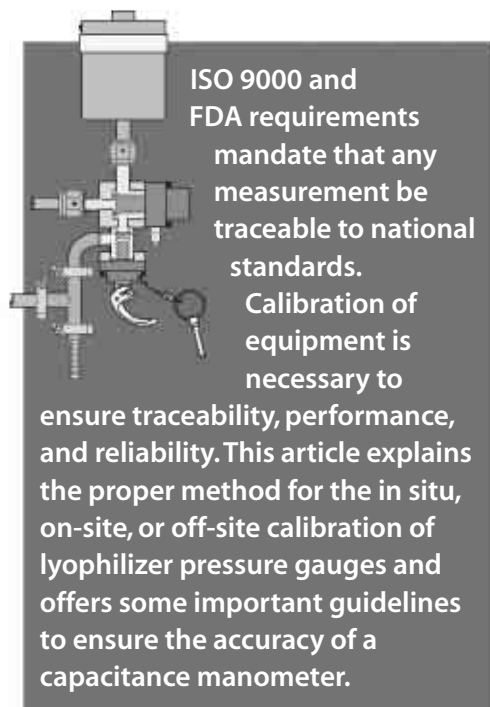


Calibration of Lyophilization Pressure Gauges

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Calibration of gauges used to measure pressure (vacuum) during freeze-drying lyophilization processes fulfills two functions: quality assurance and equipment performance. Calibration provides traceability of pressure measurements, which is necessary for compliance with ISO 9000 and FDA requirements mandating that measurements be traceable to national standards. In the United States, these standards are held by the National Institute of Standards and Technology (NIST). Such guidelines ensure that suppliers and customers are speaking the same language. With regard to performance, calibration helps improve product reliability and production time for lyophilization processes. Lyophilizer pressure affects the heat transfer from the shelf to the product, which in turn affects the drying time. A pressure that is higher than required may cause product loss, and pressure that is too low increases drying time (1). Accurate pressure measurements, obtained by periodic calibration, are required for optimal quality and productivity.

Lyophilizer vacuum measurement

The pressure during lyophilization generally ranges from 300 to 50 mtorr. Three types of pressure measurement devices operate within this range: the McLeod mercury manometer, thermal conductivity gauges, and capacitance manometers. The McLeod gauge no longer is used because it must be manually operated and can be a source of mercury contamination. Thermal conductivity (TC) gauges are on many lyophilizers, but these sensors have the drawback that the pressure reading is determined by the rate of heat loss from a hot wire to its surrounding environment. The reading depends on the heat-transfer characteristic of the vacuum medium, which depends on both pressure and gas species. Gauge manufacturers usually calibrate TC gauges relative to nitrogen. However, the most commonly used gas in lyophilization is water vapor, and under this condition a nitrogen-calibrated TC gauge will read nearly 50–100% higher than the true pressure (2). To further complicate matters, during a lyophilization process the dominant gases continually change from air to water vapor.

A capacitance manometer offers the most accurate method of lyophilization pressure measurement. A capacitance manometer provides a direct-pressure measurement that is independent of the gas composition because it depends on the force of the gas on a thin diaphragm. Pressure causes the diaphragm to de-

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flect from a zero position in which the pressure on the gauge is less than the gauge resolution. The deflection is measured by the change in capacitance between the diaphragm and adjacent electrodes. The accuracy of a capacitance manometer can be $\pm 0.5\%$ of the reading or better within a four-decade range. Heated capacitance manometers are available that prevent vapor condensation within the gauge. Ambient temperature control also reduces zero drift.

Another advantage of using capacitance manometers is that the 0–10 dc volt output signal can be used for pressure control. Pressure controllers are available that use the capacitance manometer output to control a mass-flow controller or valve. The control system can be semiautomated or totally automated with the addition of a computer equipped with an A/D converter and an RS-232 link.

Manometer calibration

Calibration is the transfer of measurement accuracy from a device of known accuracy (the standard) to a device of unknown accuracy (the unit under test, or UUT). The standard, by definition, is more accurate than the UUT and has known and documented sources of error. The operating principle and output characteristics, and hence the calibration procedures, are relatively uniform and standardized for all capacitance manometers, regardless of manufacturer.

