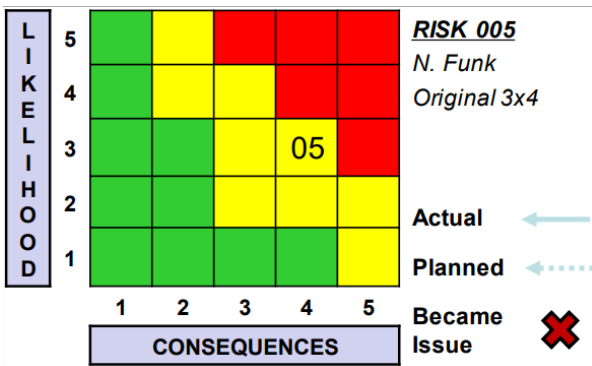


Figure 9.—Pump head tubing risk 005.

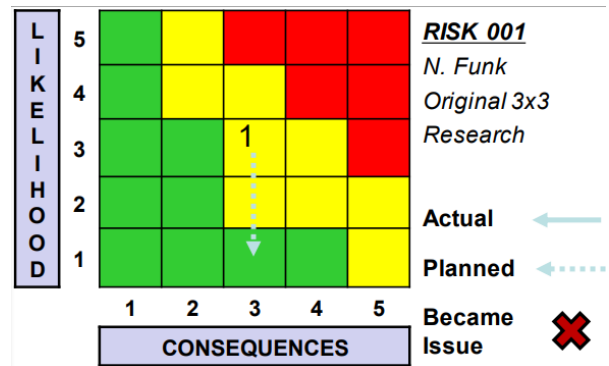


Figure 10.—Meeting USP Standards risk 001.

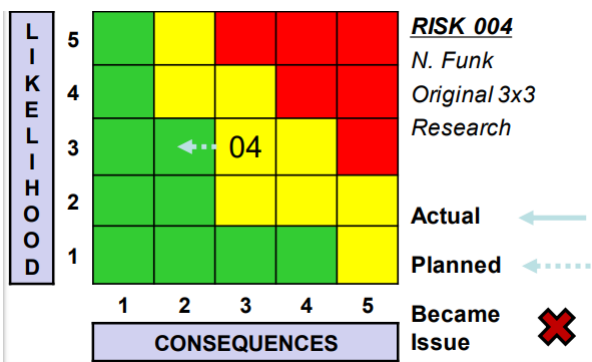


Figure 11.—Bubble Occlusion risk 004.

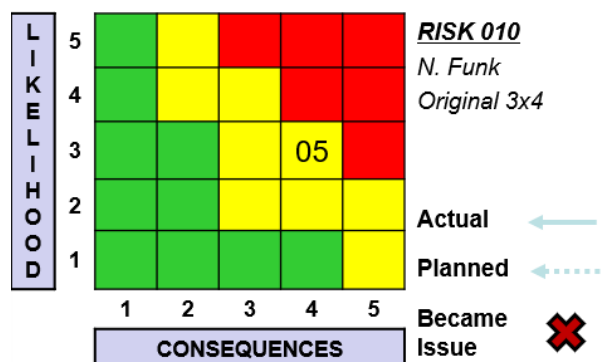


Figure 12.—Unknown pH of Source Water risk 010.

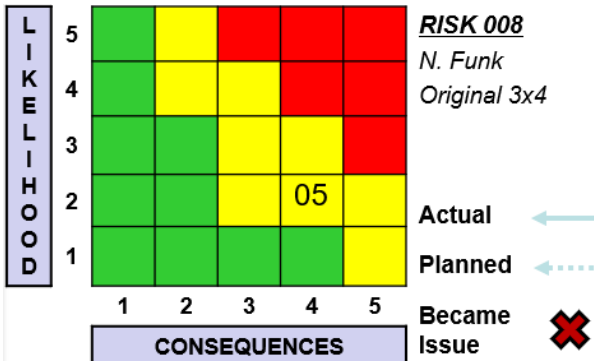


Figure 13.—Water damage to microcontroller risk 008.

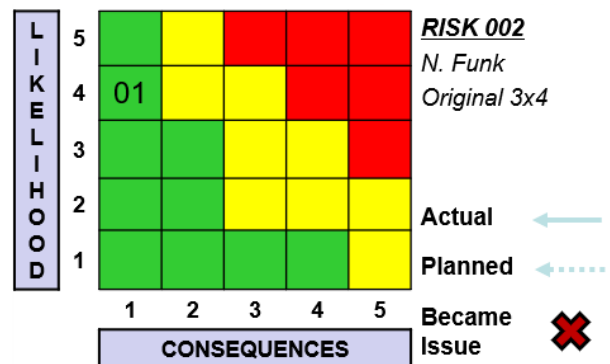


Figure 14.—IV Fluid Shelf Life risk 002.

7.5 Water Damage to Microcontroller

IVGEN Mini is a fluid handling system with electrical components. In the case of a water leak, the electronic components could be damaged, resulting in a loss of scientific data. This risk is interconnected with the pump head tubing failure because fluid would be released inside the IVGEN Mini main assembly if the peristaltic pump tubing ruptured (Figure 13). As a mitigation strategy, the circuit boards are to be conformal coated, adding protection against potential water damage. To minimize leaks in fluid systems, orbital welding can be considered to eliminate potential for leaks.

7.6 IV Fluid Shelf Life

IV fluid in a terrestrial setting has a standard shelf life of 18 months when stored at 20 to 25 °C (68 to 77 °F). The shelf life of IV fluid in non-Earth environments is unknown and may be different from its shelf life on Earth. Long-duration missions will require IV fluid to be on hand for the entire mission, which could be up to 1224 days. This issue was identified by IVGEN Mini project scientists as an issue for exploration missions and is outside of the scope of the IVGEN Mini project due to testing limited to the ISS (Figure 14).

8.0 Microgravity Fluid Bubble Behavior

A microgravity environment (MGE) is defined by the acceleration conditions pertaining to a vessel or platform (Orbital facility, sounding rocket, drop tower, etc.) in orbit. An MGE imparts to an object a net acceleration that is very small compared with that produced by Earth at its surface. Material Science and Life Science studies are largely motivated by the behavior of fluids in microgravity. Due to previous issues with bubble inclusions during IVGEN experimentation, this section will discuss the fluid mechanics of bubbles and drops to facilitate IVGEN Mini bubble inclusion analysis.

