



Understanding MFC Metrology & Calibration

Factors Impacting MFC Performance in
Biopharmaceutical Process Systems

BROOKS[®]
INSTRUMENT

Beyond Measure

Mass flow controllers

(MFCs) precisely deliver fluids, mainly process gases, into bioreactors and other process systems. The stable, reliable and repeatable delivery of these gases is a function of four key factors:

- The quality and sophistication of the MFC's design
- The application set-up, which covers the acceptable level of fluid delivery accuracy a given process requires
- Metrology: what specific techniques are used to test, measure and confirm MFC accuracy
- Calibration checks: how an MFC is calibrated on an ongoing basis

It's common to extensively investigate an MFC's technical characteristics and capabilities, as well as analyze and ensure that the MFC technology chosen fully satisfies each operation's unique process

requirements. Equally important is the role that metrology, which includes testing reference standards and calibration practices, plays in the performance and long-term value of biopharmaceutical process equipment MFCs.

In this eBook, we will provide a deeper understanding of metrology's role in how MFCs are used and managed in these systems. This includes:

- The key elements of MFC accuracy and why calibration is important
- How MFC calibration reference standards are used and why selecting the right standard matters
- The role that "uncertainty" plays in calibrating MFCs
- Factors that can lead to improper calibration

**Understanding how metrology,
reference standards and
calibration affect long-term
MFC performance – and how you
can ensure proper calibration –
can help sustain biopharmaceutical
process system results.**

Elements of accuracy

The following technical concepts are the elements essential to understanding an MFC's accuracy.

CMC (Metrology Uncertainty)

Calibration Measurement and Capability (CMC) is a measure of how closely the calibration method represents "truth" or absolute accuracy. No calibration equipment or method can perfectly reflect "truth"; therefore, the uncertainty associated with CMC is always >0 . CMC captures both the inaccuracy of the components of the calibration system and the statistical variation during its use.

Linearity

All MFCs are inherently nonlinear to some degree. To address this, a curve-fit across the calibration points is applied. Multiple data points are collected during calibration, followed by applying the best curve-fit using a given methodology (ex. third or fourth order polynomial) across that set of calibration data.

Repeatability

This represents the device's ability to repeat a flow measurement under the same conditions in a short period of time. If a specific flow rate is used repeatedly in rapid succession without changing conditions, the distribution of the flow measurement data points (in excess of the variation in the CMC) indicates the MFC's repeatability.



Elements of accuracy

Reproducibility

Repeatability describes how an individual device performs; reproducibility is how well a flow measurement can be repeated under the same conditions from device to device.

Hysteresis

This element covers an MFC's ability to accurately perform across a full range of flow rates—on the way up the scale and on the way down. For example, when calibrating, start the flow rate at zero and go up 200 cubic centimeters a minute. Then, start from a higher flow rate and decrease to 200 centimeters per minute, measuring and recording the device's ability to provide an accurate reading in each scenario.

TOTAL ACCURACY

Each of these elements contributes some amount of uncertainty to the accuracy of an MFC. The sum of those uncertainties equates to the device accuracy.

MFC calibration: systems, processes & procedures

Metrology and calibration labs utilize a variety of instrumentation technologies and appropriate calibration reference standards. However, if process equipment end users choose to perform their own MFC calibration verification and/or recalibration, selecting the correct and most trustworthy reference standard is crucial, whether for tabletop laboratory research bioreactors, pilot plants for scaling up new processes or full-scale production systems.

Selecting the most appropriate reference standard starts with defining the process uncertainty requirements. The uncertainty in the flow measurement is a combination of the uncertainties due to systematic errors and those due to random variations (typically referred to as type B and type A errors). To accomplish this, it makes sense to compare the measurements being made with those of the national standards.