Two types of standards exist: primary and transfer. Primary standards determine a measurement in terms of fundamental properties such as mass, length, frequency, and temperature. Transfer standards, sometimes called *secondary standards*, generally are calibrated by a primary standard. The transfer standard then is used to calibrate a measurement device of less accuracy. Transfer standards are used because calibrating measurement devices with primary standards usually is not feasible or cost effective.

Transfer standards must be traceable to national standards such as those maintained by NIST. NIST standards, in turn, are traceable to international standards defined by the International General Conference on Weight and Measures. Traceability implies that the sources of measurement error are known and documented. Documentation can be a test number, a report of calibration, or both. A calibration can be claimed as traceable to NIST standards if evidence of traceability is established, the calibration interval is not exceeded, and the calibration is performed properly.

Consider a capacitance manometer used to measure the pressure in a lyophilizer. The stated accuracy of this type of manometer typically is $\pm 0.25\%$ of reading. This manometer is calibrated with a transfer standard having an accuracy of $\pm 0.05\%$ of reading. The transfer standard is calibrated with a dead-weight tester (a primary standard) with an accuracy of ± 0.01 of reading. The dead-weight tester is calibrated at NIST with a National standard accurate to $\pm 0.005\%$ of reading. As long as all instruments in the chain have documented calibration certificates and are used within the recall date and the quality assurance documents are followed, the manometer on the lyophilizer is traceable to NIST. In reality, for cost effectiveness, this traceability trail typically is even longer with the addition of three or four addi-

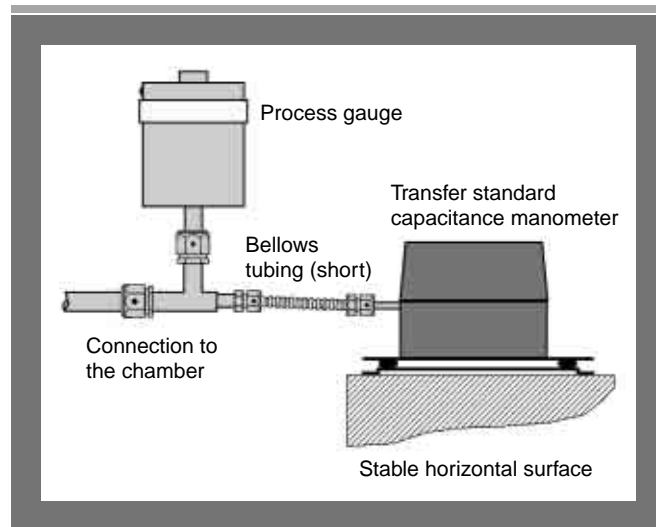


Figure 1: A transfer standard next to a UUT with a short connecting bellows tube and a T-fitting.

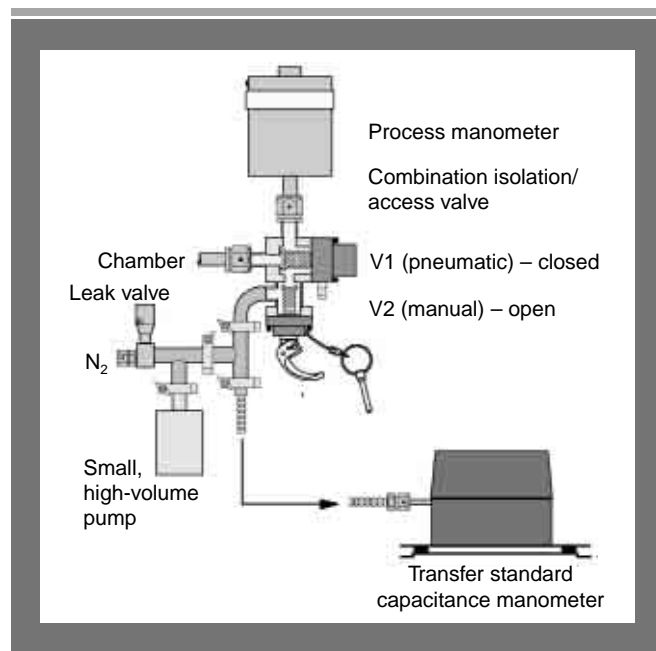


Figure 2: Connection of process gauge and transfer standard to an auxiliary high-vacuum pump and pressure-control system. The IDA valve stays with the tool. The auxiliary pump unit with precision leak goes to the standard. The design is not optimized for controlling pressure drops.

