Biotech

Validation Guide

USTR 3371

Palltronic® Guardian Leak Test Instrument

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Contents

1 Introduction

The Palltronic Guardian instrument is a point-of-use leak test device for single-use systems (SUS) used in the biopharmaceutical industry. This document explains the measurement operation of the instrument, and the qualification tests performed to establish the instrument's sensitivity, accuracy and reproducibility. It demonstrates the suitability of the instrument for the application and will assist user specific risk assessments.

Tests performed with the Palltronic Guardian instrument form part of a holistic approach to managing risk of integrity breach throughout the entire SUS lifecycle.

1.1 Validation

It is recommended that end users validate the Palltronic Guardian instrument in accordance with current Good Automated Manufacturing Practice (GAMP 5) guidelines[1]. Procedures for individual users may vary depending on the user's quality management system (QMS).

1.1.1 Risk Assessment

A functional risk assessment, focusing on the instrument's performance, was performed during development, and the results were used to determine the scope of qualification testing performed by Pall.

1.1.2 Defining the System Complexity (Software and Hardware Category)

GAMP 5 classifies groups of software and hardware to assist with an assessment of system complexity. This classification determines the required verification and documentation. The Palltronic Guardian instrument, as an 'off-the-shelf' instrument, may be classified according to the GAMP 5 guideline as software category 3 (instrument) and hardware category 1 (standard hardware).

1.2 Verification

For an 'off-the-shelf' device like a SUS leak test instrument, it is expected that extensive qualification by the supplier has been performed before release. To reduce duplication of effort, GAMP 5 guidelines recommend using the supplier documentation, when justified by a supplier assessment[2].

During development of the Palltronic Guardian instrument, the software and hardware were tested extensively. The final test protocol, performed with a standard instrument, is summarized in the separate Operational Qualification document part 1 (OQ1).

In addition to the tests conducted with a generic device, Pall recommends the following tests should be performed for the complete qualification of each individual instrument:

- Installation Qualification (IQ) confirms that the instrument is delivered as specified and can be installed correctly
- Operational Qualification part 2 (OQ2)

Table 1 summarizes the documents recommended for the specification and verification of a SUS leak test instrument and lists the supportive documents and activities available for the Palltronic Guardian instrument.

Table 1.

Documents for validation report

Phase	Documents from the User	Documents and Support Available from Pall
	Risk assessment	Functional risk assessment
	Supplier assessment	ISO 9001 certificate Audit by request
Planning	User Requirement Specification (URS)	Instrument specification Validation guide (this document)
	Installation Qualification (IQ)	Installation Qualification
Verification	Operational Qualification (OQ)	OQ1 (Generic) OQ2 (Instrument specific)
Operation	Standard Operating Procedure (SOP)	Instructions for use (IFU) Recommendations for leak test procedures Recommended leak test parameters
Service/calibration	Service and calibration agreements	Maintenance, repair and calibration services Calibration procedure

1.1 Operation and Training

Before using the instrument, Pall recommends the procedures to maintain the validated state should be defined, and operator training completed. Pall Corporation can provide operator training for the Palltronic Guardian instrument upon request.

The validity of a SUS leak test result depends on the use of the correct test parameters, which may depend on the test type, the SUS type/volume, and the test pressure. The SUS supplier should define these parameters for each SUS configuration. Failure to use the correct test parameters and procedures creates an increased risk of false results and can invalidate the test.

1.2 Calibration

To maintain the validated state of the instrument, regular calibration is required. Pall recommends a calibration interval of 12 months (minimum). The Palltronic Guardian instrument measures both air pressure and air flow. Pall offers calibration services to ensure the continued accuracy and precision of this measuring instrumentation. We adhere to the principles of calibration standards and employ equipment traceable to national standards. Pall performs these calibrations using equipment certified by an independently accredited third party.

1.3 Maintenance/Service

Regular service for the Palltronic Guardian instrument is recommended. Pall offers a comprehensive range of instrumentation services performed by engineers and technical specialists certified in Palltronic Guardian instrument calibration, qualification, and repair. Services include:

- Qualification, calibration, and preventative maintenance
- Repair, spare parts, and instrument upgrades
- Training and documentation
- Service contracts

2 Instrument Overview

This document describes testing to demonstrate the suitability of the Palltronic Guardian instrument for use as a large volume leak test device. The instrument was designed to detect leaks due to damaged film, tubing and ports in flexible SUS from 200 L to 2000 L in volume.

