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Microbiological Validation of the IVGEN System: Final Report

David A. Porter
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Purpose of the IVGEN System

The IVGEN system is intended to produce a solution of sodium chloride in water that would comply with the USP 32 monograph "Sodium Chloride Injection," using NASA Potable Water (WPA) as the starting material. The system is intended for eventual deployment on extended missions. As is expected for systems intended for off-terrestrial usage, the system must have the minimum mass suited for the purpose. Moreover, it must be capable of usage on an emergency basis having sat idle for potentially extended periods of time. The system must be operational under varying degrees of gravity ranging from zero gravity up to gravity.

USP Monograph Requirements

The monograph for "Sterile Water for Injection," in USP 32 presents the minimum requirements to be met by a saline solution intended for injection. These requirements include:

- It contains not less than 95.0% and not more than 105% of the labeled amount of NaCl
- Packaging and storage should be done in glass or plastic containers
- Labeling should indicate the mOsmol/mL
- It responds to identification for sodium and chloride (Chapter 191, Identification Tests, General)
- It contains no more than 0.5 endotoxin units/mL (assumes (NaCl) between 0.5 and 0.9%)
- pH between 4.5 and 7.0
- Meets the requirements for particulate matter
- Meets the limit of 2 ppm for iron (Chapter 241, Iron)
- Meets the limit of 0.001% based upon the amount of sodium for heavy metals (Chapter 231, Heavy Metals)
- It meets the other requirements stated in Chapter 1, Injections. Principal among these is the reference to Chapter 71 Sterility Tests.

Proof that the product of the IVGEN system is sterile is problematic. While many USP monographs refer to meeting the requirement of the sterility test as described in Chapter 71, Sterility Tests, it is important to note that the sterility test does not in fact establish that the entire lot produced by a given process is indeed sterile. The following quote taken from USP 32, Chapter 71, Sterility Tests, serves to amplify this point:

> *"These pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures."*

There are a number of reasons for why the pharmacopeial sterility test is not sufficient for proving sterility of a batch of product. The test requires growth of microorganisms in order to detect them. This means that the microorganisms present must be able to grow in the allotted time using the required media. It is possible to have microorganisms that are viable but will not grow (as in reproduce) in the culture media. However, should such microorganisms be introduced into the human body, the change in milieu may well permit replication. Also, the compendial sterility test evaluates only a portion of the product

(important assuming one wants to have product left for usage in its intended purpose). Remembering that unlike chemical solutions, microorganisms are not homogeneously distributed, it is all too possible to have a false negative result simply because the samples chosen did not have any microorganisms present. Passage of the sterility test is thus a necessary but not sufficient condition.

Therefore, the principal purpose of this report is to describe a validation process that can be performed in part on the ground prior to launch, and in space. The general approach taken is derived from standard pharmaceutical industry validation schemes modified to fit the special requirements of in-space usage.

Overview of IVGEN System

Figure 1 shows the IVGEN system prior to the author's visit.

Figure 2 shows the configuration of the IVGEN system used for development of the process validation plan. The colored regions, containing labels "section 1" through section 5", are referenced from within the following tables. Clicking on a hyperlink from within a table (an indicated part) will bring up a larger view of the relevant section. Clicking anywhere in that larger view will return the reader to the first tabular instance of the indicated part. Note that as part of the figure descriptions following each figure, a set of "link returns" is provided. Given limitations in the hyperlink formats used in this type of electronic document, a single link does not suffice to return the reader to any given table. Therefore, to return to tables other than that for which the initial instance of a part is given, click on the appropriate return link to go back to the originating table.

Figure 3 to Figure 7 show the individual shaded section from Figure 2 that are linked to the following tables.

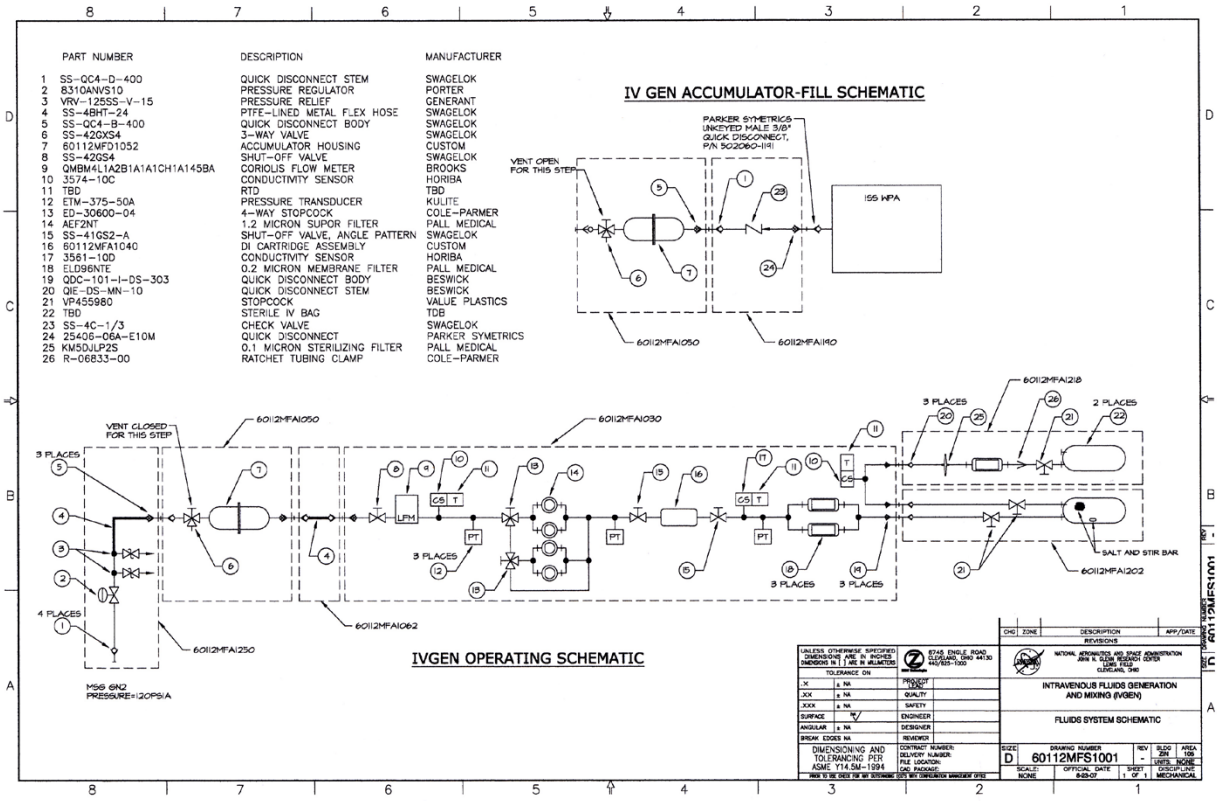


Figure 1.—IVGEN system as first evaluated in June of 2009.