The bubble is a region of the liquid occupied by a gas or vapor at a pressure slightly higher or equal to the pressure of the surrounding liquid. Gravitational effects are always present on Earth’s surface and when the density of a dispersed phase differs from that the continuous phase in a solution, the dispersed phase will sink if it is denser than the continuous phase or float if it is less dense. Many fluid-based experiments and technologies depend on this gravity-induced motion to operate. However, in experiments carried on a spacecraft such as the ISS, the apparent weightlessness on bubble or drop inclusions are negligible. For this reason, there is motivation to study motion of suspended bubbles and droplet due to forces other than gravity (Ref. 11).

The most common mechanism for moving a suspended bubble independent of gravity is the application of a temperature gradient to the continuous phase. Temperature gradients move objects within a fluid because of the change in interfacial tension, the force of attraction between the molecules at the interface of two fluids, with temperature. Generally, for fluids, Interfacial tension tends to decrease nearly linearly with a decrease in temperature (Ref. 12). The Marangoni effect is a phenomenon where liquid flows away from regions of low surface tension due to a gradient in the interface tension. In the case of temperature dependence, the thermo-capillary convection arises from a temperature gradient at the interface. The bubble will move toward the warmer fluid due to a decrease in tension in the direction of the applied temperature gradient (Ref. 13).

9.0 Previous IV Fluid and Medical Grade Water Production Space Flight Experiments

9.1 The Fluid Therapy System

In an effort led by Johnson Space Center (JSC), NASA began to explore the possibility producing IV fluids on orbit as part of the Health Maintenance Facility of the Space Station Freedom Program. The Fluid Therapy System (FTS), tested on Spacelab-J in September 1992, was one of the first in-flight demonstrations of intravenous (IV) administration of fluids. The tests had examined the production of medicines and the administration of IV fluids in the absence of gravity. The FTS evaluation consisted of two functional objectives. The first was to make and store sterile water and IV solutions onboard the spacecraft. The second was to repeat the verification of the FTS infusion pump. The experiment also demonstrated the technique of starting an IV in microgravity.

The FTS device contains nine major assembly components: Source Water Container (SWC), Sterile Water for Injection Assembly (SWI), Intravenous Reconstituting Device (IRD), Large Volume Parenteral Bags (LVP), Intravenous Fluid Infusion Pump (IV Pump), Payload and General Support Computer (PGSC), Fluid Administration Set (FAS), Sample Containment Device (SCD), and Flight Infusion System Test (FIST) equipment.

The SWC was a steel tank containing pressurized tap water and was the main water source throughout the experiment. Water from the SWC passed through the SWI. The SWI is a filtration system consisting of a bed of activated carbon, followed by a bed of 50:50 activated carbon and deionizing resin, then several beds of 100 percent deionizing resin, an ultrafilter, and finally a sterilizing microfilter. After filtration, a conductivity sensor was used to confirm the sterility of the water. The sterilized water was stored in a PVC bag. The saline mixing mechanism in this system is the IRD. The IRD is a pouch containing liquid concentrates. Sterile fluid is mixed with the concentrate to produce single units of IV solution. Fittings allow the sterile water bag and concentrate bag to be removed and replenished with fresh supplies. A standard commercial IV pump with two pumping channels allowed for mixing two separate solutions at different rates. Fluid is delivered via PVC connective tubing to the SCD. The SCD contains ten bags that are used to hold the samples. The PGSC computer controls the IV pump operation.

In the final stages of the experiment, a manikin arm with venous channels was used to simulate a patient's arm. The IV pump inserted into the simulant arm was operated at several infusions rates and failure scenarios were identified. Samples from the experiment were taken and post flight operations were conducted to validate water sterility and saline concentrations met USP standards.

Testing and analysis on the ground revealed the generated IV solution met the USP tolerance criteria for solution concentration (± 5 percent of desired concentration). However, this discovery was not a verification of the success of the in-flight fluid mixing system rather a validation that the concentration of solute in the final solution was correct. Vibrations from landing and post-landing handling could have

easily amalgamated the solution before testing occurred, thus invalidating results obtained from FTS fluid mixing mechanism. The ground testing also showed that the solution exceeded the maximum Total Organic Carbon (TOC) limit. Lastly, it was noted by the STS-47 crew that serious bubble occlusions were present during in-flight fluid generation (Ref. 14).

The FTS system utilizes a similar fluid mixing approach as the current IVGEN Mini design, sterile water is mixed with a premade solution containing the constituents (liquid concentrates) to reconstitute single units of intravenous fluids. However, the IVGEN Mini design reduces space and weight by increasing the concentration of the concentrate to fit the solution in a syringe rather than a pouch. The main difference between the IVGEN Mini system and the FTS is the IVGEN Mini has two separate intakes for the concentrate and water, while the FTS utilizes an IV pump with two pumping channels. A custom designed PVC connector titled the Fluid Administration Set (FAS) is used by the crew to directly attach to the saline concentrate to the IV pump.

Due to the parenteral method of IV fluid administration, air bubble inclusions can cause air embolus to be injected into the patient's circulatory system, a potentially fatal condition. Bubbles can also cause system blockages. The STS-47 crew witnessed serious bubble problems in the FTS system that obstructed tubing leading to errors in the pump computer and total failure. Niederhaus et al. hypothesized the extreme bubble problems were caused by the pressurization of the source water container. Inside the source container contained a collapsible bladder used to force the liquid out. This process would facilitate gas diffusion and create bubbles (Ref. 15).

Applying this information to the IVGEN Mini system, the IVGEN Mini syringe mechanism may introduce bubbles to the system. A syringe is a simple reciprocating pump that operates through pressure. When the plunger is moved in the syringe to increase the volume, and the volume of liquid in the syringe is roughly constant, the volume of gas in the bubbles must increase thus creating bubbles. This phenomenon is explained by the ideal gas law.

9.2 A Sterile Water for Injection System (SWIS) for Use in the Production of Resuscitative Fluids Aboard the Space Station

In support of the Health Maintenance Facility (HMF) of the Space Station, the Sterile Water for Injection System (SWIS) was developed in 1988. The SWIS is a disposable cartridge designed to purify the Space Station potable water to USP XXI Water for Injection (WFI) quality. Subsequently, the product water would be mixed with salt concentrates to reconstitute intravenous solutions. The system's purification steps consisted of particulate prefiltration, carbon adsorption, mixed bed deionization, ultrafiltration, and sterilizing microfiltration. The device is passive, requiring only tap pressure as the driving force for filtration, and was designed to produce 6 L of WFI at a 6 L/hr flow rate. The work was limited to the production and bagging of sterile WFI.