tional transfer standards included in the chain. More-complete explanations of primary and transfer vacuum standards and references to the calibration literature can be found in vacuum technology texts (3).

Calibration site. Vacuum gauge calibration can be performed in situ, on site, or off site. The vacuum gauge can be calibrated in situ without removing it from the lyophilizer. Alternatively, the gauge can be removed from the lyophilizer and calibrated on site or brought to an off-site calibration laboratory. The choice of calibration location determines the cost, the type of calibration equipment required, and the turnaround time.

In situ calibration. In situ calibration requires that the transfer standard be connected to the vacuum chamber by means of a port located as close to the UUT as possible. This config-



Figure 3: Self-contained portable vacuum gauge calibration system.

uration is particularly important for systems that do not have positive shutoff to the vacuum pump. In such systems, the internal lyophilizer volumes closest to the vacuum pumps will be significantly smaller than those near the gas inlet. If the calibration port cannot be adjacent to the measurement device port, it should be placed the same distance (in terms of vacuum conductance) from the inlet gas and vacuum pump as the UUT.

Because the pressure for the lyophilization process is less than 1 torr, gas flow is in the transition-flow regime. This means that vacuum conductance plays a large role in accurate pressure readings. For this reason, the line lengths between the standard and the UUT should be as short and as large in diameter as possible. The optimum location would have the standard mounted on a T-connection next to the UUT as shown in Figure 1. In many situations, this design is not practical and compromises must be made. Because the conductance of a short tube is directly proportional to its length but proportional to the square of its diameter, increasing the diameter of a connection tubing relative to the standard is preferred over decreasing its length. One must allow sufficient time for equilibrium to be reached and the proper pressures to be read by the standard and the UUT. The time that is required depends upon the vacuum conductances in the system.

An in situ calibration requires a transfer standard and readout. High-accuracy, temperature-controlled capacitance manometers are the typical accepted transfer standards. The minimum recommended warm-up time for these measurement standards is four hours.

In situ calibration requires that the lyophilizer vacuum pumps and pressure controller establish the pressure setpoints. Unfortunately a lyophilizer vacuum pump will not produce a low enough vacuum to properly zero capacitance manometers. A 1-torr full-scale manometer has a recommended zeroing pressure of 1×10^{-5} torr, and a typical mechanical pump has a base pressure of 1×10^{-3} torr. If a leak detector is available, it may be attached as an auxiliary pump to establish a low base pressure. If a high-vacuum pumping station is available at an alternative location, it can be used to zero the standard, which then can be valved off and moved to the lyophilizer. The UUT can be adjusted to read the same as the standard at the lowest attainable pressure.

The preferred calibration setup is a pressure-controlled high-vacuum pumping system with the UUT isolated from the system (see Figure 2). The valve between the UUT and the chamber allows the isolation of the chamber and the UUT yet still allows connection to the calibration system.

On-site calibration. With this method the UUT is removed from the lyophilizer and connected to a calibration manifold, thereby

eliminating conductance and dynamic effects. This method is recommended if a long vacuum line is required to connect the standard to the lyophilizer. On-site calibration requires a high-vacuum pumping system, a standard, and a pressure-control system. Using this method, one can calibrate quickly the UUT and replace it on the lyophilizer without the need for a spare replacement gauge. Figure 3 shows a portable, self-contained vacuum gauge calibration system. This system also can be used for in situ calibration.