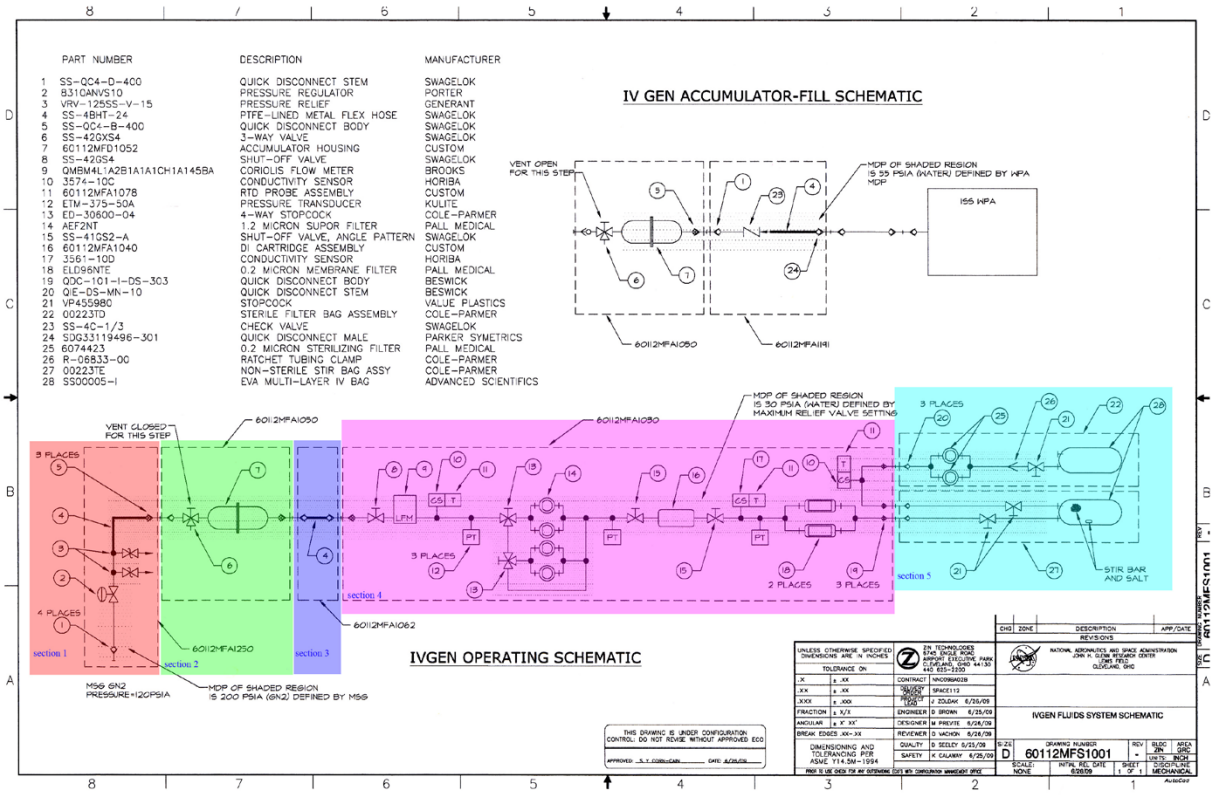


Figure 2.—Configuration of the IVGEN system used in the development of the process validation plan.

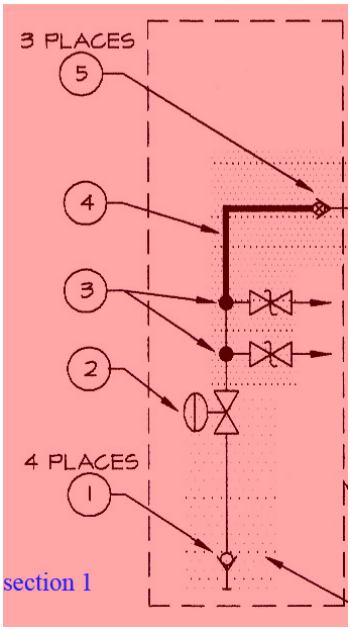


Figure 3.—Section 1 from Figure 2. (Link returns: Integrity, pressure relief valve, PTFE-lined metal flex hose, accumulator, leakage tests, operational qualification)

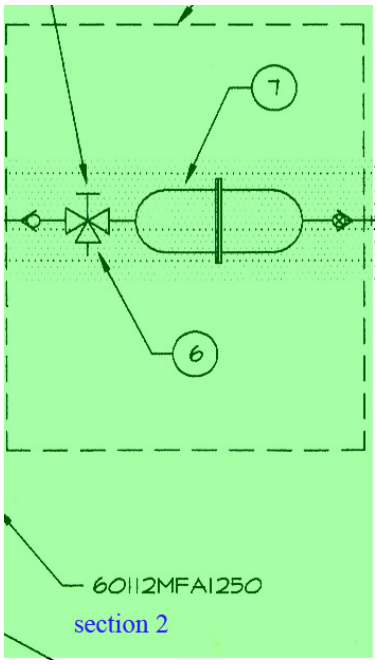


Figure 4.—Section 2 from Figure 2. (Link returns: Integrity, leakage test, operational qualification)

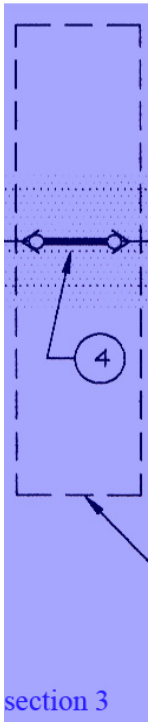


Figure 5.—Section 3 from Figure 2. (Link returns: Integrity, leakage tests)

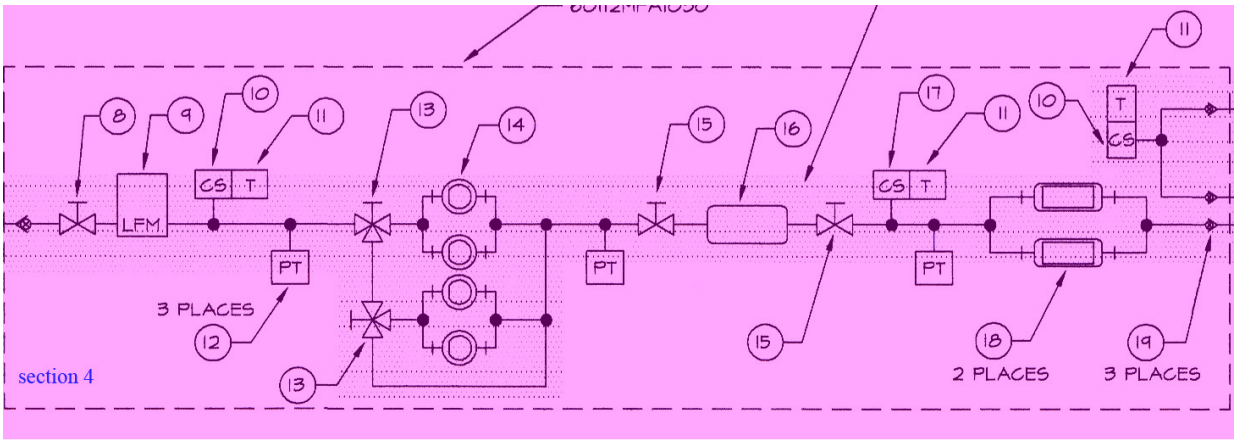


Figure 6.—Section 4 from Figure 2. (Link returns: Expiry, integrity, shut-off valve, Coriolis flow meter, four-way stop cock, shut-off valve-angle pattern, DI cartridge, 0.2 µm membrane filter, leakage tests, operational qualification)

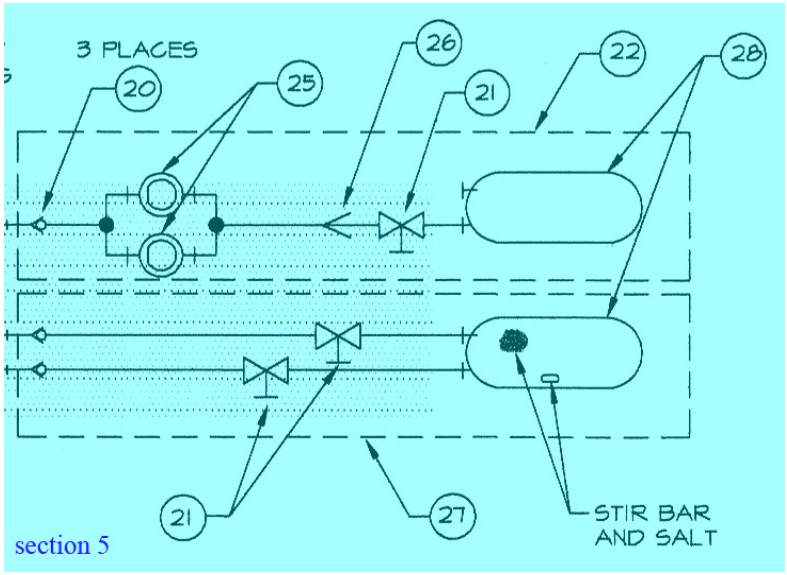


Figure 7.—Section 5 from Figure 2. (Link returns: Expiry, integrity, stop cock and connection, EVA multilayer IV bag, 0.2 µm sterilizing filter, ratchet tubing clamp, leakage tests, operational qualification)

Following is the validation plan for the IVGEN system. It is largely the same as was provided previously (in July 2009) in a document entitled "Validation Plan for IVGEN." There have been some modifications of the plan, however, in terms of further elaboration, addition of hyperlinks, and clarifications.