Two major challenges were identified for SWIS. The first challenge was water purification for medical applications. The paper discusses each purification step and the rationale for material choice and construction. The first step in the purification process, prefiltration, glass wool, had been chosen as the prefiltration medium for SWIS. Glass wool was chosen due to its ability to retain particles larger than 8 μm and does not support bacterial growth such as cotton or polyester. Sterilization by gamma radiation had been selected as the preferred method to sterilize the SWIS device to prevent bacterial growth during storage. Glass wool can withstand the required dosage of sterilizing gamma radiation. Glass wool will also be used as a post-filter after the carbon and deionization beds to protect the ultrafilter from flux decay.

The primary purpose of carbon in the SWIS is to absorb and remove iodine, a potable water disinfectant used on the space station. The secondary need is to remove organic contaminants. Granular activated carbon has been chosen for SWIS based on its superior combined iodine and organic removal capabilities.

Deionization is the process of removing dissolved solids. Deionization was accomplished by mixed bed strong acid, strong base deionization resin. The choice of resin was not mentioned in the paper.

Ultrafiltration is a type of membrane filtration in which forces like pressure or concentration gradients lead to a separation through a semipermeable membrane. The purpose of ultrafiltration is to achieve high endotoxin rejection. A separate device for ultrafiltration was developed based on the Millipore UF membrane that had demonstrated a reduction in endotoxin concentration by 5 to 6 orders of magnitude. Utilizing a new technology, specifically developed at Millipore for SWIS, titled Millipak™, which had a high integrity bond of a small disk of the UF membrane to a “Millipak™” support disk. A Millipak™ is a self-contained, disposable microfiltration device in which the microporous membrane is bonded to support disks.

To assure the sterility of the WFI produced by SWIS, the Sterivex™ 0.22 urn sterilizing microfilter from Millipore was used. The microfilter was directly integrated into the IV bagging system, included in the tubing that feeds the bag. The filter acts as a last measure to ensure sterility and protect the IV bag from bacterial contamination during and after filling.

The second challenge was to ensure adequate performance in microgravity. Microgravity fluid flow was considered to assure proper performance while the device was being designed. Air trapped inside a fluid does not float in microgravity and will not necessarily migrate to the top of its container. For the DI cartridge to be fully wetted and function, the air must be fully displaced by water. Another wetting problem considered is channeling. If the cross-sectional area of the flow path is too large, the water will not distribute well in the purification medium; rather, it will channel through a path of least resistance.

A series of upward and downward flow experiments were performed to determine the optimal fluid flow path to prevent channeling. The downward flow tests were used to best simulate zero gravity. In comparison, upward flow experiments were performed to simulate an “ideal” flow where the air is displaced, and the effects of gravity cause the fluid to distribute radially throughout the resin. Both flow experiments were performed with tubular flow paths of differing cross-sectional areas until a maximum diameter was found, for which upward and downward flow breakthrough results were the same. Once the diameter was found, channeling could be considered negligible. Based on results from the tests, the selected diameter for the flow path for prefiltration, carbon, and deionization will be formed from 1-in. tubes. The tubing length was then decided based on the volume and time needed to ensure adequate residence times of the carbon and DI resin media.

Output water quality was checked by a conductivity sensor attached to the ultrafilter with go/no go indicator lights. These lights will let the operator know whether the water quality is adequate. The conductivity sensor had a cutoff of 5 $\mu\text{S}/\text{cm}$. The maximum allowable conductivity for WFI is approximately 20 $\mu\text{S}/\text{cm}$ at 25 °C, providing a safety factor of 4. Conductivity is directly proportional to the temperature of a given level of contaminants. The safety margin allowed for an operating temperature range of 15 to 32 °C. A step before the final step in the sterilization process, the water has reached the quality of WFI but is not yet sterile WFI. The 0.22- μm final filter is the device that assures product sterility.

Since SWIS is a passive system, a device was developed to prevent over fill of the IV bag. the SWIS Volumetric Assurance Containment Device is a hinged box with the shape of a filled 1-L IV bag molded inside. The operator places the empty bag inside the device, closes it and begins filling. Once the bag

reaches the limit of the device, it stops filling. Preliminary tests proved the Volumetric Assurance Containment Device yielded fill volumes consistently within 1 percent of 1 L.

Tests were conducted to verify the SWIS system's ability to generate USP grade WFI. For deionization and carbon performance, tests were run using a positive displacement peristaltic pump at a flow rate of 100 cc/min (6 L/hr). The input/challenge water contained approximately 1000 ppm TDS (NaCl), 10 ppm iodine, and 5 ppm total organic carbon (TOC). Ultrafiltration experiments were performed separately to determine endotoxin rejection. The results of deionization testing of the product water were presented in terms of conductivity. A temperature compensated conductivity meter was used for conductivity measurements. The results of conductivity testing indicate that the cartridge can maintain product water quality well below both the USP XXI conductivity limit of 20 $\mu\text{S}/\text{cm}$ at 25 °C and the SWIS specified cut-off of 5 $\mu\text{S}/\text{cm}$ at 25°C.

Product water carbon adsorption was tested using the Hach Company Assay Kit (DPD Method), which uses a spectrophotometric method. The results of these tests were presented in terms of ppm iodine. The results of carbon absorption testing indicated that the SWIS cartridge could reduce iodine concentration by three orders of magnitude.

The ultrafiltration device was challenged with high concentrations of bacterial endotoxin. USP XXI sets a standard of 0.25 EU/mL of WFI. During the test, the concentrated endotoxin challenge solution was agitated continuously on a shaker to ensure no accumulation of the endotoxin lipopolysaccharide. The units were pressurized with 15 psig feed pressure. Endotoxin concentration was measured using the Whittaker M.A. Bioproducts QCL-I000 Quantitative Chromogenic Limulus Amebocyte Lysate (LAL) assay. The results from endotoxin testing showed that the SWIS ultrafiltration device could reduce endotoxin concentration by approximately 5 orders of magnitude. Based on the results discussed, the production of Water for Injection that meets USP XXI quality standards from Space Station drinking water is feasible (Ref. 16).

Two primary microgravity fluid behavior challenges drove the SWIS system design. The first design challenge was the priming of the device. Since air does not float in microgravity, it will not necessarily migrate to the top of the device when filling. Water must be fully displaced within the SWIS device, or the carbon and DI media will fail to fully wet, potentially allowing contaminants to pass through. Testing the IVGEN Mini fluid flow path in a simulated microgravity setting to find the optimal yet practical configuration for the flow path to prevent underfilling would ensure efficient utilization of the DI cartridge. The second design challenge considered for the SWIS system is Channeling. Channeling occurs when the cross-sectional area of the flow path is too large. The water does not fully distribute in the purification medium; rather, it will “channel” through a path of least resistance (Ref. 16). This may also lead to contaminants passing through the DI cartridge.