During each test, the Palltronic Guardian instrument inflates the SUS to 20 mbar air pressure and monitors the air flow rate required to hold the SUS at this pressure. The test pressure of 20 mbar was selected to avoid compromising the structural integrity of the SUS and the hardware containing it. The instrument is provided with pneumatic tubing for connections to a compressed air supply and to the SUS, which must have a sterile point of connection. Open air flow paths (such as through filters or connectors) should be eliminated prior to the leak test.

Before starting a test, the Palltronic Guardian instrument inlet port should be connected to a compressed air supply via the pneumatic tubing supplied. The outlet port should then be connected to the SUS to be tested, and a leak test can be initiated using the instrument's on-screen navigation.

During the measurement phase of a leak test, the film of the SUS will stretch requiring airflow into the SUS to maintain test pressure. This effect can initially show behavior similar to a leak. A test duration of 60 minutes was selected to allow sufficient data to be acquired and thus mitigate the risk of a false fail result. Any large leaks prevent the system from reaching test pressure and will result in a failed test before the measurement phase begins. Thus, the full 60-minute test time will only be required in the case of passed tests or small leaks close to the limit of sensitivity of the instrument.

The results of the test protocol described in this document show the functional performance of the Palltronic Guardian instrument.

2.1 Summary of Technology

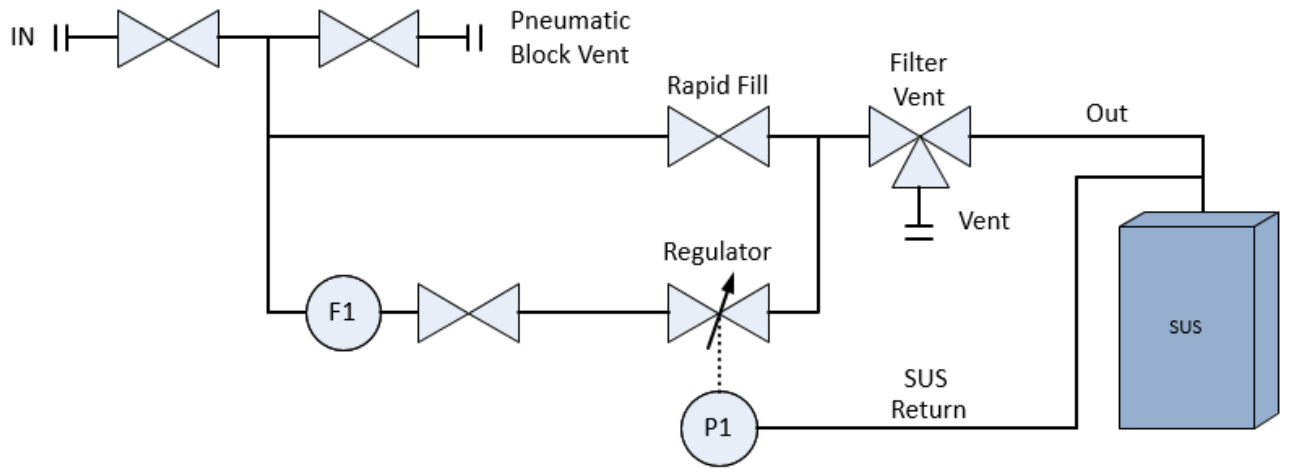
The core technology of the Palltronic Guardian instrument measures the volume of air required to maintain a constant test pressure in the pressurized volume. The measurement module consists of high-precision pressure transducers and a mass flow meter.

Figure 1 illustrates the pneumatic system, controlled by custom software inside the instrument. A touch-screen Human Machine Interface (HMI) is provided for data entry and display.

The mass flow meter (F1) feeds through a dedicated pressure regulator. The regulator is controlled by a pressure transducer (P1), which measures the pressure close to the SUS via a dedicated pneumatic hose. This configuration provides high accuracy for pressure control and flow measurement.

Figure 1.

Palltronic Guardian instrument pneumatic system



2.2 Summary of Qualification Testing

Accuracy and precision for both the pressure measurement (at P1) and the flow measurements (at F1) were verified using external reference meters during the measurement phase of the test.

Low volume SUS with artificial leaks, laser-drilled in, were characterized by hole size and tested under the same pressure over a large number of repeat tests.

