Fall 10-20-2015

Risk Reduction in Single-Use Assemblies by Implementing Helium Integrity Test and a New Point-of-Use Leak Test Using Palltronic® Flowstar LGR Instrument for Critical Formulation and Filling Applications

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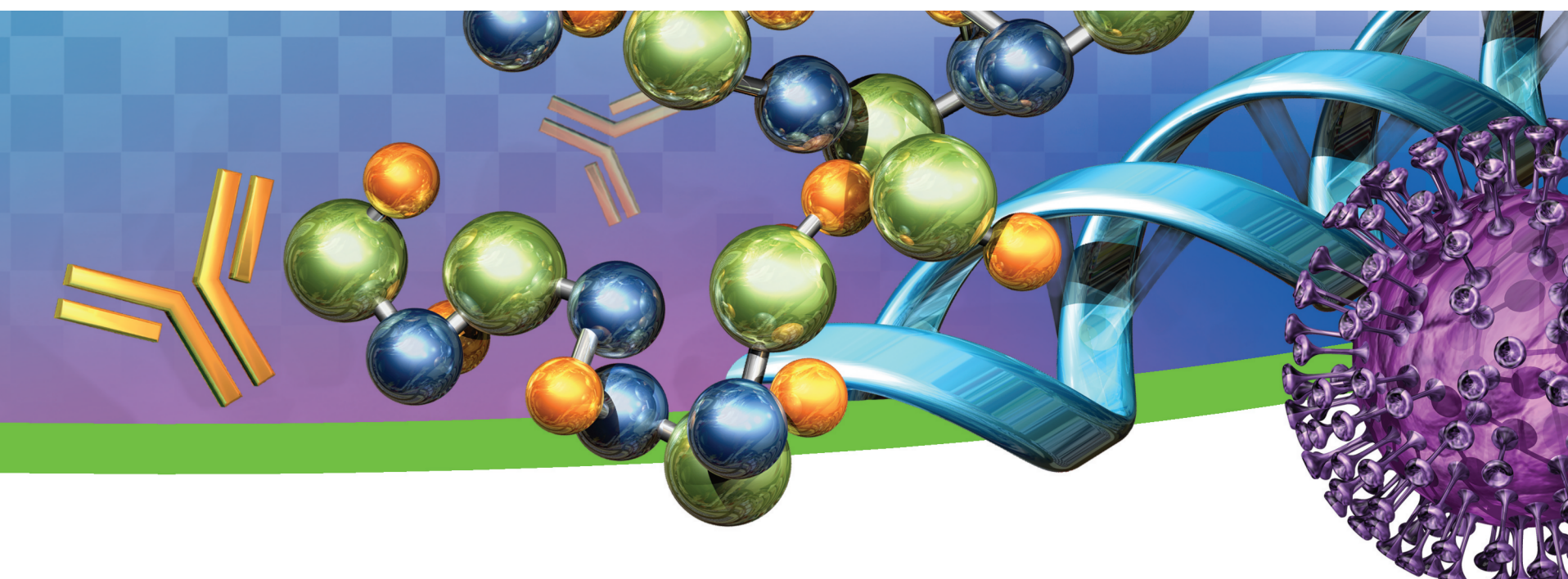*Pall Lie Sciences*

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Risk Reduction in Single-Use Assemblies by Implementing Helium Integrity Test and a New Point-of-Use Leak Test Using Palltronic® Flowstar LGR Instrument for Critical Formulation and Filling Applications

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INTRODUCTION

Single-use (SU) technologies are gaining increased attention and usage for bioprocessing as a result of the numerous benefits they offer including ease of use, quick set up time, flexibility in multiproduct facilities, reduced capital costs etc. The technology's initial adoption was focused on media and buffer storage applications and it is now also considered for critical and demanding applications such as final formulation and final filling. For these critical applications, the potential loss of expensive product or the risk of exposure to highly potent drug product due to damaged single-use assemblies has severe consequences. In current practices, QbD (Quality by Design), validated assembly methods, testing of critical components and operator training at the point-of-use have been adopted by component manufacturers, system integrators and end users to reduce the risk of potential failure. Additionally, most biocontainer manufacturers also use a pressure decay test to confirm the integrity of biocontainers during manufacturing. Figure 1 shows a typical work flow.