10.0 Medical Grade Water Generation

10.1 Microwave Powered Gravitationally Independent Medical Grade Water Generation

Researchers James R. Akse, Delfino Zavala, Richard R. Wheeler, Jr., Roger W. Dahl and Thomas W. Williams from UMPQUA Research Company and DeVon W. Griffin from NASA Glenn Research Center developed a microwave-based Medical Grade Water (MGW) generator. The MGW generator efficiently couples microwaves to a single flowing stream, resulting in super-autoclave temperatures. This method is advantageous for space missions because it eliminates the need for filtration membranes or cartridges (reduces equivalent system mass) by inactivating endotoxins (gram-negative bacteria walls) and is gravitationally independent. The MGW generator also fulfills other medical mission requirements,

including preparation of water for injection, reconstitution of pharmaceutical agents, and biological experiments.

The main sterilization mechanism of the MGW generator is based upon the inactivation of microbes and spores with an exponential temperature increase. The lethality factor, F_0 , represents the statistical probability of microbial death. An F_0 value of 16 corresponds to sterilization achieved by autoclaving. (121 °C, 204.8 kPa, for 16 min). At temperatures of 100 °C water is in the liquid/vapor region its Temperature and Specific Volume diagram. To maintain water as a single phase, the system must be pressurized or consist of a single gas phase. For a single-phase operation of liquid water, the pressure must be maintained above the equilibrium vapor pressure for water at a given temperature. In the MGW's microwave-based sterilization system, water is volumetrically heated (coupling of microwaves with water) by microwaves in a full chamber, ensuring compatibility with microgravity conditions. Microwaves penetrate the water and are absorbed, distributing heat accordingly. Microbially lethality was achieved at a much shorter time interval than under standard autoclave conditions.

Two microwave sterilizer designs were used to heat a single-phase water stream to temperatures in excess of autoclave conditions. The first design was based on waveguide elements, and the second was based on a cylindrical chamber with an antenna-based microwave input.

Microwaves from a magnetron enter the waveguide of the wavelength sterilization chamber design (WSC) via a sealed quartz window. The microwaves are reflected from the opposite end by a solid metal closure. The WSC is sealed with gaskets on both sides of the quartz window. The gaskets are compressed between two metal plates and the plates are bolted together. Inlet and outlet water streams are made of two T connectors, which are screwed into the waveguide flange and backplate. Sterile water and a solution containing colony forming units of vegetative bacteria cells and pores was flushed through the WSC system separately to test the system's sterilization performance. Both the sterile water and bacterial samples were sterile after flushing. Effective sterilization of bacteria laden solutions was achieved.

The Antenna Sterilization Chamber (ASC) has several advantages over the WSC design. The direct injection of microwaves into a water stream via an antenna offers flexibility in chamber design, increase in volumetric density, and decrease of overall ASC size. The ASC consists of an insulated copper tube with compression fittings at the inlet and outlet connections. An antenna runs down the center of the tube. Microwave power is delivered via a coaxial cable that is screwed into a coaxial connector mounted midway on the tube. Microwave power from a magnetron is transmitted from the waveguide to the coaxial cable using a transition. The ASC system's sterility ability was tested. The results of the test suggested that the high temperatures achieved are sufficient to inactivate endotoxins, replacing the need expendable filtration membranes. It was also found that 80 percent of incident microwave energy is captured by water following through the ACS system providing a more effective means of microbial sterilization of a flowing water stream than the volumetric microwave absorption method most similar to a traditional autoclave. Both systems examined in this experiment produce super autoclave conditions above 150 °C. Under these conditions, microbe lethality was achieved at much shorter time intervals than standard autoclave conditions (Ref. 17).

This paper demonstrated the feasibility of a continuous, energy-efficient, gravitationally independent generation of Medical Grade Water using a Microwave Sterilization System (MSS) to achieve super autoclave temperatures. Efficient sterilization of water streams containing *B. Stearothermophilus* and endotoxin releasing gram-negative *E. coli* was achieved. A couple of beneficial aspects of the MSS technology over the original IVGEN sterilization mechanism are eliminating the need for presterilized system components and the MSS's capability to inactivate endotoxins via temperature and pressure conditions.

The original IVGEN tests results satisfied all IV fluid requirements except saline concentration meaning the removal of suspended solids, biocides from the source water, destruction of bacteria, and the elimination of endotoxins were adequate. The original IVGEN system used a DI resin cartridge for purification. Although the original IVGEN was successful at sterilizing the fluid, it is important to explore other sterilization options to further increase the IVGEN Mini TRL level. This method described in Section 10.1, *Microwave Powered Gravitationally Independent Medical Grade Water Generation* would increase the TRL by eliminating the need for filtration membranes or cartridges and reducing the overall mass of the system.

10.2 Device for On-Site Production of Sterile Water for Injection in a Disaster Zone

The project described in this paper sought to design and produce a device for the on-site manufacture of sterile water to be subsequently used to produce IV fluid for injection in “disaster zones”. The device would effectively decrease the cost of emergency relief, as there would be less IV fluid to transport to emergency location sites. The final design of the system includes carbon block filter, UV light treatment, pump, reverse osmosis treatment, and finally a storage solution.

The carbon block filter is the first stage of water sterilization. The filter dechlorinates the input water. The activated carbon in the filter participates in a chemical reaction and the free chlorine is converted to chloride. Dechlorination must occur before the water reaches the reverse osmosis membrane, a Thin Film Composite membrane (TFC), which can be damaged by the presence of chlorine. Carbon filters are also effective for total organic carbon (TOC) reduction which is one of the criteria for producing water for injection (WFI) according to USP standards.

The UV light treatment is the second stage of water sterilization. The UV-C range of UV light breaks molecular bonds of DNA, viruses, and bacteria, rendering them unable to reproduce and effectively killing them. Transparency of the water, turbulence, and a high flow rate can UV light transmittance and therefore the effectiveness of UV light as a sterilization mechanism.