Validation Protocol for IVGEN

Preparation

This draft protocol was prepared by Vectech Pharmaceutical Consultants Inc. for the validation of the IVGEN system under development by the NASA Glenn Research Center.

Background

The purpose of this system is to allow for the creation of injectable saline (0.9%) that would meet the requirements for the USP 32 monograph "Sodium Chloride Injection," in most respects. The feed water will be water equivalent to NASA Potable Water (WPA) when the system is operated in the International

Space Station or in other nonterrestrial locations. The product must be equivalent to medical grade injectable saline because of its potential usage with injured or otherwise unwell personnel in space.

Validation

The protocol for validation was developed using in part validation approaches used for terrestrial pharmaceutical production. Traditional pharmaceutical process validation has as its goal proving that a process can be depended upon to consistently produce product of the required quality. There are three phases commonly executed in the validation process:

- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ)

The protocol developed for IVGEN contains portions analogous to the ones described above for standard pharmaceutical production. There are some notable differences between the usual terrestrial pharmaceutical production processes and those to be employed by the IVGEN system in space.

For a standard terrestrial pharmaceutical system, the installation is not expected to be moved about, certainly not to be sent into space. Therefore, the installation should be qualified while it is on the ground, and also after it is in space to ensure all of its components are still as they should be following the rigors of the launching into space. Therefore, there are aspects to the IQ that should be performed solely by ground personnel (e.g., certifying expiry date acceptability), and aspects to be performed both by ground personnel in the initial system qualification and by space personnel to ensure system integrity.

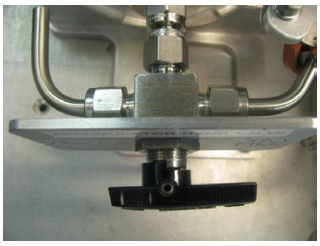
Operational qualification serves to prove that all of the system components are operating as per expectations. For the same reasons as provided for IQ, there are portions that should be done solely by ground personnel and by both ground and space personnel. It is possible that the leakage section of the IQ section could fit under the OQ section. My belief is that it would be more appropriate to keep the leakage testing as part of the IQ. The approach used in the leakage test is to open up the entire system to water flow sequentially. This should ensure a minimal amount of water leakage should there be a loss of integrity somewhere in the IVGEN system. This can also be done as part of the validation of the sterilizing filters prior to use.

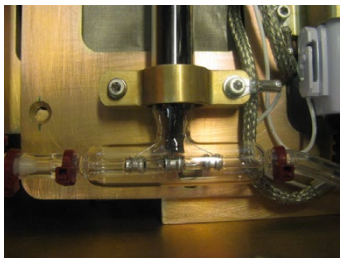
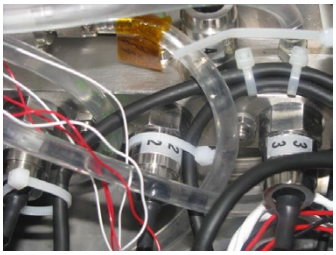
Performance qualification is done to prove that the system shown to be acceptable by IQ and OQ can reliably produce the intended product ("Sodium Chloride Injection" USP, 0.9%) reproducibly. Unlike a typical terrestrial system, the IVGEN system is expected to produce no more than 9 liters of product. As such, there are no aspects of this protocol pertaining to the cleaning, replacement of parts, regeneration of components such as the deionization cartridge, etc. Some of the PQ testing can be done in space; most will need to be done terrestrially. The requirements to be met by the product are addressed in the USP monographs for "Sterile Water for Injection," and "Sodium Chloride Injection." The PQ section requires the preparation of water containing known challenges to the system (ionic loads, organic loads, endotoxin) to provide evidence that the system functions as expected. Usually the USP sterility (Chapter 71) test cannot be used to prove that an entire lot of pharmaceutical product is sterile. However, it is possible to use this test effectively with the nine liters of product produced terrestrially. This is because all nine liters can be filtered through a sufficient number of sterility test membranes. This gets around the Poisson distribution limitation usually associated with the compendial sterility test. Note that this use of all of the product is applicable only in the initial testing of the system in space, and would require that all the product produced in space be returned. Note also that this product is therefore unavailable for actual use as intended (IV administration to personnel).

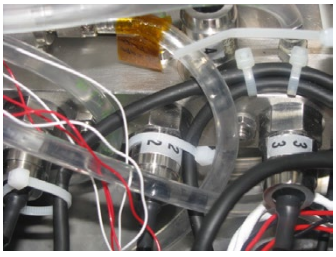
The general approach taken for the protocol is a description of a step, followed by an evaluation of the outcome. Results are either in the form of yes/no or pass/fail. It may be desirable to add an additional column to the table into which the initials and date of the operator may be entered. This would be consistent with creating documented evidence of the system suitability. The same goal could be accomplished by initialing the appropriate yes/no or pass/fail box in the table.

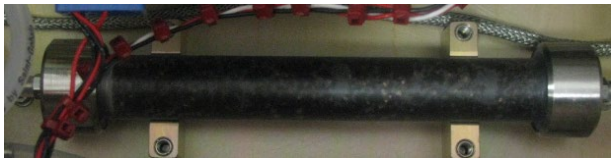
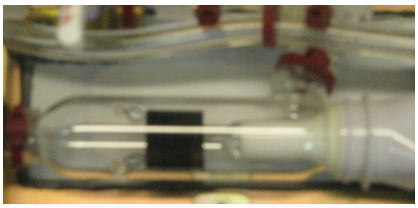
Installation Qualification

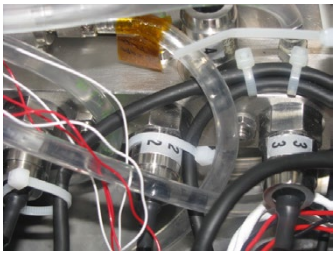
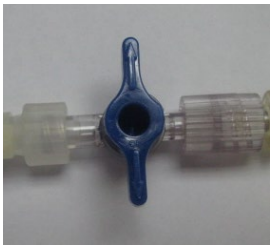
Check IVGEN instrument calibrations (done by ground staff)		
Step	**Yes**	**No**
Pressure regulator calibrated? (This and all other similar calibrations can be done by an in-house metrology group, or be contracted out (indicated by (Calibration Note) below) (Section 1 part label: 2)		
Coriolis flow meter calibrated? (Calibration Note) (Section 4 part label: 9)		
Conductivity sensor prior to two parallel 1.2 µm Supor filters calibrated? (Calibration Note) (Section 4 part label: 10)		
RTD probe assembly prior to two parallel 1.2 µm Supor filters calibrated? (Calibration Note) (Section 4 part label: 11)		
Pressure transducer prior to two parallel 1.2 µm Supor filters calibrated? (Calibration Note) (Section 4 part label: 12)		
Pressure transducer prior to DI cartridge calibrated? (Calibration Note) (Before Section 4 part label: 15)		
Conductivity sensor after DI cartridge calibrated? (Calibration Note) (Section 4 part label: 17)		
RTD probe assembly after DI cartridge calibrated? (Calibration Note) (Section 4 part label: 11 (after part 17))		
Pressure transducer after DI cartridge calibrated? (Calibration Note) (Section 4 part label: 12 (before part 18))		
Conductivity sensor prior to bank of two 0.2 µm membrane filters calibrated? (Calibration Note) (Section 4 part label: 10 (before part 25, Section 5))		
RTD probe prior to bank of two 0.2 µm membrane filters calibrated? (Calibration Note) (Section 4 part label: 11 (before part 25, Section 5))		
Check IVGEN component expiry dating (determined by ground staff)		
Step	**Yes**	**No**
1.2 µm Supor filters within expiry dating, with enough time for usage prior to mission completion? (Well into the future, it may be possible for mission durations to exceed the standard expiry periods. It may be necessary to have the filter manufacturers test for membrane integrity beyond the usual lengths, or else the manufacturers might need to develop longer lasting filter assemblies.) (Section 4, part 14)		
DI resin material within expiry dating, with enough time for usage prior to mission completion? (See note above for 1.2 µm Supor membrane expiry dating.) (Section 4, part 16)		
0.2 µm membrane filters within expiry dating, with enough time for usage prior to mission completion? (See note above for 1.2 µm Supor membrane expiry dating.)(Section 4, part 18)		
NaCl used in EVA multilayer IV bags within expiry dating, with enough time for usage prior to mission completion? (See note above for 1.2 µm Supor membrane expiry dating.)(Section 5, part 28)		
0.2 µm sterilizing filters within expiry dating, with enough time for usage prior to mission completion? (See note above for 1.2 µm Supor membrane expiry dating.)(Section 5, part 25)		
EVA multilayer IV bags within expiry dating, with enough time for usage prior to mission completion? (See note above for 1.2 µm Supor membrane expiry dating.)(Section 5, part 28)		