The above tests verify the instrument's accuracy and repeatability.

3 Qualification of Pressure Measurement and Pressure Control

3.1 Introduction

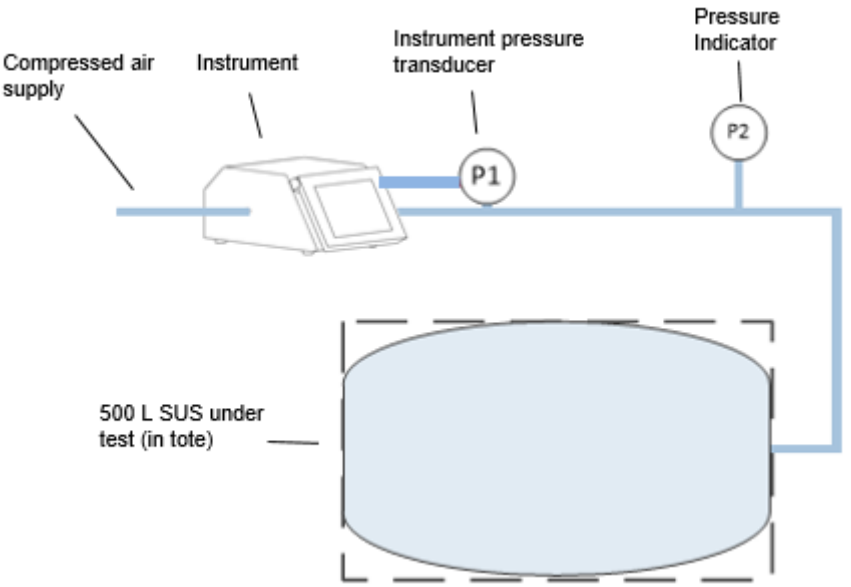
The goal of this test was to demonstrate that the Palltronic Guardian instrument maintains a stable and accurate test pressure during the measurement phase of a SUS leak test.

3.2 Test Method

The instrument was connected to a SUS, incorporating a 500 L Allegro™ 3D storage biocontainer installed in a suitable tote, according to the Palltronic Guardian Instruction for Use (IFU)[3]. A digital pressure indicator (Druck DPI 104, model number DPI 104, accuracy 0.15% full scale 0.7 bar) was used as a reference pressure gauge (P2) and connected inline between the instrument and the SUS being tested (Figure 2)

Figure 2.

Test set up for pressure measurement and control testing



A standard leak test at 20 mbar test pressure was performed, with a measurement phase of 60 minutes. The readings from the pressure indicator and the Palltronic Guardian instrument were recorded every 300 s, starting at 60 s into the measurement phase. The qualification was performed with two different test instruments (serial number [s/n] 15009699 and 17009899).

3.3 Results

The test results are detailed in Table 2 and Table 3.

Table 2.

Stability of test pressure during measurement phase at 20 mbar for a 500 L Allegro 3D storage biocontainer, using Palltronic Guardian instrument s/n 17009899

Test Time (s)	Reference Pressure (mbar)	Palltronic Guardian Instrument Pressure (mbar)	Deviation (mbar)
60	19.85	20.00	0.15
300	20.05	20.00	-0.05
600	20.08	20.00	-0.08
900	20.09	20.00	-0.09
1200	20.12	20.00	-0.12
1500	20.11	20.00	-0.11
1800	20.10	20.00	-0.10
2100	20.10	20.00	-0.10
2400	20.10	20.00	-0.10
2700	20.09	20.00	-0.09
3000	20.10	20.00	-0.10
3300	20.10	20.00	-0.10
3600	20.10	20.00	-0.10

Table 3.

Stability of test pressure during measurement phase at 20 mbar for a 500 L Allegro 3D storage biocontainer, using Palltronic Guardian instrument s/n 15009699

Test Time (s)	Reference Pressure (mbar)	Palltronic Guardian Instrument Pressure (mbar)	Deviation (mbar)
60	20.00	19.97	0.03
300	20.00	19.99	0.01
600	20.00	20.01	-0.01
900	20.00	20.02	-0.02
1200	20.00	20.03	-0.03
1500	19.98	20.04	-0.06
1800	19.99	20.06	-0.07
2100	20.01	20.06	-0.05
2400	20.00	20.07	-0.07
2700	20.00	20.09	-0.09
3000	20.00	20.09	-0.09
3300	20.01	20.12	-0.11
3600	19.95	20.08	-0.13

3.4 Summary

During the test, the maximum deviation from the set point of 20 mbar was 0.12 mbar across both Palltronic Guardian instruments. The maximum offset between the pressure indicator and the instruments was 0.15 mbar, which occurred at the start of the test for instrument s/n 17009899.