As a third filtration measure, a reverse osmosis system was used. Reverse osmosis systems are used to reduce levels of total dissolved solids and suspended particles within water. These types of filters do not remove most organic compounds, bacterial microorganisms, chlorine by-products, or dissolved gasses. Reverse osmosis removes contaminants from feed water when pressure forces the water through a semipermeable membrane. A residential reverse osmosis system was placed after the pump to ensure maximum water pressure was supplied to the filter membrane to achieve maximum permeate flow. Despite this, the system did not maintain a high enough flowrate to (approx. 0.12 L/hr) to run the feed water through the system again to achieve double pass reverse osmosis as originally designed.

To test the efficacy of the water sterilization system, feed water was contaminated with pregrown *E. coli* bacteria. The output water was tested for bacteria count, conductivity, total organic carbon and endotoxins. The results of the tests did not conform to USP 24 standards for WFI. However, the sterilization system did drastically reduce bacteria colony count compared to the unfiltered feedwater in plate count agar tests. The conductivity of the product water was measured to be higher than the input water. Although high ion concentration can cause an increase in conductivity, the increase in conductivity is attributed to the carbon contamination from the reverse osmosis membrane. Carbon and salts trapped in a reverse osmosis membrane increases the conductivity of permeate produced (Ref. 18).

A senior design project from the mechanical engineering department of Trinity College in Hartford, Connecticut, is discussed in this paper. An insightful finding of this paper shows a conductivity increase in the generated water from the carbon block filter particulates trapped in the reverse osmosis filter membrane. To prevent this from happening, the system was flushed with water to remove loose carbon particles, a mitigation technique already presents in the IVGEN Mini project plan. However, it may be

valuable to conduct studies to determine how the IVGEN Mini's DI resin cartridge affects the conductivity of the final IV solution. For long-term use, other components that makeup IVGEN Mini should be examined for chemical interaction and leeching into the final IV solution.

10.3 Remote Site Production of Sterile Purified Water from Available Surface Water

MainStream™ a device developed by PRISMEDICAL Corporation, American Canyon, California, is a device that provides a means of producing Sterile Purified Water that is US Pharmacopeia (USP) standardized in remote locations from EPA grade drinking water. The main components of the device are a reservoir bag, a purification pack, and a collection bag. Before use, the device was sterilized with a validated dose of Gamma Irradiation. The device can produce 3 L of sterile water in 45 min using only gravity, but this time can be reduced to 15 min with the addition of an external pressurization source and a weights reservoir bag.

The literature described aims to test and evaluate the functional capabilities of the MainStream™ device. Testing of the device's capacity for remote site purification of drinking water to meet the water quality attributes of Sterile Water for Injection, USP11 (SWFI) and Sterile Purified Water, USP12 (SPW) occurred. Surface water quality data analysis was conducted using a database of water quality information consisting of >40 years of testing over a wide portion of the globe. Box plots were constructed from the data to determine the probability of encountering any given contaminant concentration in a given water source. A standardized procedure to make contaminated water was developed to provide a way to test the capabilities of the water purification device. This water, also known as challenge water (CW), was augmented with bacteria, endotoxin, and dissociable ions to mimic surface water.

Three liters of CW were added to the filled bag of the MainStream™ device. Product water (PW) was collected by gravity flow through the purification pack and into the collection bag. Chemical testing was performed on the PW to ensure USP standards for Sterile Purified Water (SPW) were met. The chemical testing procedures were derived from the USP Monograph for SPW. First, the PW PH was measured using a PH meter. The product water was augmented with 0.3 mL of saturated potassium chloride/100 mL of water to measure the PW conductivity. The concentrations of ammonia, calcium, carbon dioxide, chloride, sulfate, and oxidizable substances were tested.

Ammonia Concentration Testing: A 100 mL sample of PW was mixed with alkaline mercuric potassium iodide (Nessler's Reagent).

Calcium Concentration Testing: Two mL of 3.5 percent ammonium oxalate was added to a 100 mL of PW. The acceptance limit was no turbidity in the test sample.

Carbon Dioxide Concentration Testing: A 25 mL sample of PW was mixed with 25 mL of 0.3 percent calcium hydroxide solution.

Chloride Concentration Testing: Five drops of nitric acid in 1 mL of 0.1 N silver nitrate were added to a 20 mL sample of PW. Acceptance was based upon less turbidity in the test sample than a positive control containing 0.5 mg/L Cl.

Sulfate Concentration Testing: One mL of barium chloride test solution (12 g barium chloride/100 mL) was added to 100 mL of PW test sample. Acceptable PW test samples did not develop turbidity.

Oxidizable Concentration Testing: A 100 mL PW sample was mixed with 10 mL of 2 N sulfuric acids and heated to boiling, followed by the addition of 0.2 mL of 0.1 N potassium permanganate. In acceptable PW test samples, the pink color does not disappear.

The USP tests do not address water purification requirements. Therefore, additional tests were developed demonstrate PW retention of bacteria, endotoxin, and viruses. Testing also included removal of

dissociable ions. Based on testing, the MainStream™ PW met the requirements for Sterile Water for Injection, USP, Sterile Purified Water, USP (Ref. 19).

The MainStream™ device takes advantage of Earth's gravity to move water through the device without an external power source. However, IVGEN Mini relies on the Boxer 9QQ Miniature Peristaltic Pump, a miniature peristaltic pump with a stepper motor and encoder, to transport fluid. While outside the scope of the current IVGEN Mini project, future iterations of the device should consider methods to induce an artificial gravity aboard the ISS, such as a centripetal action, to further reduce the system's dependence on external resources like power and consumables.

10.4 Intravenous (IV) Fluidmaker: A Disposable Device for Preparation of Sterile Water for Injection in a Field Setting

The paper details the U.S. Army Institute of Surgical Research (USAISR) general performance requirements suitable for developing a disposable device to manufacture IV fluids from potable water for the resuscitation of burn patients. The device, named Fluidmaker, must produce sterile, pyrogen-free water, which can be introduced directly into sterile bags with sterile additives to make 1.0 L of Ringer's lactate and 1.0 L of 5 percent dextrose in water or other parenteral products suitable for IV infusion into humans. The source water is defined as long-term potable water, and its target is to generate sterile WFI as defined by the USP XXII.

Past studies, such as the Resuscitation Fluids Production System (REFLUPS), ruled out reverse osmosis due to the high production requirement and the uncertainty of an external power supply. On the other hand, earlier studies showed that pyrogen removal and sterility could be achieved using a solid matrix-activated carbon and zeta adsorbent filter (commonly used for household tap water purification). The Fluidmaker system layout consisted of a strong acid/strong base mixed resin ion exchange column, carbon filter, fine particle filter, and a 0.2- μ m sterilizing filter.