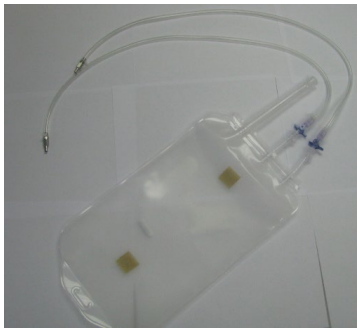
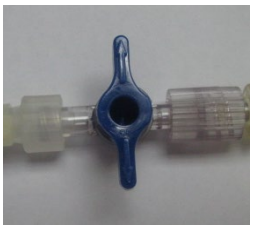
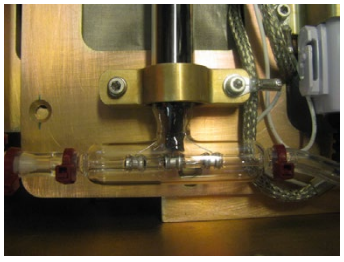
Visible System Integrity (determined by ground, space staff, all steps)		
Step	**Yes**	**No**
(a) Pressure regulator has no obvious visible defects present.)(Section 1, part 2) 		
(b) Pressure relief valve has no obvious visible defects present? (Section 1, part 3) 		
(c) PTFE-lined metal flex hose has no obvious visible defects (fraying, rust) present? (Section 1, part 4) 		
Connections among (a) to (c) look tight? (Section 1)		
Three-way valve integrity has no obvious visible defects present? (Section 2, part 7)		
Connections from accumulator (Section 3, part 4) to shut-off valve look tight?		
Shut-off valve has no obvious visible defects present? (Section 4, part 8) 		
Connections from shut-off valve to Coriolis flow meter look tight? (Section 4)		

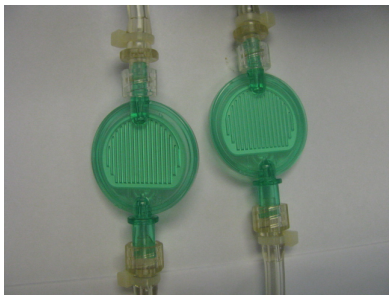
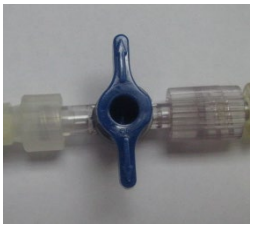
Visible System Integrity (determined by ground, space staff, all steps)		
Step	**Yes**	**No**
Coriolis flow meter integrity has no obvious visible defects present? (Section 4, part 9) 		
Connection from Coriolis flow meter to conductivity sensor looks tight? (Section 4)		
Conductivity sensor integrity has no obvious visible defects (cracks) present? (Section 4, part 10) 		
Connections from conductivity sensor to RTD probe assembly look tight? (Section 4)		
RTD probe assembly integrity has no obvious visible defects present? (Section 4, part 11) 		
Connection from RTD probe assembly to pressure transducer looks tight? (Section 4)		
Pressure transducer has no obvious visible defects present? (Section 4, part 12) 		
Connection from pressure transducer to first four-way stopcock looks tight? (Section 4)		

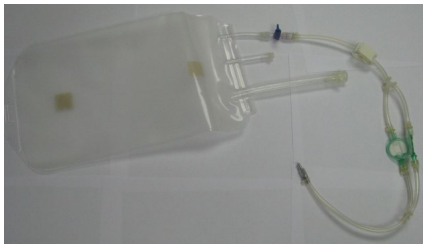
Visible System Integrity (determined by ground, space staff, all steps)		
Step	**Yes**	**No**
Four-way stopcock has no obvious visible defects present? (Section 4, part 13) 		
Connection from first four-way stopcock to first bank of two 1.2 µm Supor filters looks tight? (Section 4)		
Connection from first four-way stopcock to second four-way stopcock looks tight? (Section 4)		
Connection from second four-way stopcock to second bank of two 1.2 µm Supor filters looks tight? (Section 4)		
Connection from first bank of two 1.2 µm Supor filters to pressure transducer looks tight? (Section 4)		
Connection from second bank of two 1.2 µm Supor filters to pressure transducer looks tight? (Section 4)		
Connection from second four-way stopcock to pressure transducer (bypass) looks tight? (Section 4)		
1.2 µm Supor filters have no obvious visible defects (cracks) present? (Section 4, part 14) 		
Pressure transducer has no obvious visible defects present? (Section 4, after 1.2 µm Supor filters) 		
Connection from pressure transducer to shut-off valve, angle pattern, looks tight? (Section 4)		

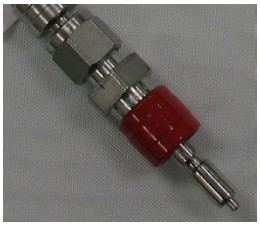
Visible System Integrity (determined by ground, space staff, all steps)		
Step	**Yes**	**No**
Shut-off valve, angle pattern, has no obvious visible defects present? (Section 4, part 15) 		
Connection from shut-off valve, angle pattern, to DI cartridge looks tight? (Section 4)		
DI cartridge has no obvious visible defects present? (Section 4, part 16) 		
Connection from DI cartridge to shut-off valve, angle pattern, integrity looks tight? (Section 4)		
Shut-off valve, angle pattern, has no obvious visible defects present? (Section 4, part 15) 		
Connection from shut-off valve, angle pattern, to conductivity sensor looks tight? (Section 4)		
Conductivity sensor has no obvious visible defects (cracks) present? (Section 4, part 17) 		
Connections from conductivity sensor to RTD probe assembly look tight? (Section 4)		
RTD probe assembly has no obvious visible defects present? (Section 4, part 11) 		
Connection from RTD probe assembly to pressure transducer looks tight? (Section 4)		

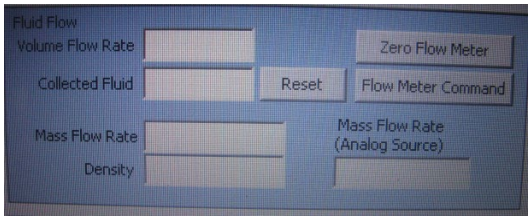
Visible System Integrity (determined by ground, space staff, all steps)		
Step	**Yes**	**No**
Pressure transducer has no obvious visible defects present? (Section 4, prior to part 18) 		
Connection from pressure transducer to bank of two 0.2 µm membrane filters looks tight? (Section 4)		
0.2 µm membrane filter has no obvious visible defects (cracks) present? (Section 4, part 18) 		
Connections from 0.2 µm membrane filters through quick disconnects look tight? (Section 4)		
Connection from quick disconnect stem to stopcock looks tight? (Section 5)		
Stopcock has no obvious visible defects present? (Section 5, part 21) 		
Connection from stopcock to EVA multilayer IV bag containing salt and stir bar looks tight? (Section 5)		