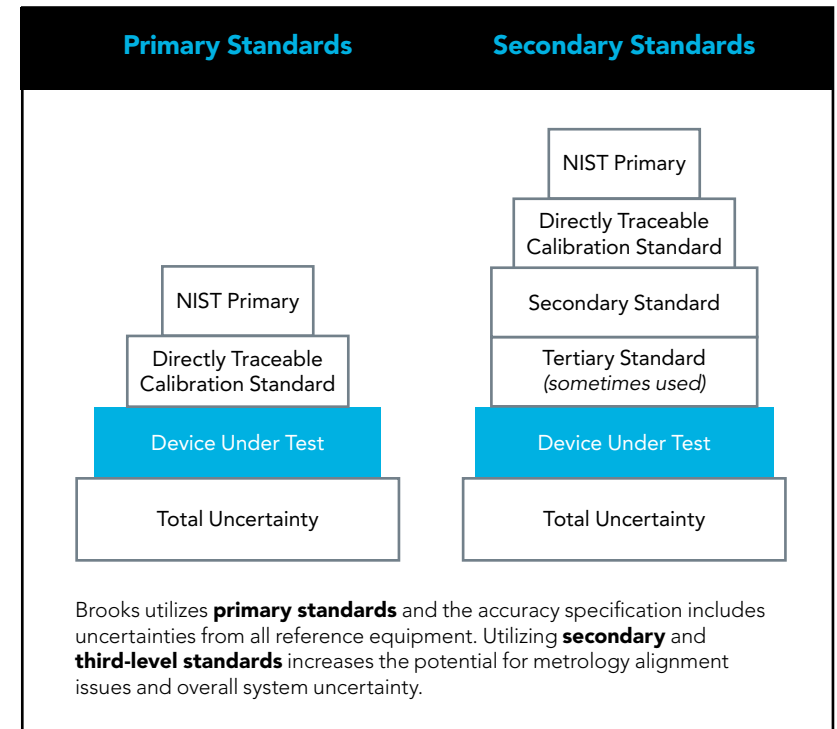
MFC calibration: systems, processes & procedures