The following text details the Fluidmaker's materials and methods of operation. The systems Water Supply Pump consisted of a Masterflex Model 7018 peristaltic pump and Masterflex variable speed controller (Cole Parmer Instrument Co., Chicago, IL) to supply challenge water to the system. The pressure was monitored by using a 15 psi (100 kpa) pressure gauge. Tygon tubing was utilized for the pump tubing and all other connections throughout the system.

An Ion Exchange Column was used to reduce charged inorganic species in the feed water to acceptable levels; specifically, Barnstead/Thermolyne Corp (Dubuque, IA) IE columns (cat. no. D8902) were utilized. These were ultrapure strong acid/strong base mixed resin units. The next step in the purification process was a Water Purification Filter. The function of the water purification filter is to remove endotoxins and other organic materials. Seagull water purification filter cartridges, type RS1-SG (lot number 2765), were acquired from General Ecology, Lionville, Pennsylvania. Lastly, a Filterite (Timonium, MD) UIA4A spiral wound string filter cartridge was used to serve as the system's Fine Particle Filter. The function of the fine particle filter is to protect the sterilizing filter, part of the receiver set, from blockages by small particles shed by the Seagull filter. Since this is the last step in the sterilization process, the cartridge and connected tubing were autoclaved before use.

The following discusses the system testing procedures. Receiver sets, manufactured by Abbott Laboratories (North Chicago, IL), consisted of sterilizing filters, a bagging device, and a spring scale was used for all testings. The challenge water was prepared by amending 400 gal (1500 L) of Fort Detrick tap water with 824 mg/L of pulverized rock salt, bringing the TDS level to ca. 1000 mg/L and the conductivity to ca. 1200 μ mho. The water was dechlorinated by vigorous mixing for 2 days, then was allowed to stand for 2 weeks to build up the level of naturally occurring bacteria and endotoxins.

Each test was defined in terms of a run and a series. A system test with uninterrupted product flow is defined as a run, whereas a series is several runs using the same challenge water. The first test series consisted of two runs. For Series 1, Run 1, new filters and a new ion exchange column were installed. Tygon connections were cleaned with alcohol; the pump was activated and set at a 500 mL/min rate as the system filled the total system pressure registered 10 to 13 psi. After each bag was filled to 1 kg, the connecting fill hose was sealed with a pressure clamp to assure no cross-contamination among bags when the receiver set was removed from the bagging device. After the bags were filled, the first receiver set (Set 1) was replaced, and the second set (Set 2) of bags were filled and removed in the same manner. Sets 1 and 2 were tested for sterility and conductivity. The unit was allowed to continue running with samples being collected by a clean catch method (no bags) following the ion exchange column; a total of 50 L was collected from all sets.

The initial test system met all the requirements, having produced sterile, pyrogen-free water from potable water at a rate of 0.5 L/min at a feed pressure of one atmosphere or less from a potable water source levels of bacterial, pyrogen, and endotoxin that greatly exceeded normal drinking water levels.

The strengths and deficiencies of the Ion Exchange Column, Water Purification Filter, Fine Particle Filter, and Bagging device will be discussed in order. Levels of inorganic components of the feed water can be approximated in terms of conductivity. The efficacy of the Ion Exchange Column was determined based on the conductivity levels of the product water compared to the USP XXII standards for WFI. The USP XXII standards claim WFI should have conductivity greater than ca. 1 μ S (or resistivity no less than 1 M Ω). The Barnstead cartridge was determined suitable for the initial reduction of conductivity. The Water Purification Filter removes endotoxins and other organic materials. The Seagull IV RS1-SG filter reduced the endotoxins to below the Limulus Amebocyte Lysate (LAL) (a method for the detection of bacterial endotoxin) detection limit (0.06 EU/mL) and well below the USP XXII standard (0.25 EU/mL). However, it was observed that there is significant leaching of conductive materials from the RS1-SG filter. This problem was corrected by employing a second, much smaller ion exchange column in series with the filter. The function of the Fine Particle Filter was to protect the receiver set sterilizing filter from blockages caused by small particles shed by the Seagull filter. The fine particle filter protected the sterilizing filter but plugged after 43 L of product water. For later runs, a Filterite wound string cartridge was used. This new cartridge protected the sterilizing filter and showed no signs of a blockage for more than 100 L of product. Lastly, Fluid transfer into the Bagging Device was readily achieved, and no leakage occurred. However, due to errors in the sampling procedure, two bags showed bacterial contamination. A suitable method for sealing the IV bags was considered to prevent future contamination (Ref. 20).

While the Fluidmaker met all initial testing requirements and produced sterile, pyrogen-free water from potable water at a rate of 0.5 L/min, five objectives were left unresolved.

1. The ability of the water purification filter to depyrogenate at least 54 L of challenge water
A method to deionize the weakly conductive flow from the water purification filter
2. It is possible that Filterite fine particle filters may provide false positive LAL endotoxin test, testing must be done to be sure this will not happen
3. A suitable method for sealing the IV bags in the field should be devised
4. A method for introducing parenteral concentrates must be developed

Objectives 1 to 3 relate to water sterilization problems that could present and be considered as possible issues for IVGEN Mini. IVGEN Mini's second set of Pall filters is responsible for depyrogenation, or the removal of bacteria and endotoxin. This method of endotoxin removal was proven effective in IVGEN.

IVGEN Mini achieves water deionization through a DI resin cartridge, a packed bed column that contains spherical resin beads containing anion and cation absorbers to deionize the water, which is also successful for IVGEN. Lastly, the IVGEN system does not plan to use Filterite fine particle filters or a similar component, but each component within IVGEN should be tested for interference between all of the planned USP testing requirements.

11.0 Pharmaceutical Generation Devices

11.1 A Compact, Portable, Reconfigurable, and Automated System For On-Demand Pharmaceutical Solution Manufacturing

In collaboration with Massachusetts Institute of Technology, Andrea Adamo et al. (Ref. 21) developed a refrigerator sized device for continuous-flow synthesis and formulation of active pharmaceutical ingredients in a compact, reconfigurable manufacturing platform. Batch processing, a method whereby a group of identical products are produced simultaneously, is the primary approach for manufacturing pharmaceuticals on an industrial scale. Disadvantages of this approach include long production times and supply chain disruptions. This paper discusses an alternative approach to pharmaceutical manufacturing, an on-demand portable continuous-flow production system.