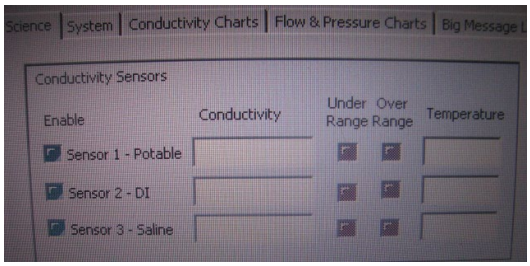
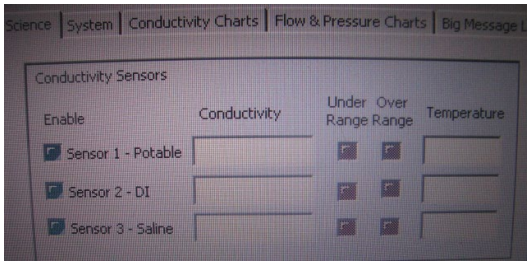
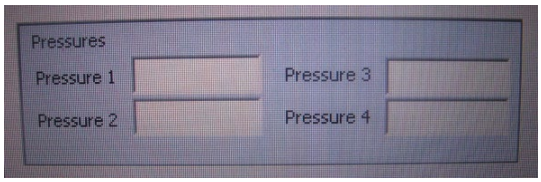
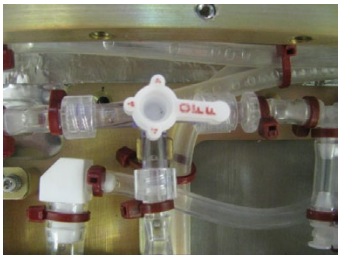
Visible System Integrity (determined by ground, space staff, all steps)		
Step	**Yes**	**No**
EVA multilayer IV bag containing salt and stir bar has no obvious visible defects present? (Section 5, part 28) 		
Salt and stir bar visible in EVA multilayer IV bag? (Section 5, part 28)		
Connection from EVA multilayer IV bag containing salt and stir bar to stopcock looks tight? (Section 5, part 21)		
Stopcock has no obvious visible defects present? (Section 5, part 21) 		
Connection from stopcock through disconnects looks tight? (Section 5)		
Connection from quick disconnect body to conductivity sensor looks tight? (Section 4)		
Conductivity sensor has no obvious visible defects (cracks) present? (Section 4, part 10) 		
Connection from conductivity sensor to RTD probe assembly looks tight? (Section 4)		

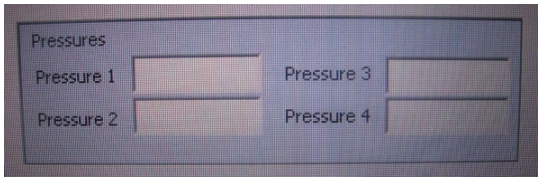
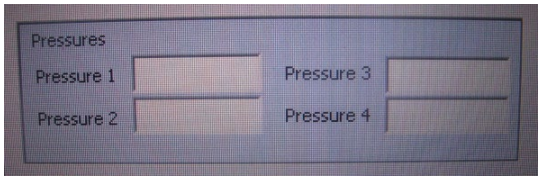
Visible System Integrity (determined by ground, space staff, all steps)		
Step	**Yes**	**No**
RTD probe assembly has no obvious visible defects present? (Section 4, part 11) 		
Connection from RTD probe assembly through quick disconnects looks tight? (Section 4)		
Connection from quick disconnect stem to 0.2 µm sterilizing filters looks tight? (Section 5)		
0.2 µm sterilizing filters have no obvious visible defects (cracks) present? (Section 5, part 25) 		
Connection from 0.2 µm sterilizing filters to ratchet tubing clamp looks tight? (Section 5)		
Ratchet tubing clamp has no obvious visible defects present? (Section 5, part 26) 		
Connection from ratchet tubing clamp to stopcock looks tight? (Section 5)		
Stopcock has no obvious visible defects present? (Section 5, part 21) 		
Connection from stopcock to EVA multilayer IV bag looks tight? (Section 5)		

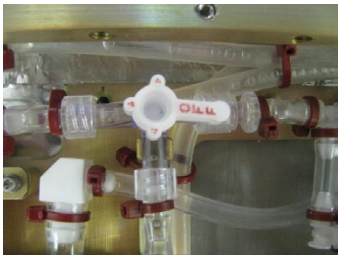
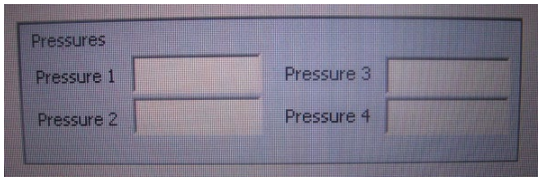
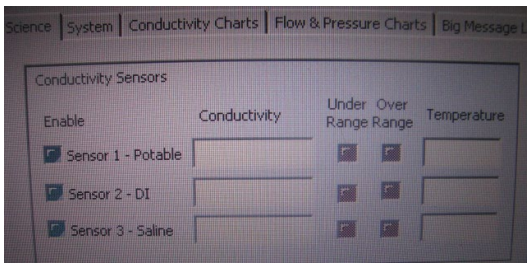
Visible System Integrity (determined by ground, space staff, all steps)		
Step	**Yes**	**No**
EVA multilayer IV bag has no obvious visible defects present? (Section5, part 28) 		

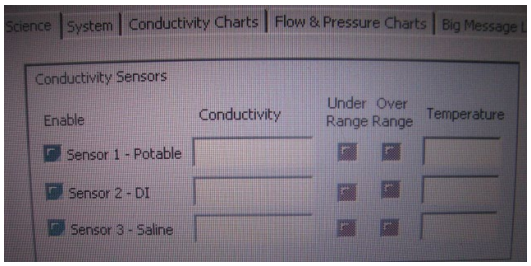
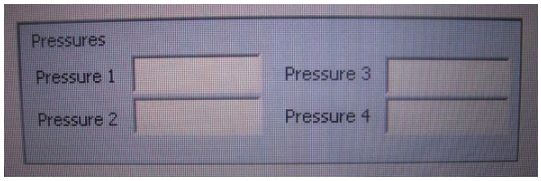
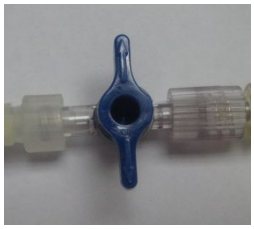
Operational Qualification		
Steps (numbered below, all done by both ground, space staff)	**Yes**	**No**
1. Set all valves/stopcocks to occlude flow. Apply pressure by connecting MSG GN_2 to quick disconnect stem at pressure regulator. 	N/A	N/A
Pressure regulator maintains desired pressure set-point (2.0 psi) (Section 1, part 2) 		
2. Increase pressure at regulator to exceed relief pressure setting	N/A	N/A
Pressure relief valves function at proper relief pressure (apply over-pressure)? (Section 1, part 3) 		