Figure 1
A typical work flow from manufacturing to final disposal.
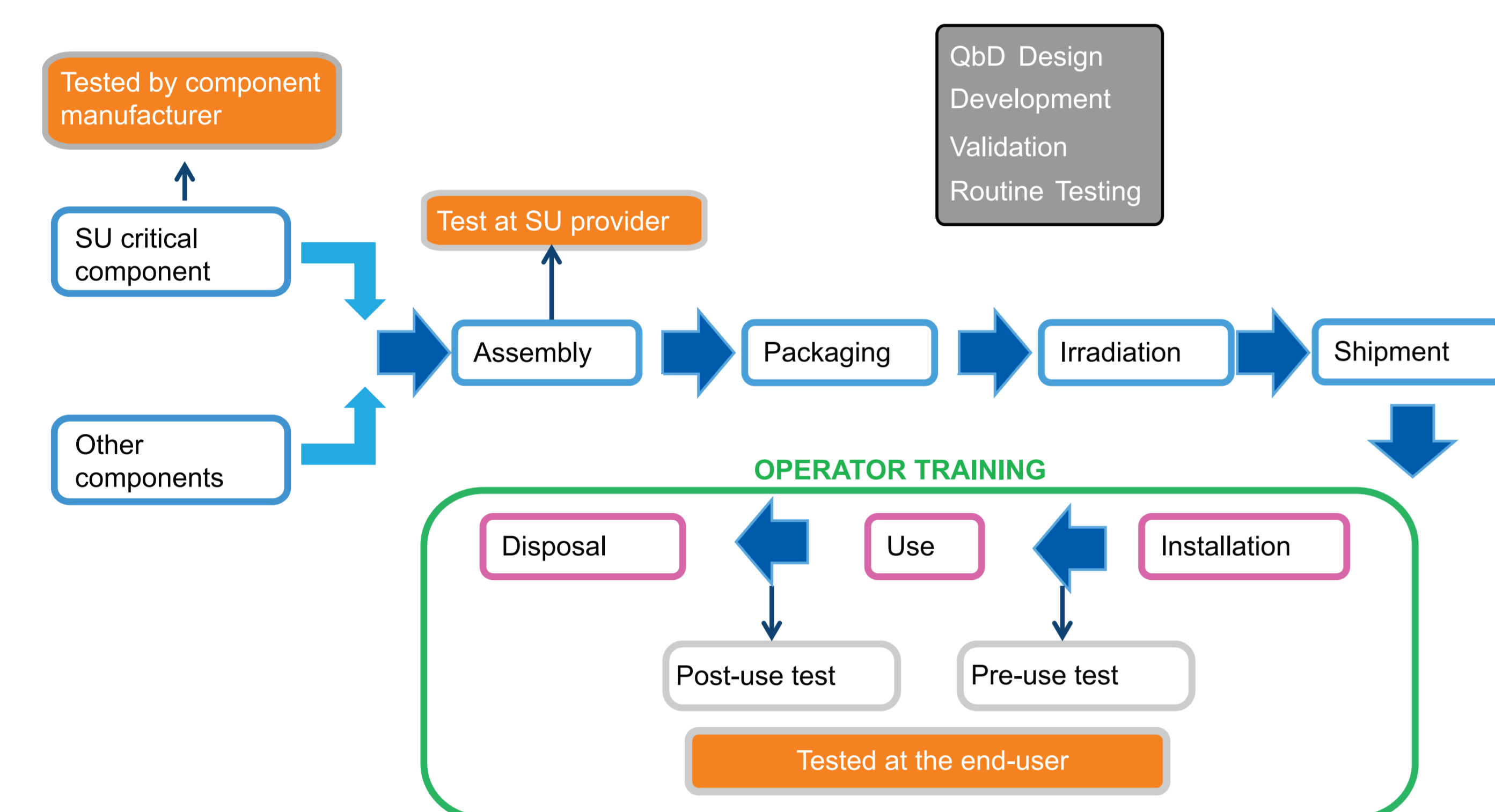
OBJECTIVES