The system combines both synthesis and final drug product formulation into a single, highly compact unit (about the size of a refrigerator). Four consumable oral or topical liquid pharmaceuticals, (1), lidocaine hydrochloride (2), diazepam (3), and fluoxetine hydrochloride (4), were produced in the study to demonstrate the chemical synthesis capabilities of the system.

The system features upstream and downstream units, both are reconfigurable. The upstream unit houses the equipment necessary for producing active pharmaceutical ingredients (API'S) including, feeds, pumps, reactors, separators, and pressure regulators and has a maximum power requirement of 1.5 kg. The downstream unit is responsible for the purification and formulation of the drug product. This unit features tanks to precipitate the crude API from reaction mixtures, crystallizers, and filters. Temperature, pressure, flow, and level sensors are included monitor and support real-time production control. LabVIEW programs were also implemented to output pressure, reactor temperature, and flow rates. The same LabVIEW platform was also used to automate different units, including heating reactors, pumps, gravity-based separators, and multichannel valves. While the downstream unit consisted of precipitation, filtration, redissolution, crystallization, filtration, and formulation units. The study focused on producing concentrated aqueous or alcohol-based formulations, nonsolid formulations or tablets.

To begin the process, a reaction of excess neat 2-dimethylaminoethanol and neat chlorodiphenylmethane at a temperature of 180 °C and a pressure of 1.7 MPa generated by a back pressure regulator. (The product of reaction has a melting point of 162 °C) The molten salt product was then treated with a stream of preheated (140 °C) aqueous NaOH, an inline purification and extraction process. As a final step, an activated charcoal filter was used to remove color impurities introduced from the diphenhydramine. Diphenhydramine API solution was produced with an 82 percent yield and met USP standards (Ref. 22).

The on-demand pharmaceutical manufacturing device and IVGEN Mini have the similar objective to develop a continuous fluid-based drug manufacturing platform that combines both synthesis and final drug product formulation into a single, highly compact unit. The on-demand pharmaceutical manufacturing device achieves real-time process monitoring using LabVIEW (National Instruments) programs and high- and fast-performance modular X Series data acquisition (DAQ) device and sensors to monitor pressure, reactor temperature, flow rates and automate different units, including heating reactors, pumps, gravity-based separators, and multichannel valves. While the prior IVGEN and current IVGEN

Mini technology demonstrations lack a complex drug formulation monitoring system, it may be advantageous to explore and implement a similar system to the current IVGEN mini design. Quantitative monitoring values are transmitted to a wire-connected laptop to the on-demand pharmaceutical manufacturing device. The IVGEN Mini monitoring system could be designed to connect to any computer aboard the ISS for real-time process monitoring, ensuring the IV fluid produced meets USP standards without the need for post-process laboratory testing on the ground.

12.0 Fluid Mixing Techniques

12.1 Versatile Fluid-Mixing Device for Cell and Tissue Microgravity Research Applications

The hardware described in this report, Biomodule, is a computer-controlled fluid mixing device that can accommodate the diverse requirements of microgravity and life-science research. In 1994, when the article was written, NASA's austere research budget prevented the expansion of a microgravity research program despite considerable interest from the scientific community. Biomodule was developed to resolve this issue by providing environmental control and versatility to accommodate several investigators, thereby providing greater yield at a lower cost. The first Biomodule prototype was initially flight-tested in 1989 on Consort 2. It flew on five sounding rockets and one mission aboard the Space Shuttle.

The Biomodule can hold 40 to 60 samples per mission, and its payload is autonomous in its operation. The test samples are arranged within a T-tube configuration. Biological samples are added to the sample chamber located in the T-tube, while the sample solutions are added to the two lateral compartments. A yoke bar opens and closes the lateral compartments controlled by a computer-activated solenoid. In addition to the latching function, the computer also collects temperature data. The unlatching of the yoke bar initiates the transfer of pressurized fluids contained within the side chamber to the sample chamber. Eight sterile disposable T-tubes are inserted into each Biomodule, and adjustments are made to the yoke bar latching mechanism. Prior to launch, 0.15 mL of an appropriate test solution is added to all eight chambers, and biological samples are added to the sample chambers. A pressure plate assembly mechanism applies a constant mechanical force to the fluids and wall of the chamber. When the yoke bar latch system is released, the force from the pressure plate forces fluids from the side chamber of the T tube to the sample compartment. Since the fluid entering the sample chamber is forced to move at a 90° angle, sufficient turbulence is generated to obtain nearly instantaneous fluid mixing (Ref. 23).

The objective of the Biomodule is to be able to automatically transfer a test solution from a storage container to a sample. While this technology demonstration is not related to a medical system, it discusses a fluid mixing method in a microgravity environment, a necessary function of the IVGEN Mini system. The biomodule's main mixing mechanism is the 90° bend that the solution and biological samples pass over when the latch mechanism is open, creating turbulence in the solution. Turbulence causes the solution and biological sample to mix rapidly. The elbow creates secondary flow and increases the turbulence intensity, altering the fluid's mixing quality (Ref. 24). Utilizing the geometry of a simple 90° bend may benefit the mixing quality of the sterile ISS potable water and NaCl solution in the IVGEN Mini System. A few benefits of this type of fluid mixing include simple geometric design, does not introduce contaminants like a cartridge filter, and can be built into the system to prevent contamination.

12.2 Intravenous Fluid Mixing in Normal Gravity, Partial Gravity, and Microgravity: Down-Selection of Mixing Methods

A fluid mixing study was conducted by NASA GRC scientists Charles E. Niederhaus and Fletcher J. Miller to develop a method of mixing powders and concentrates with sterile water to produce medications for potential ISS and exploration mission use. The mixing techniques described in this report include, a recirculation loop, inline mixer, magnetic stir bar, shaft with impeller, vibrating rod, shape change, vibrating surface, and acoustic streaming. The mixing techniques were evaluated on their potential effectiveness for exploration missions. The selection criteria used to evaluate the technique include, efficiency, sterility, flexibility, equivalent system mass, microgravity confidence, operations, and development ease. Based on the selection criteria, two fluid mixing methods were selected for further consideration: magnetic stir bar and vibrating surface.

12.2.1 Magnetic Stir Bar Mixing in Bag

A magnetic stirrer bar is placed into the bag, and an external rotating magnet or rotating magnetic field moves the bar to produce mixing (Figure 15). This method produces large internal velocities capable of dissolving most solutes. During fluid production, the stir bar can be sterilized and prepackaged inside the IV bag eliminating external sources of contamination. A couple of disadvantages of this method include the effect of trapped gas in dead zones of the bag where the stir cannot reach and the locomotion of the stir bar breaking free from the magnetic field at high velocities.