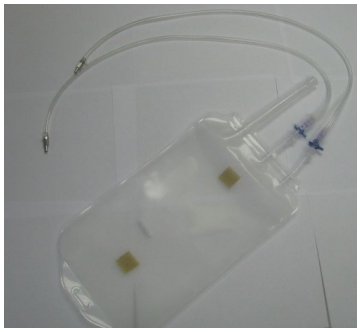
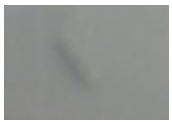
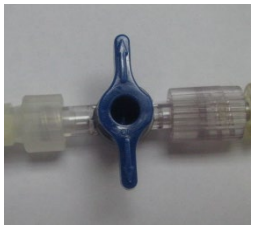
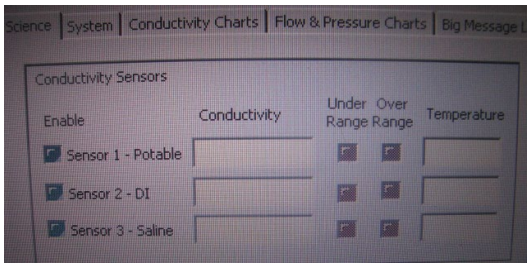
Operational Qualification		
Steps (numbered below, all done by both ground, space staff)	**Yes**	**No**
3. Set three-way valve between quick disconnect stem and accumulator to send flow to accumulator 	N/A	N/A
Does the three-way valve direct flow properly? (Section 2, part 6)		
4. Set three-way valve between quick disconnect stem and accumulator to send flow away from accumulator 	N/A	N/A
Does the three-way valve direct flow properly? (Section 2, part 6)		
5. Fill accumulator to intended volume with potable water (conductivity of source water checked with validated, calibrated conductivity meter and the temperature is recorded with a NIST-traceable thermometer) (how is volume determined?)	N/A	N/A
Does the accumulator contain the desired volume? (Section 2, part 7)		
6. Turn shut-off valve between quick disconnect body and Coriolis flow meter to on position 	N/A	N/A
Does the Coriolis flow meter indicate the correct flow rate? (Section 4, part 9) 		

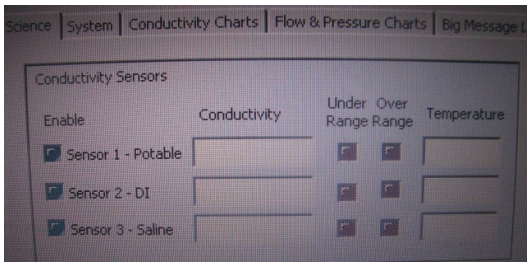
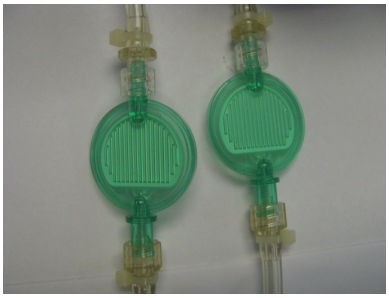
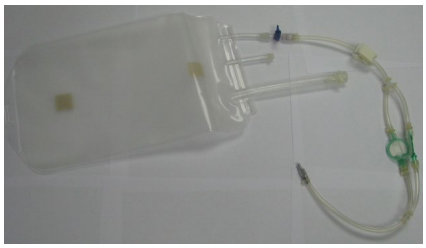
Operational Qualification		
Steps (numbered below, all done by both ground, space staff)	**Yes**	**No**
Does the conductivity meter reading match (within 1%) that recorded in step 5? (Section 4, part 10) 		
Is the output from the RTD probe assembly reasonable in comparison to reading taken in step 5? (Section 4, part 11) 		
Is the pressure reading consistent with the supplied pressure? (Section 4, part 12) 		
7. Open the four-way stopcock connected directly to the pressure transducer following the Coriolis flow meter to send flow through the first bank of 1.2 µm Supor filters. 	N/A	N/A

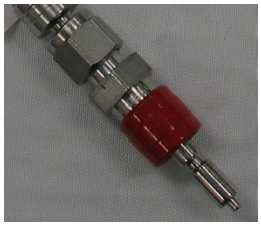
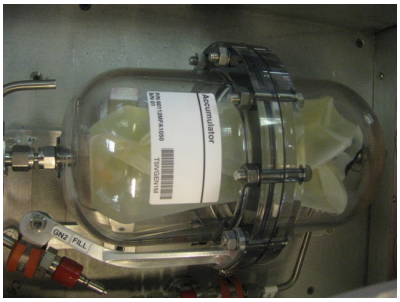
Operational Qualification		
Steps (numbered below, all done by both ground, space staff)	**Yes**	**No**
Is fluid clearly flowing through the 1.2 µm Supor filters? (Section 4, part 14) 		
Is the pressure reading within the expected range? (Section 4, part 12) 		
8. Redirect the four-way stopcock connected directly to the pressure transducer following the Coriolis flow meter to send flow through the second bank of 1.2 µm Supor filters via the second four-way stopcock.		
Is fluid clearly flowing through the 1.2 µm Supor filters? (Section 4, part 14) 		
Is the pressure reading within the expected range? (Section 4, part 12) 		

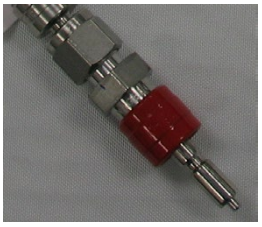
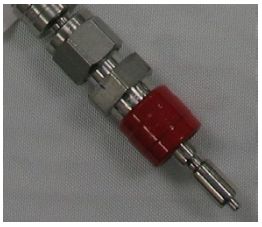
Operational Qualification		
Steps (numbered below, all done by both ground, space staff)	**Yes**	**No**
9. Redirect the second four-way stopcock such that the flow bypasses both 1.2 µm Supor filters going directly to the pressure transducer. 		
Is the pressure reading within the expected range? (Section 4, part 12) 		
10. Open the shut-off valve, angle pattern, immediately preceding the DI cartridge. 		
Is fluid clearly flowing through the DI cartridge? (Section 4, part 16)		
11. Open the shut-off valve, angle pattern, immediately following the DI cartridge. 		
Does the reading from the conductivity sensor fall within the acceptable level for WFI (≤ 5 µS/cm, given temperature of 25 + 1 °C)? (Section 4, part 17) 		

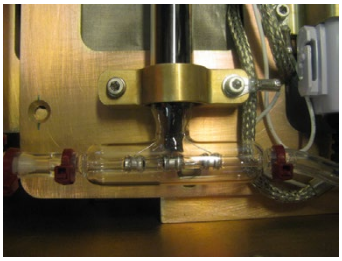
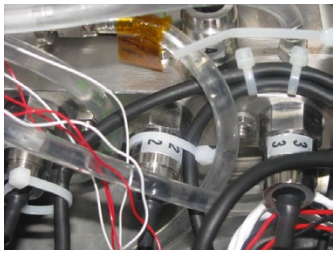
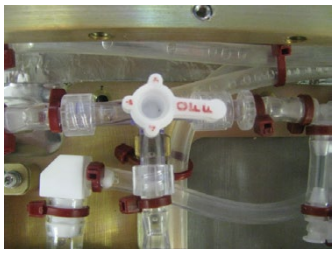
Operational Qualification		
Steps (numbered below, all done by both ground, space staff)	**Yes**	**No**
Does temperature indicated by RTD probe assembly fall within expected operating range? (Section 4, part 11) 		
Does pressure reading fall within acceptable limits (determined previously using freshly prepared cartridge)? (Section 4, part 12) 		
Is fluid clearly present within the 0.2 µm membrane filters? 		
12. Open stopcock immediately preceding the EVA multilayer IV bag with salt, stir bar. Turn on the stirring apparatus. 		