Off-site calibration. To conduct off-site calibration, one removes the measurement device and sends it to a calibration laboratory, which may or may not be located at the facility. This calibration requires a spare calibrated gauge to replace the gauge sent out for recalibration. The advantages of this method are that calibration equipment need not be kept on the production floor and that downtime is minimal when spares are used.

Calibration guidelines

A few important guidelines should be followed to ensure accurate calibration of a capacitance manometer.

To achieve temperature stability, the manometer should be operated for four hours after power has been applied. The manometers also must be at normal operating temperatures. This recommendation applies to the standards as well as to the UUT.

The capacitance manometer must be zeroed properly before a valid calibration can be performed. Proper zeroing is critical. One should keep in mind that capacitance manometers measure absolute pressure referenced to a “perfect” vacuum. The standards also must be zeroed to obtain a common reference point for comparing the reading of the standard with that of the UUT. The manometer must be zeroed at a pressure low enough to exceed the resolution of the manometer. A recommended zeroing pressure is four decades below full scale. Therefore, a 1-torr, full-scale manometer requires a pressure of 1×10^{-4} torr for proper zeroing. An ionization gauge should be used to verify a low zeroing pressure.

Six data points usually are adequate to ensure that a process capacitance manometer is within calibration specification. Recommended calibration points are at 10, 20, 40, 60, 80, and 100% of full-scale reading.

If the capacitance manometer has a full-scale pressure of 1 torr or lower, a correction for thermal transpiration is required for maximum accuracy. Thermal transpiration errors result when the pressure is in the molecular-flow regime and a tube connects two volumes at different temperatures. The error in pressure is proportional to the square root of the ratio of the absolute temperatures of the two connecting regions (4). Thermal transpiration errors decrease as the pressure increases and become negligible as the pressure approaches 1 torr. The simplest way to avoid thermal transpiration errors is to ensure that the standard, the UUT, and the connecting plumbing all are at the same temperature. If required, tables of correction factors can be obtained from the manufacturer of the calibration equipment.

Calibration and zeroing intervals. Establishing appropriate calibration intervals requires the collection of historical data. The lyophilization process and the treatment of the manome-

ter play a large role in the determination of how often the manometer requires zeroing and calibration. For example, if a 1-torr, full-scale manometer routinely is exposed to atmospheric pressure, its zero should be checked more frequently than the zero of a manometer that is isolated with a positive shut-off valve whenever the process chamber is brought up to atmosphere. An isolated manometer also will require less frequent calibration. A manometer exposed to a harsh environment must be recalibrated more often than one that is only exposed to benign gases.

Steam sterilization of a lyophilization unit, typically performed at pressures of 35 psia, will require an un-isolated manometer to be checked more frequently. Initially, one should start with zeroing intervals of once per month and calibration intervals of once every 2–3 months for a steam-sterilized manometer. The calibration intervals of manometers not exposed to steam sterilization may be extended to beyond three months.

Manometers that are isolated from atmospheric pressure may have quite long intervals between zeroing and calibration requirements. For these devices, one should maintain a history of in- and out-of-tolerance conditions and adjust the interval to maximize the time between calibrations. A good goal is to establish a calibration interval in which 70% of the calibrations are within specifications. This specification may not have to be that of the manometer manufacturer, but the specification should be such that the lyophilization process is consistent and reliable. Statistical studies have indicated that a 70% in-tolerance goal is an optimum trade-off for system perfor-

mance and cost effectiveness for calibration. The ultimate goal when establishing calibration intervals is to ensure process reliability and yield at minimum cost.

Conclusion

Calibration of lyophilization process pressure measurements is necessary to meet ISO 9000 and FDA requirements. Calibration of pressure measurement devices also ensures optimum lyophilization and increased batch reliability and yield. The development and management of a calibration program is neither trivial nor inexpensive, and some thought must be put into the determination of the best and most economical approach for calibration. The various calibration approaches — in situ, on site, and off site — have individual setup and program maintenance costs. Calibration approaches can be combined to establish the optimum calibration program. When established correctly, a calibration program can meet all the quality assurance requirements and be cost effective.

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