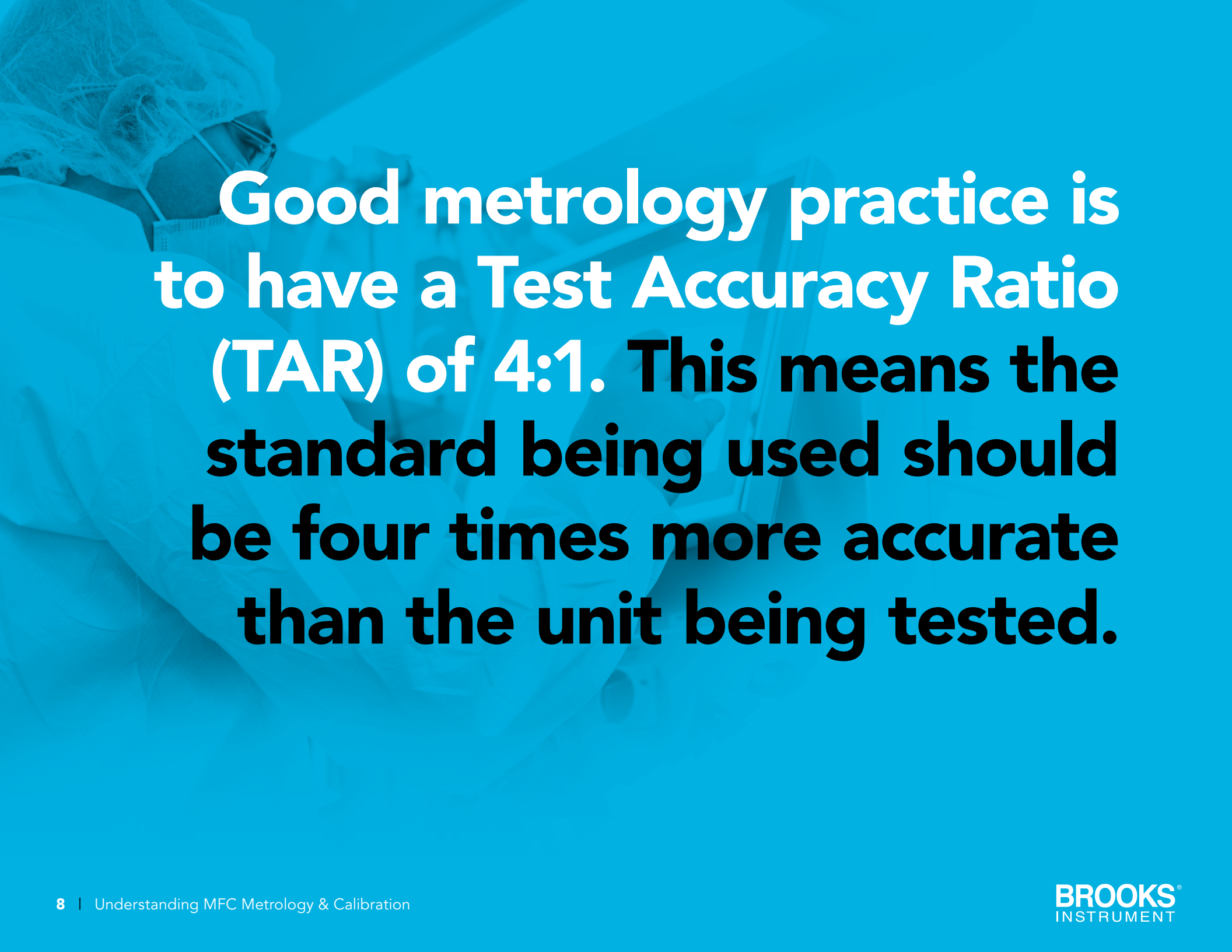
Two types of flow standards

There are two types of standards that can be selected for MFC reference standards (typically done by the manufacturer):

Primary standards: These can be directly traced to volume (length), time, temperature and pressure readings, which are established and maintained by recognized standards bodies, such as the National Institute of Standards and Technology (NIST).

Secondary standards: Transfer or secondary standards are MFCs or other flow measurement devices that are calibrated against another standard. These secondary standards are not directly traceable to a primary standard and are one step further removed from National Laboratory traceability.



A person wearing a white lab coat, a white hairnet, and a white face mask is working with a piece of equipment. The background is a solid blue color.

Good metrology practice is to have a Test Accuracy Ratio (TAR) of 4:1. This means the standard being used should be four times more accurate than the unit being tested.

MFC calibration: systems, processes & procedures

In cases where a flow standard does not meet the 4:1 recommendation for TAR, an increase to the allowable “error band” on accuracy verifications should be considered. However, there are some inherent risks in establishing and managing your own levels of MFC uncertainty. Brooks metrology experts routinely work with bioprocessing systems OEMs, systems integrators and end users to establish flow control limits.

For Brooks, our MFC flow metrology/traceability starts with primary flow standards that are traceable to the National Institute of Standards and Technology (NIST) or other similar traceable International Metrology Labs with the 4:1 TAR.

Table 1. Primary gas flow calibration capabilities within the NIST Fluid Flow Group¹.

Flow Standard	Flow Range (L/min)	Gas	Pressure Range (kPa)	Uncertainty (k = 2) (%)
34 L PVTt	1 - 100	N ₂	100 - 7000	0.03 - 0.04
	1 - 100	Air	100 - 1700	0.05
	1 - 100	CO ₂	100 - 4000	0.05
	1 - 100	Ar	100 - 7000	0.05
	1 - 100	He	100 - 7000	0.05
677 L PVTt	10 - 150	N ₂	100 - 800	0.02 - 0.03
	10 - 2000	Air	100 - 1700	0.05
26 m ³ PVTt	860 - 77600	Air	100 - 800	0.13

1. Wright, John D., “Gas Flowmeter Calibrations with the 34 L and 677 L PVTt Standards”, NIST Special Publication 250-63

MFC calibration: systems, processes & procedures

Brooks is ISO/IEC 17025 accredited with extensive understanding and documentation of these measurement uncertainties and has defined processes to control them when calibrating Brooks MFCs.

There are approximately 30 different items specified in the 'uncertainty budget'; these are the factors that can contribute to uncertainty about the validation of the MFC's calibration.