Pressure control of the instrument is confirmed to be accurate to within the specification of ± 0.3 mbar, which equates to a 1.5% margin of error.

4 Qualification of Flow Measurement and Flow Accuracy

4.1 Introduction

The goal of these tests was to qualify the accuracy and reproducibility of the Palltronic Guardian instrument's flow measurement system over the entire measuring range of 20–2000 mL/min. Low flows were used because this range is critical at the intended limits of detection.

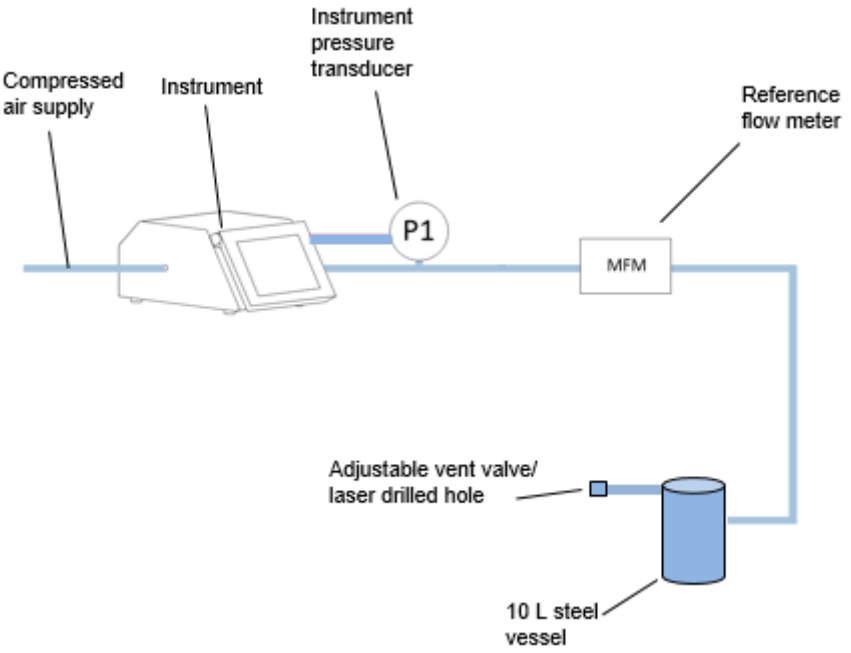
4.2 Test Method

The instrument was connected, according to the Palltronic Guardian IFU[3], to a 10 L steel vessel. An adjustable vent valve (for high flow rates) or laser-drilled hole welded on a low volume Allegro 2D biocontainer (for low flow rates) was connected to a port on the steel vessel. The use of a rigid vessel avoided any flow contribution due to SUS film expansion; the flow contribution from the expansion of the low volume 2D biocontainer was deemed negligible.

A reference mass flow meter was connected between the Palltronic Guardian instrument and the steel vessel (Figure 3). For flow rates below 350 mL/min, a Burkert mass flow meter was used (model 8741, accuracy ±0.8%, measured value ±0.3% full scale, range 0–500 mL/min). For the flow rates above 350 mL/min, a Vogtlin mass flow meter was used (model Red-y, accuracy 1.5% full scale, range 0–5 L/min).

Figure 3.

The flow measurement qualification set up



A SUS leak test was run at 20 mbar test pressure, with a 600 s measurement phase. When a rigid vessel is used, the background flow is negligible and the system can reach stability quickly, allowing a test time of 600 s to be used without compromising accuracy.

In the high-flow range above 350 mL/min, the flow rates of 1000 mL/min and 2000 mL/min were used to assess performance of the Palltronic Guardian instrument. Readings were taken from the reference mass flow meter throughout the measurement phase at 100 s intervals. Each test was performed twice.

In the low-flow range ≤350 mL/min, six flow rates between 20 mL/min and 350 mL/min were used to assess performance of the Palltronic Guardian instrument. Readings were taken from the reference mass flow meter during the last 50 s of the measurement phase. This flow range was critical, representing the expected flow rates at the target minimum detectable leak rates of the instrument, so each test was performed 10 times.