The experimental results of this mixing method are as follows. In a laboratory environment, standard size 1- by 3/8-in. stirrer bars spinning at 1000 rpm could mix a 1-L 0.9 percent saline solution from a liquid NaCl concentrate in under 45 sec. A Schlieren system and a Planar Laser-Induced Fluorescence system were used to qualitatively determine when solutions were fully mixed. A drop tower experiment was conducted to study bubble formation in microgravity. The first experiments were inconclusive due to the short microgravity period, but no major deficiencies were found.

12.2.2 Vibrating Wall Induced Mixing in Bag

Vibrating surfaces at low frequencies (~1 kHz) produce steady streams of fluid perpendicular to the surface due to viscous forces at the boundaries (Figure 16). Vortices from this fluid flow produce internal motion to mix the solution. This method produces moderate velocities for mixing the solution. The vibration system does not come in contact with the fluid and thus there are no sterility issues. Dead zones in the corners of the bag will form that will have to be minimized or eliminated.

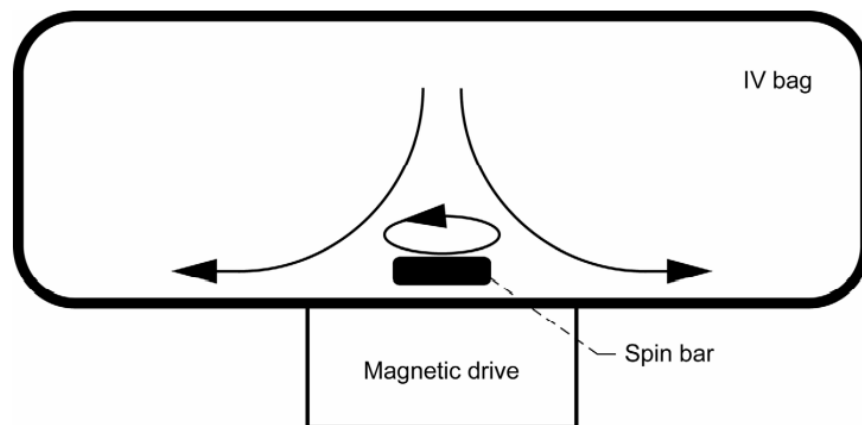


Figure 15.—Magnetic stirrer bar mixing.

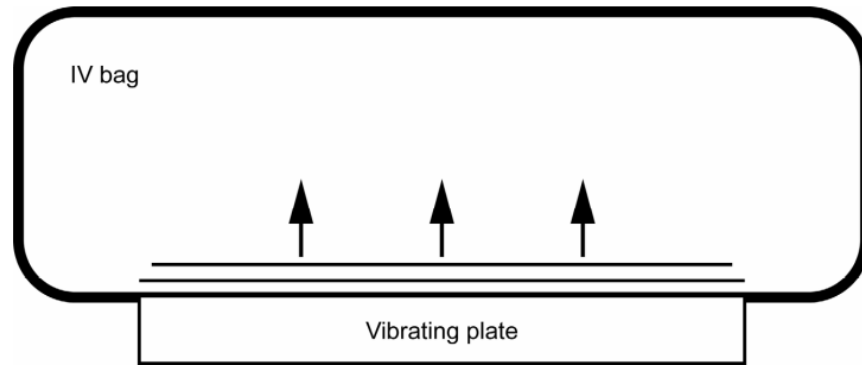


Figure 16.—Vibrating wall mixing.

The vibrating surface experiments were conducted using an ultrasonic bath apparatus, as well as a shaker table. The results of the experiment indicated efficient mixing. However, the waves and resulting mixing are gravity-capillary waves as the result of the Faraday instability. These types of waves cannot form without a gravity field, and thus this mixing method would not function in microgravity (Ref. 25).

The magnetic stirrer bar experiments produced significantly greater mixing than any of other suggested mixing techniques. The total mass of the stirring plate and stirrer bars was ~1.2 kg for 100 L of solution (1 kg stirrer plate plus ~2g/bar) was also less than the vibrating plate apparatus of ~15 kg. For these reasons, the magnetic stir bar was chosen as the preferred mixing method for microgravity mixing of IV fluids.

In the final design of IVGEN, a mixing assembly was manufactured to support the IV bag and house a mixer motor and its controller. The mixer used two samarium cobalt rare earth magnets on a rotor driven by a direct current (DC) motor. The motor had a maximum speed of 900 rpm. Inside the mixing bag, Teflon (DuPont) resin coated, and octagonal shaped stir bar was used. The bar measured 28.6 by 7.9 mm.

The new IVGEN mini skips the need for mixing by using premixed concentrated saline solution in syringes that is inserted into a fluid receiving port on the side of the system. Saline solution from the port is mixed with ISS potable water from a separate port. The ISS potable water and saline solution mixed by the system so that a 0.9 percent normal saline concentration is achieved. This document is an assemblage of IVGEN and IVGEN Mini information, past IV fluid and Water for Injection generation in extreme environment experiments, microgravity fluid mixing, and general on-demand parenteral fluid production, and was undertaken to support IVGEN Mini project scientists to further develop and increase the TRL of the IVGEN Mini.

13.0 Conclusion

IVGEN Mini is a Water sterilization and pharmaceutical salt mixing system that produces United States Pharmacopeia (USP) grade IV fluid from the ISS potable water supply. IVGEN Mini is a technology demonstration, and it builds on the success of the first IVGEN experiment performed over 10 years ago. The purpose of this Technology Demonstration is to raise the filtration and mixing mechanisms' technology readiness level (TRL) to a level sufficiently tested and verified that it could be utilized effectively by a crew of astronauts to produce IV fluids when needed with a minimum of either physical resources or technical support. Other goals include miniaturizing the system, developing long-term storage, and, most importantly, producing sterile and safe to use IV fluid for injection.

This document is an assemblage of IVGEN and IVGEN Mini documentation, past IV fluid and Water for Injection generation in extreme environment experiments, microgravity fluid mixing, general on-

demand parenteral fluid production, and was undertaken to support IVGEN Mini project scientists to further develop and increase the TRL of IVGEN Mini. The main risks and possible deficiencies for the IVGEN Mini system include failure of the pump head tubing, bubble occlusions, and meeting USP standards for 0.9 percent NS solution. To meet the current project resolution date and to ensure the success of IVGEN Mini, project scientists will need to review and access the IVGEN Mini system based on the success and failure of prior experiments and the other documentation provided.

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