For critical formulation and fill applications, an added level of security is desired. For these applications, we are considering a two-step approach for confirming the integrity of single-use systems. Specifically, we have tested the use of a more sensitive helium integrity test for ensuring integrity of biocontainers during manufacturing coupled with a leak test using the new point-of-use Palltronic Flowstar LGR test instrument to detect leaks post installation of the single-use system and prior to processing the product.
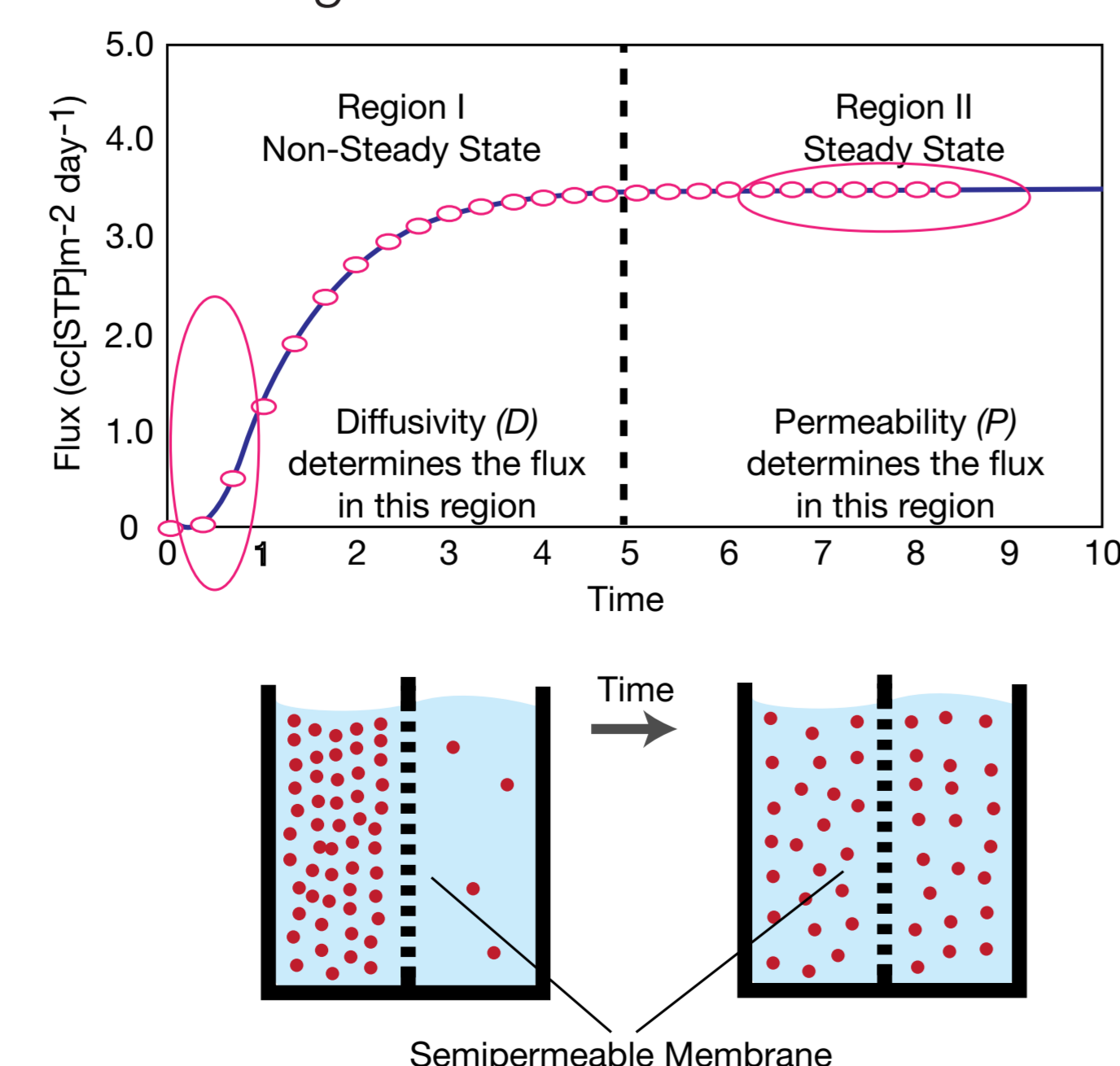
HELIUM INTEGRITY TEST

Test involves: (a) loading the biocontainer in the vacuum chamber with biocontainer support; (b) pulling vacuum in the test chamber and the biocontainer; (c) introducing a known quantity of Helium to the biocontainer rapidly under pressure, and (d) measuring the concentration of Helium permeating out of the biocontainer with time using a highly sensitive mass spectrometer. Figure 2 shows results demonstrating that the Helium integrity test can be used successfully for detecting defects of 5 µm or larger in 2D or 3D biocontainers up to 200 L.