In total, three different Palltronic Guardian instruments were used across the tests (s/n 14009599, 15009699, and 17009899) and the mean results were reported.

An average of the last 50 s of logged flow values during the measurement phase was used to calculate the mean flow rate for the Palltronic Guardian instrument and the Burkert flow meter. For the flow rates above 350 mL/min, measured with the Vogtlin flow meter, manual readings were taken from the on-screen display at 100 s intervals, due to no digital logging capability.

4.3 Results

Figure 4.

Accuracy of flow measurements for different flow rates across the measurement range

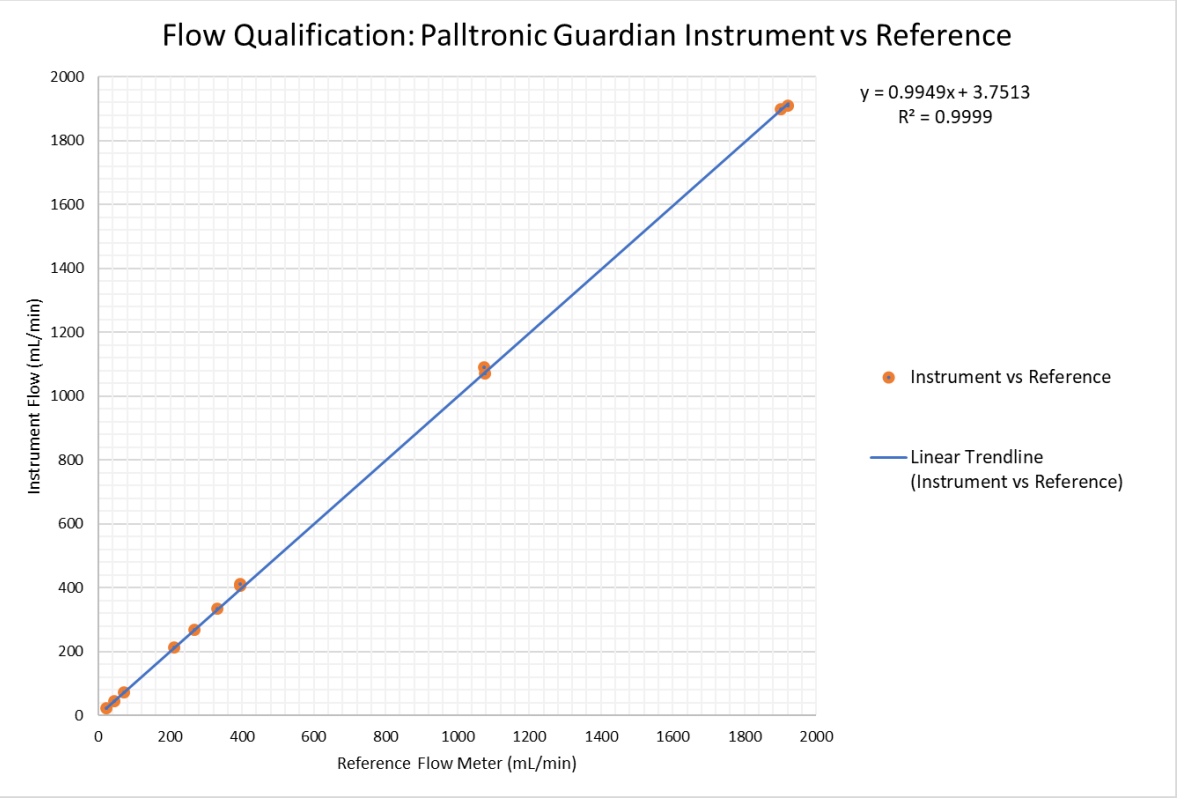
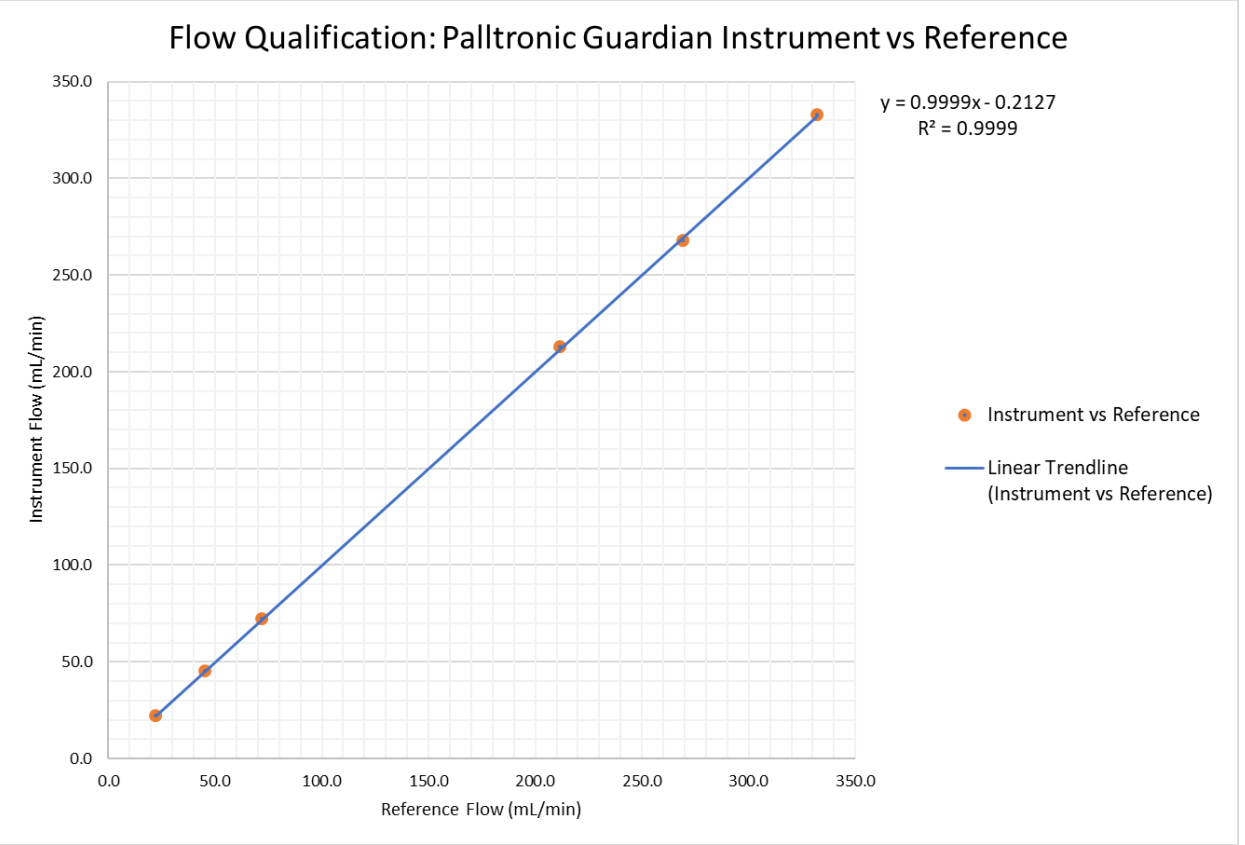