They can include:

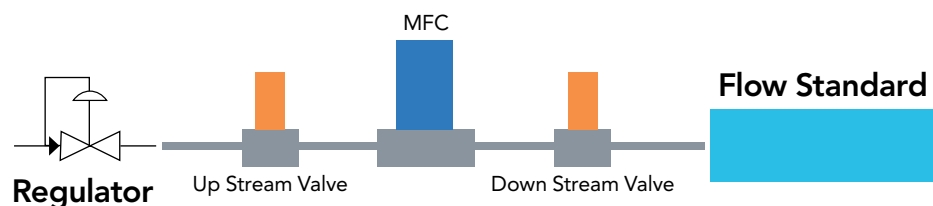
- Volume of the reference standard
- Temperature of the medium/gas before the reference standard
- Temperature of the medium/gas prior to the Device Under Test (DUT) ex. the MFC
- Time measurement – aligning flow and response
- Measurement of the flow on the DUT

Factors impacting accurate calibration

There are several external factors that affect calibrating MFCs to the selected standard. While not a comprehensive list, these are key issues you should rule out to ensure that your calibration efforts have inputs and outputs you can trust.

Pressure settings: MFCs are configured for a specific set of process conditions. If those conditions change, there may be some impact on the device performance. If there is a filter in line with the MFC and that filter begins to clog, the device may not be able to achieve full-scale flow, choking the flow to the MFC. The pressure also has some small impact on the device accuracy. It's important to confirm the actual process pressure to properly calibrate the MFC.

Pressure regulator movement: Typically, pressure regulators are the devices used to control pressure. If the regulator is not sized properly or is of poor quality, the regulator may not be able to keep the pressure on-target as flow rates change; pressure hysteresis, either higher than it's supposed to be or lower, may result. Confirming the pressure regulator is functioning properly is also recommended when conducting MFC calibration ... and during the actual process.



Factors impacting accurate calibration

Transient & dynamic temperature changes: Some biopharmaceutical production environments and calibration labs have large temperature swings. These can result in noise and temporary MFC shifts (no matter how well engineered and manufactured). Understanding how these temperature changes can affect MFC accuracy can help process managers and metrology technicians better plan calibration checks and recalibration maintenance intervals.

MFC warm-up: Thermal mass flow controllers should be thermally stable before a calibration check is conducted. Brooks Instrument recommends warming up its MFCs for 45 minutes to achieve best accuracy and to do calibration verification.

No flow when zeroing: Prior to zeroing a flow controller, you need to make sure that you don't have any flow. Because it's such a simple (and obvious) step, it's easy to overlook. If a gas line has blocking valves, either upstream or downstream of the MFC, it's recommended that you pressurize the device to the processed pressure, close the blocking valves to ensure that there's absolutely no flow and then zero the MFC.



Brooks: Experts in MFC metrology and performance

Stable and accurate MFC performance helps ensure highly accurate research results and consistent biopharmaceutical production. At Brooks, MFCs like our SLA 5800 Series have long-term zero stability, delivering decades of failure-free operation in a wide range of industrial process systems.

Our experience engineering ultra-precise MFCs equips us to understand the principles and application of world-class metrology practices. From Reynolds number, specific heat capacity, gas linearity and pressure drop, to Péclet number, Joule-Thomson effect, gas temperature effect and in-situ calibration, we can apply that knowledge to support defining acceptance limits, end-user metrology set-up and training.



How can we help?

The best way to ensure your MFCs are properly calibrated is to count on the Brooks Instrument Factory Service experts. When you trust Brooks to recalibrate your devices, you will be able to:

- Verify and ensure accuracy and reliability
- Increase production yields
- Optimize process resources
- Ensure process consistency
- Provide repeatable results and peace of mind

CONTACT US TODAY.

T: 215-362-3527

Brooks.Mktg@BrooksInstrument.com

Brooks Instrument
407 West Vine Street
Hatfield, PA
19440-0903 USA

All specifications are subject to change without notice.
Brooks is a trademark of Brooks Instrument, LLC.



© Copyright 2017 Brooks Instrument, LLC All rights reserved.

BROOKS[®]
INSTRUMENT

Beyond Measure