Figure 2
Helium Integrity Test

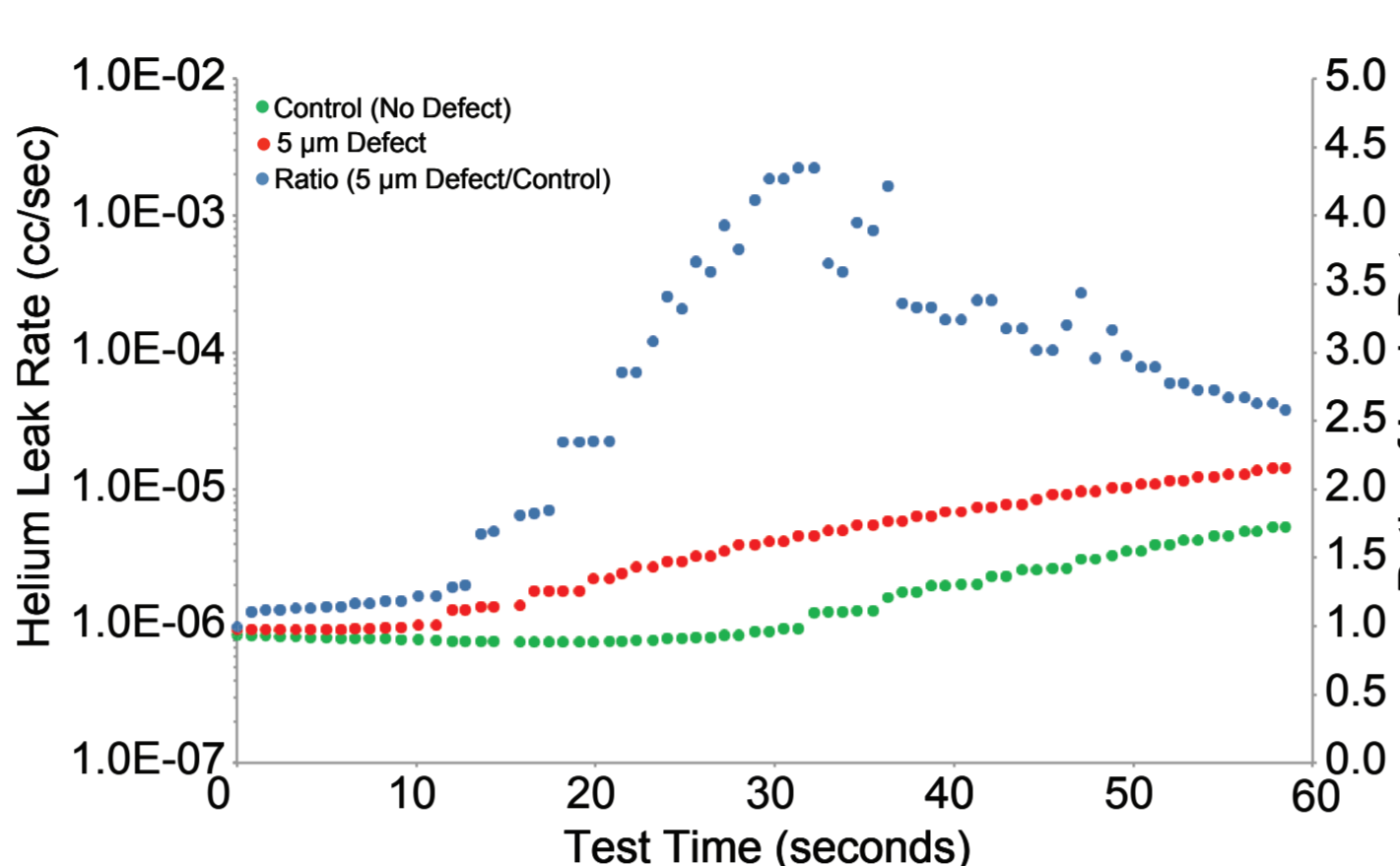**A.** *Experimental set up*

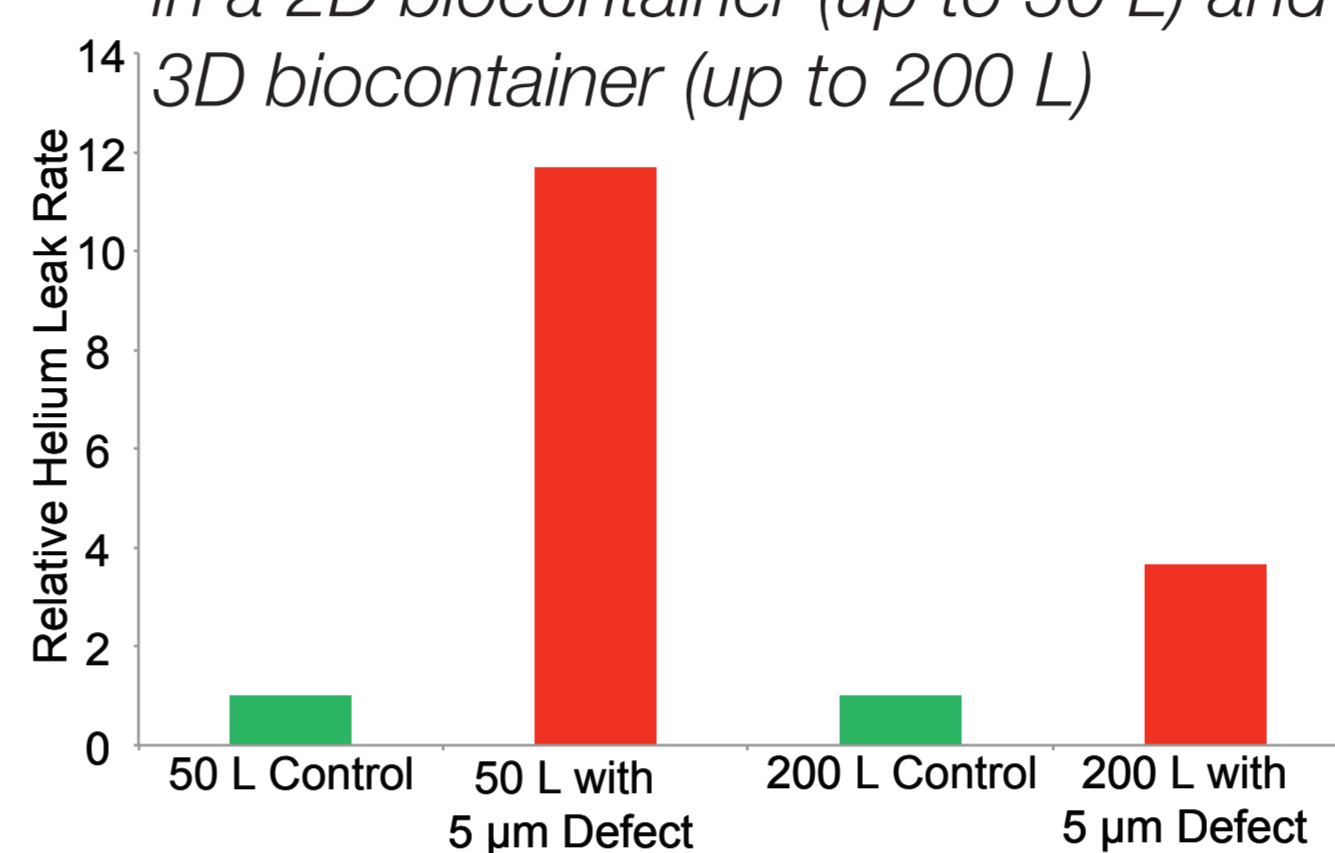**B.** *Region of interest for increased sensitivity in detecting defects*