Figure 5.

Accuracy of flow measurements for different flow rates; close-up of low-flow range



4.4 Summary

The flow data from three Palltronic Guardian instruments was compared with the reference, Figure 4. The flow rates up to 350 mL/min are shown in Figure 5 to highlight the accuracy of the critical measurement range. Linear trend lines are plotted for both the full range up to 2000 mL/min and the critical measurement range up to 350 mL/min. The equation of the straight line is included. The R^2 values are 0.9999 for both regions demonstrating almost all variability being described by the linear model, indicating a linear fit. For the lower flow range, from the equation of the trend line, the gradient is 0.9999 indicating a linear fit. The intercept value shows a deviation of -0.2127 mL/min between the instrument and the reference. For the critical measurement range below 350 mL/min, the maximum deviation between the instrument and the reference flow meter was 1.3% (corresponding to 0.6 mL/min for the test at 45 mL/min). For all tests in this range, the standard deviation is less than 1.5% of the mean flow rate. The following calculation was used for all standard deviations:

$$\sigma = \sqrt{\frac{\sum(x-\mu)^2}{N}}$$

σ = Population standard deviation Σ = Sum of x = Individual value μ = Population mean N = Sample

The instrument to instrument variation was also assessed at each data point. For the critical measurement range below 350 mL/min, the highest deviation between the instruments (s/n 15009699 and 14009599) was a 1.4% offset for the data point at 330 mL/min. Flow measurement is confirmed to be accurate within the specified limits of ±1.5% reading ±0.5% full scale (from manufacturer specification of flow meters where full scale is 2000 mL/min).