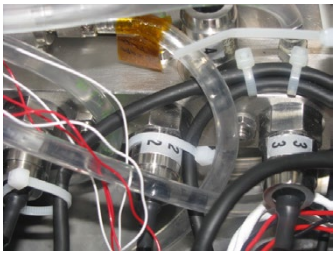
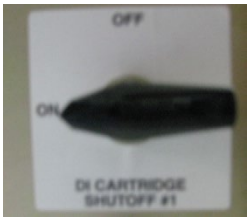
Operational Qualification		
Steps (numbered below, all done by both ground, space staff)	**Yes**	**No**
Is fluid evident in the EVA multilayer IV bag? (Section 5, part 28) 		
Is the stir bar turning? (Section 5, part 28) 		
Is the salt clearly being agitated? (Section 5, part 28)		
13. Open stopcock immediately following the EVA multilayer IV bag with salt, stir bar. 		
Does the reading from the conductivity meter fall within the acceptable level for 0.9% Sodium Chloride Injection USP? (Section 4, part 10) 		

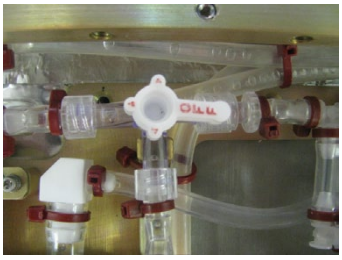
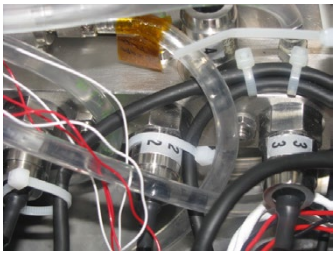
Operational Qualification		
Steps (numbered below, all done by both ground, space staff)	**Yes**	**No**
It the temperature reported by the RTD probe assembly within the expected operating range? (Section 4, part 10) 		
Is fluid clearly flowing through the 0.2 µm sterilizing filters? (Section 5, part 25) 		
14. Open the ratchet tubing clamp and the stopcock. 		
Is the final EVA multilayer IV bag filling with fluid? (Section 5, part 28)		
15. Close the ratchet tubing clamp and the stopcock.		
Does the EVA multilayer IV bag appear to be tightly sealed? (Section 5, part 28) 		

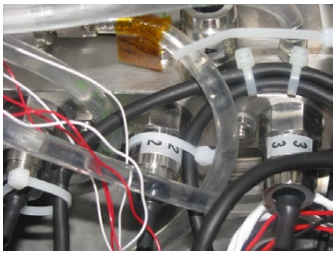
Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
1. Apply pressure by connecting MSG GN2 to quick disconnect stem at pressure regulator. Set all valves/stopcocks to occlude flow.	N/A	N/A
Quick disconnect stem to pressure regulator (Section 1, part 2) 		
Pressure regulator to pressure relief valves (two in series) (Section 1, part 3) 		
Pressure relief valve (second in series) to PTFE-lined metal flex hose (Section 1, part 4)		
PTFE-lined metal flex hose to quick disconnect body (Section 1, part 5)		
Quick disconnect body to quick disconnect stem (Section 2, part 1)		
Quick disconnect stem to three-way valve (Section 2, part 6) 		
2. Open three-way valve prior to accumulator to permit flow into accumulator.	N/A	N/A
three-way valve to accumulator housing (Section 2, part 7) 		

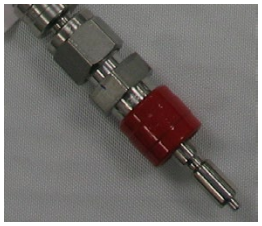
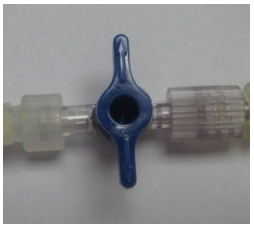
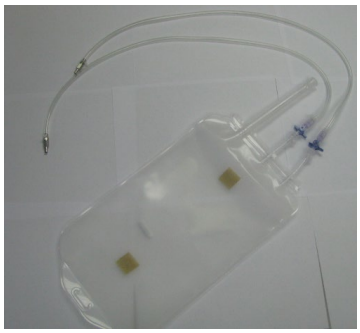
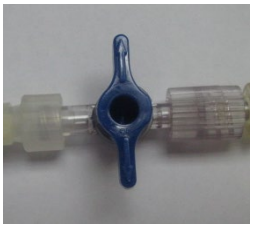
Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
Accumulator housing to quick disconnect body (Section 2, part 5) 		
Quick disconnect body to quick disconnect stem (Section 2), part 1 		
Quick disconnect stem to PTFE-lined metal flex hose (Section 3, part 4)		
PTFE-lined metal flex hose to quick disconnect stem (Section 3, part 1) 		
Quick disconnect stem to quick disconnect body (Section 4, part 5) 		
Quick disconnect body to shut-off valve (Section 4, part 8) 		
Shut-off valve to Coriolis flow meter (Section 4, part 9)		
3. Open shut-off valve to Coriolis flow meter.	N/A	N/A

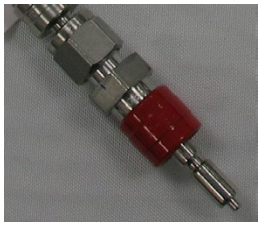
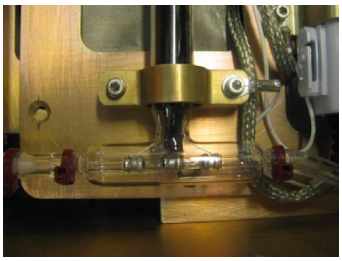
Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
Coriolis flow meter to conductivity sensor (Section 4, part 10) 		
Conductivity sensor to RTD probe assembly (Section 4, part 11) 		
RTD probe assembly to pressure transducer (Section 4, part 12) 		
Pressure transducer to four-way stopcock (Section 4, part 13) 		
4. Open four-way stopcock after first pressure transducer.	N/A	N/A

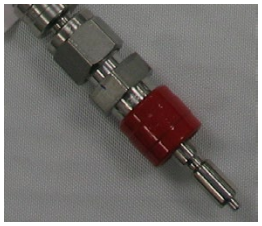
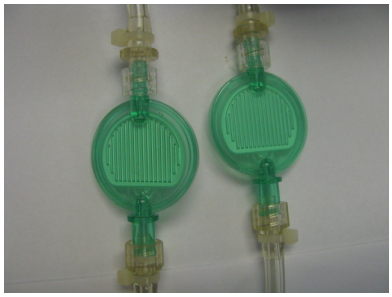
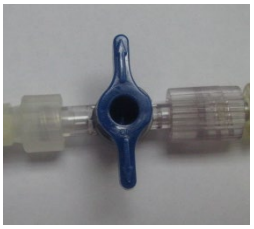
Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
Four-way stop cock (from pressure transducer) to: a. Second four-way stopcock (Section 4, part 13) b. First bank of two parallel 1.2 µm Supor filters (Section 4), part 14  c. Pressure transducer (Section 4, part 12 (unlabeled in figure, just after bank of 1.2 µm Supor filters))  d. Shut-off valve, angle pattern, prior to DI cartridge (Section 4, part 15) 		
5. Open four-way stopcock connected to first four-way stopcock	N/A	N/A

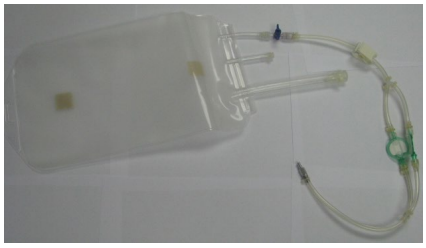
Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
Four-way stop cock (attached to four-way stop cock that is attached to pressure transducer) to: (Section 4, part 13)  a. Second bank of two parallel 1.2 µm Supor filters (Section 4, part 14)  b. Via bypass of second bank of two parallel 1.2 µm Supor filters to pressure transducer (Section 4) c. Pressure transducer . Pressure transducer (Section 4, part 12 (unlabeled in figure, just after bank of 1.2 µm Supor filters))  d. Shut-off valve, angle pattern, prior to DI cartridge (Section 4, part 15)		
6. Open shut-off valve prior to DI cartridge, angle pattern,.	N/A	N/A
Shut-off valve, angle pattern to DI cartridge (Section 4, part 15) 		

Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
DI cartridge to shut-off valve, angle pattern 		
7. Open shut-off valve, angle pattern, after DI cartridge.	N/A	N/A
Shut-off valve, angle pattern to conductivity sensor (Section 4, part 15) 		
Conductivity sensor to RTD probe assembly (Section 4, part 11)		
RTD probe assembly to pressure transducer (Section 4, part 11) 		
Pressure transducer to bank of two 0.2 µm membrane filters (Section 4, part 12, (unlabeled in Figure 2, found just before bank of two 0.2 µm membrane filters)) 		
Bank of two 0.2 µm membrane filters to quick disconnect body (Section 4, part 18) 		

Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
Quick disconnect body to quick disconnect stem (Section 4, part 1) 		
Quick disconnect stem to stopcock (Section 5, part 21) 		
8. Open stopcock to EVA multilayer IV bag	N/A	N/A
Stopcock to EVA multilayer IV bag (Section 5, part 28) 		
EVA multilayer IV bag to stopcock (Section 5, part 21) 		
9. Open stopcock after EVA multilayer bag	N/A	N/A

Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
Stopcock to quick disconnect stem (Section 5, part 20) 		
Quick disconnect stem to quick disconnect body (Section 4, part 20) 		
Quick disconnect body to conductivity sensor (Section 4, part 10) 		
Conductivity sensor to RTP probe assembly (Section 4, part 11) 		
RTD probe assembly to quick disconnect body (Section 4) 		

Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
Quick disconnect body to quick disconnect stem (Section 5, part 20) 		
Quick disconnect stem to bank of two 0.2 µm sterilizing filters (Section 5, part 25) 		
Bank of two 0.2 µm sterilizing filters to ratchet tubing clamp (Section 5, part 26) 		
Ratchet tubing clamp to stopcock (Section 5, part 21) 		
10. Open stopcock prior to final EVA multilayer bag	N/A	N/A

Leakage at IVGEN connections?		
Steps (numbered below, all done both by ground, space staff)	N/A	N/A
Stopcock to EVA multilayer IV bag (Section 5, part 28) 		

Performance Qualification

Steps (numbered below, done by ground staff)	Pass	Fail
1. Prepare 10 liters of water (potable) containing: **a. 1 vial of USP Particle Count RS/lt** **b. 1 vial of USP Endotoxin RS/lt** **c. 12 mg USP Sucrose RS/lt** **d. 100 mL USP Ammonia TS/lt** **e. Mixture of ionic materials as listed in NASA Potable Water quality table (each at MCL/liter)** **NOTE: Do NOT use salt in the first EVA multilayer IV bag for each of the 10 bags produced.**	N/A	N/A
2. Make 10 liters of sterile WFI using water from Step 1, evaluating each liter for acceptance criteria (end product testing as per USP):	N/A	N/A
a. Particulate matter (USP 788): < 12 particles/mL larger than 10 µm		
b. Bacterial Endotoxins (USP 85): < 0.25 EU/mL		
c. Ammonia (USP "Sterile Water for Injection" monograph): ≤ 0.3 mg/L		
d. Calcium (USP "Sterile Water for Injection" monograph): no turbidity		
e. CO_2 (USP "Sterile Water for Injection" monograph): mixture remains clear		
f. Chloride (USP "Sterile Water for Injection" monograph): turbidity no greater than control		
g. Sulfate (USP "Sterile Water for Injection" monograph): no turbidity		
h. Oxidizable substances USP "Sterile Water for Injection" monograph): if precipitate forms, pink color does not completely disappear		
i. Total organic carbon (USP 643): RU ≤ rs – rw		
j. Conductivity (USP 645): conductivity ≤ 5 µS/cm		
k. Sterility (USP 71): Process entire contents of each liter bag separately (10 testing membranes)—all bags pass test		

Steps (numbered below, done by ground staff)	Pass	Fail
3. (in process testing done during production of the 10 liters in Step 2 above; record run number, time for each quantitative value along with the value itself)	N/A	N/A
a. Conductivity measurement immediately following accumulator nominal (relative to prepared water):		
b. Temperature immediately following accumulator within expected operational range:		
c. Pressure measurements immediately following accumulator within expected operational range:		
d. Track presence of bubbles preceding 1.2 µm filters. If any are present, they are removed (no longer visible) following the 1.2 µm filters:		
e. Pressure measurements immediately following 1.2 µm filters within expected operational range:		
f. Conductivity measurements following DI cartridge ≤ 5 µS/cm:		
g. Temperature measurements following DI cartridge within expected operational range:		
h. Pressure measurements following DI cartridge within expected operational range:		
i. Temperature measurements immediately preceding sterilizing filters within expected operational range:		
j. Conductivity measurements immediately preceding sterilizing filters ≤ 5 µS/cm:		
4. Prepare 10 liters of water (potable) containing: **a. 1 vial of USP Particle Count RS/lt** **b. 1 vial of USP Endotoxin RS/lt** **c. 12 mg USP Sucrose RS/lt** **d. 100 mL USP Ammonia TS/lt** **e. Mixture of ionic materials as listed in NASA Potable Water quality table (each at MCL/liter)** **NOTE: Add salt in the first EVA multilayer IV bag for each of the 10 bags produced.**	N/A	N/A
5. During process testing for the production of the 10 liters in Step 2 above; record run number, time for each quantitative value along with the value itself	N/A	N/A
a. Conductivity measurement immediately following accumulator nominal (relative to prepared water):		
b. Temperature immediately following accumulator within expected operational range:		
c. Pressure measurements immediately following accumulator within expected operational range:		
d. Track presence of bubbles preceding 1.2 µm filters. If any are present, they are removed (no longer visible) following the 1.2 µm filters:		
e. Pressure measurements immediately following 1.2 µm filters within expected operational range:		
f. Conductivity measurements following DI cartridge ≤ 5 µS/cm:		

Steps (numbered below, done by ground staff)	Pass	Fail
g. Temperature measurements following DI cartridge within expected operational range:		
h. Pressure measurements following DI cartridge within expected operational range:		
i. Temperature measurements immediately preceding sterilizing filters within expected operational range:		
j. Conductivity measurements immediately preceding sterilizing filters equivalent to value expected for Sodium Chloride Injection USP:		
5. During process testing additional end product testing for "Sodium Chloride Injection" USP, perform on each of the 10 liters produced separately:		
a. Sodium (USP 191)--- responds positively:		
b. Chloride (USP 191)--- responds positively:		
c. Bacterial Endotoxins (USP 85) ≤ 0.5 USP Endotoxin Unit /mL:		
d. pH (USP 791) between 4.5 to 7.0:		
e. Particulate matter (USP 788) < 12 particles/mL larger than 10 μm:		
f. Iron (USP 241) ≤ 2 ppm:		
g. Heavy metals (USP 231) ≤ 0.009%:		
h. Conductivity equivalent to that previously measured for "Sodium Chloride Injection" USP:		
i. Assay ("Sterile Water for Injection" USP monograph)= assay value = expected amount of NaCL (9 mg/mL):		

Additional Notes Pertaining to Validation Plan

It is always critically important to remember that a process validation serves to prove that a given process reliably produces a product meeting its specifications. The following quote from the FDA's "Guideline of General Principles of Process Validation," is useful:

> "*Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."*

The purpose of the IVGEN system is to produce saline meeting the USP monograph requirements for "Sodium Chloride Injection," starting with NASA Potable Water (WPA) as the starting material. Note that any significant change either to the process itself, or to any starting materials, would need to be carefully evaluated for potential effects on the process. For example, using source water other than WPA would constitute such a change.

Although not strictly a portion of process validation, it would be useful to perform an assessment of the integrity of the various filters used prior to using the IVGEN system to generate water for potential IV usage. In routine pharmaceutical manufacturing processes using membrane filters, filter integrity is evaluated both before and after their use (see http://www.millipore.com/techpublications/tech1/tb039 for link to useful information regarding test methods for this). It is recommended that such testing be written in the standard operating procedure for the system. Given the presence of pressure gauges and a pressurized system, it should not be difficult to develop such integrity testing.

The current system as shown in Figure 2 does not contain an activated charcoal step. The source water will have been filtered with activated charcoal filters, thus the water as initially produced by the WPA system should have little to no unusual organic compounds. However, the microbial limit for the WPA water does permit a low level of viable microorganisms. It is possible that unusual organic compounds can be made by viable microorganisms which could constitute a hazard should the water be used in the IVGEN system with no subsequent removal step. These potential compounds would not likely constitute a hazard if included in water for drinking. Should an activated charcoal filtration step be added to the system in the future, the validation plan would need to be revised to account for the additional step.