HELIUM INTEGRITY TEST *(continued)*

C. *Typical data collected from an experimental run*


D. *Experimental data showing a 5 µm defect can be successfully detected in a 2D biocontainer (up to 50 L) and 3D biocontainer (up to 200 L)*
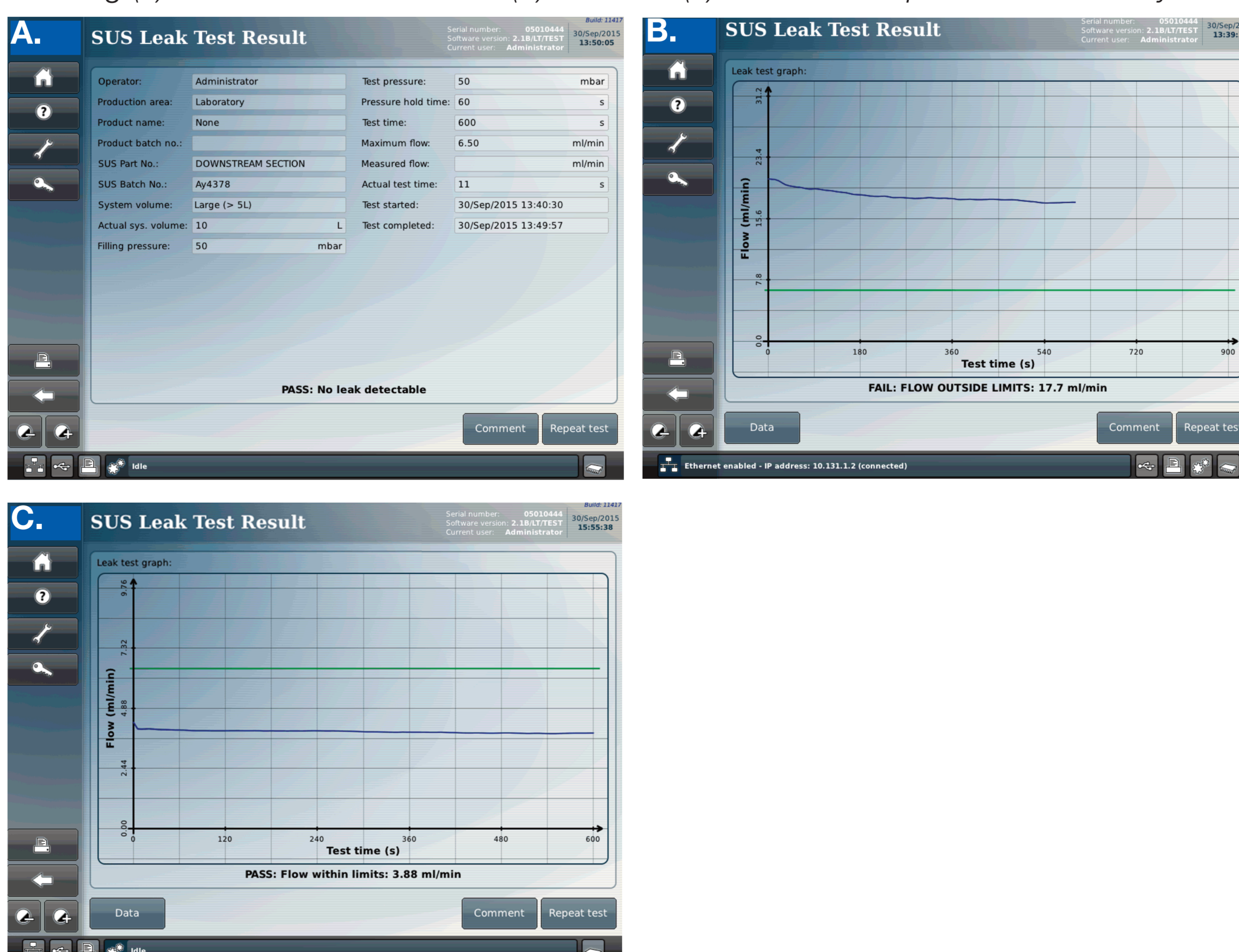

PALLTRONIC FLOWSTAR LGR INSTRUMENT BASED LEAK TEST

Test requires (a) a closed single use system by closing tube clamps on tubings connected to gas permeable components (vent filters, connectors , filling needles, etc.); (b) pressurizing the system using air or nitrogen to a specified test pressure; and (c) measuring the air flow rate required to maintain the test pressure. A typical test system and sequence of events during a test is shown in Figure 3. Figure 4 shows typical measurement results for testing system with and without a defect; and Figure 5 shows examples of the single-use systems that have been successfully tested. The test is fully automated, can be used on biocontainers and assemblies up to 200 liters .The Palltronic Flowstar LGR instrument can also be used for integrity testing of filters.