5 Qualification of Flow Measurement through Holes

5.1 Introduction

The goal of these tests was to qualify the accuracy and reproducibility of the Palltronic Guardian instrument's flow measurement system across a large number of replicate tests on a range of hole sizes.

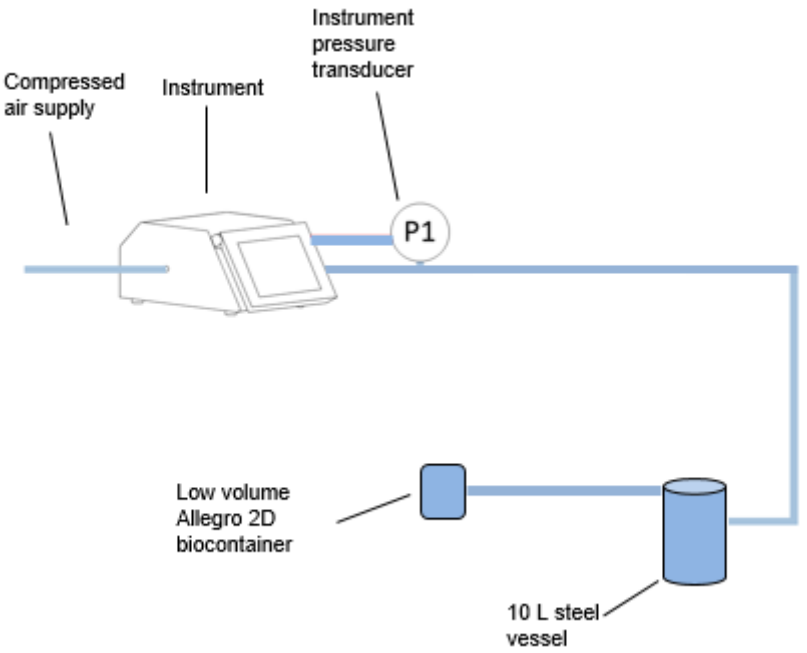
5.2 Test Method

The instrument was connected, as per Section 4.2, to a 10 L steel vessel. A laser-drilled hole welded on a low volume Allegro 2D biocontainer was connected to a port on the steel vessel. The use of a rigid vessel avoided any flow contribution due to SUS film expansion; ensuring only the flow through the hole was being measured.

Holes ranging in diameter from 50 µm to 450 µm (at 50 µm intervals) were tested in sequence at a test pressure of 20 mbar, Figure 6. A standard leak test was performed with a duration of 600 s, with a minimum of 40 replicate tests being performed for each hole size using three different Palltronic Guardian instruments (s/n 11009299, 14009599, and 15009699). This protocol allowed flow rate to be correlated with leak hole size at 20 mbar.

Figure 6.

Flow through hole test set up



5.3 Results

The flow data for each hole size, reported as ‘Mean Flow Rate’ and ‘Standard Deviation’, is shown in Table 4.

Table 4.

Mean flow rate and standard deviation for flow through laser-drilled holes at 20 mbar test pressure

Hole Size	Mean Flow through Hole (mL/min)	Standard Deviation (mL/min)
50 µm	5.2	0.5
100 µm	22.0	0.5
150 µm	45.3	2.8
200 µm	71.7	1.8
250 µm	122.7	2.2
300 µm	167.5	1.0
350 µm	216.6	2.0
400 µm	276.4	2.8
450 µm	345.2	4.3

The largest deviation from the mean was for the 450 µm test, which equated to 0.5% of the mean, equating to ± 1.83 mL/min. The margin for error was less than 5% of the mean across the full range of hole sizes, highlighting strong accuracy of the flow measurement over a large number of tests.

6 References

1. GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems

2. GAMP 5: Appendix D5 ‘Test Strategy’; page 201, ‘4.2.3 Using Results of Supplier Assessments’

3. Pall USD 3343, Instructions for Use: Palltronic Guardian Integrity Test Instrument

Visit us on the Web at www.pall.com/biotech

Contact us at www.pall.com/contact

Corporate Headquarters
Port Washington, NY, USA
+1.800.717.7255 toll free (USA)
+1.516.484.5400 phone

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone

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