Figure 3
Palltronic Flowstar LGR instrument for leak test: (a) experimental setup; (b) sequence of events for a given test.
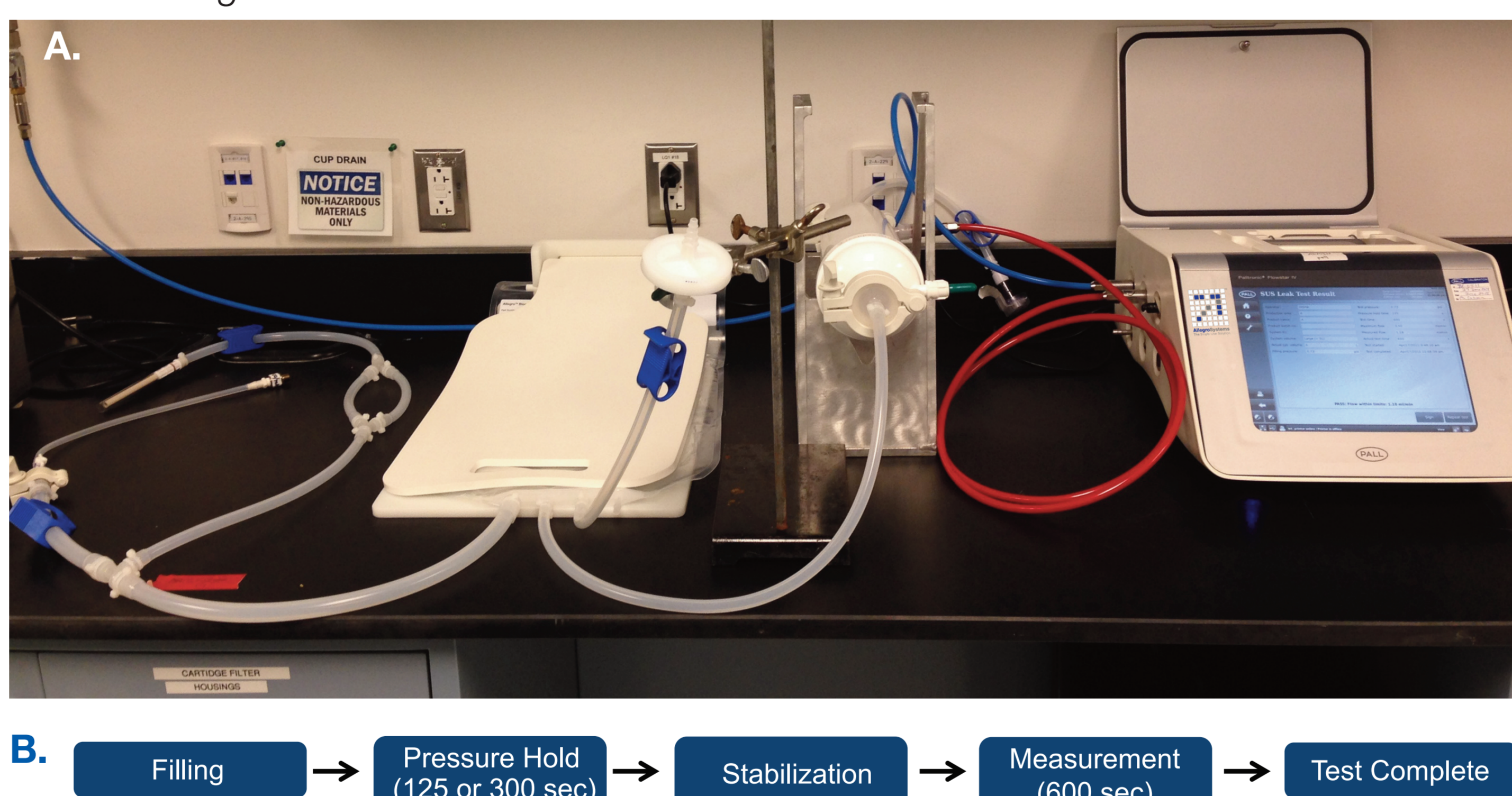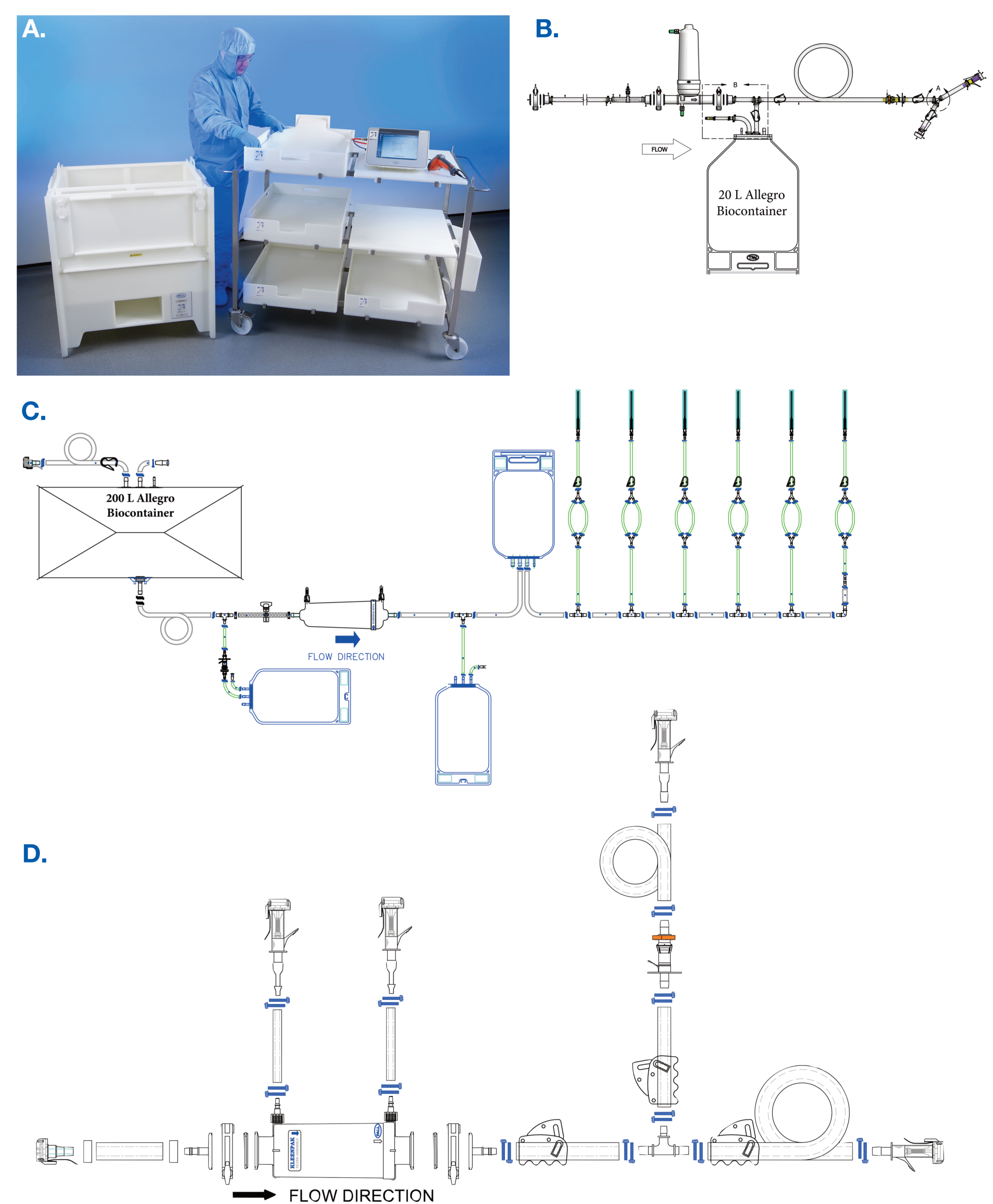

Figure 4
Screenshots from method development with Palltronic Flowstar LGR test instrument showing (a) results of measurement (b) with and (c) without a 30 µm defect in the system.

PALLTRONIC FLOWSTAR LGR INSTRUMENT BASED LEAK TEST *(continued)*

Figure 5
Example of single-use assemblies successfully been tested using Palltronic Flowstar LGR instrument.

RESULTS AND DISCUSSION

Factor	Helium Leak Test	Palltronic Flowstar LGR Leak Test
Sensitivity	≥ 5 µm	≥30 µm*
Enviromental Influences	Low	Medium (Temperature)
Volume Impact	Low – Medium	Medium
Handling	Complex	Simple
Test Time	Low	Medium

*Volume dependent, without volume reduction by testing between plates

Due to its increased sensitivity over current pressure decay test method, the helium integrity test is best suited for ensuring integrity of biocontainers in manufacturing for critical applications such as formulation and filling ones. In addition, the implementation of the point-of-use leak test using the Palltronic Flowstar LGR instrument for post installation/pre use testing would further ensure that single-use assembly was not compromised during the steps from its initial packaging.

CONCLUSIONS

In critical applications such as final formulation and filling, a reduction of risk with single-use systems with a volume up to 200 L could be potentially achieved by implementing a more sensitive test for detecting defects during manufacturing (Helium integrity test) and by performing a single-use leak test at the point-of-use, post installation and pre use, with the compact and easy to use Palltronic Flowstar LGR test instrument. For additional Information, please contact: Anil Kumar, Sr. R&D Manager, Pall Life Sciences; anil_kumar@pall.com; +1-508-871-5321 (office)