



Boosting Bioreactor Performance by Enhancing MFC Accuracy

Technology Insights for
Biopharmaceutical Production

BROOKS[®]
INSTRUMENT

Beyond Measure

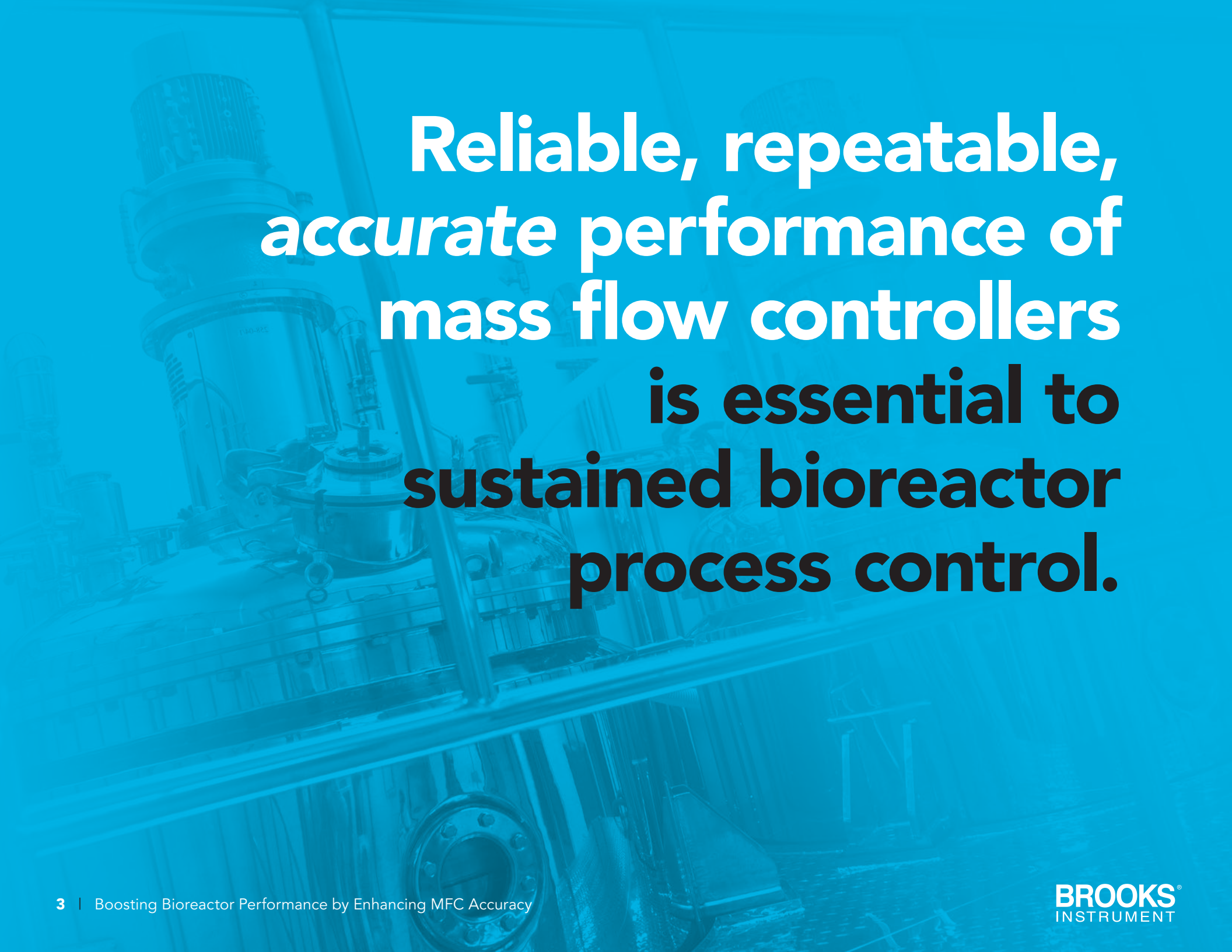
Advancing therapeutic value. Saving lives.

Today's biopharmaceuticals are revolutionizing healthcare. Pioneering drugs to treat complex cancers, chronic conditions such as rheumatoid arthritis and new gene-based therapies offer new hope to people around the world.

Researching and producing these cutting-edge biologics requires some of the most complex manufacturing processes known to man. The newest generation of bioreactors often uses complex botanical or mammalian cell cultures, which are highly sensitive and require a stable, precisely controlled growth environment.

To create those environments, bioreactors require accurate, stable gas control to maintain critical process parameters, combined with maximum uptime to reach target yields.





**Reliable, repeatable,
accurate performance of
mass flow controllers
is essential to
sustained bioreactor
process control.**

Serving biopharmaceutical process requirements

As the global leader in mass flow control (MFC) technology, Brooks Instrument has a deep understanding of the key role MFCs play in biopharmaceutical process yields and productivity.

Biopharmaceutical Requirements:

Tight control of DO and pH during experiments and production

NO unplanned downtime due to high cost of losing a batch or experiment

Ability to rapidly diagnose and resolve issues with bioreactors or fermentation equipment

Cost-effective method for adhering to regulatory requirements

Excellent technical support and rapid response for equipment service

Brooks Instrument Provides:

Stable and accurate control of gas supply (low drift)

Extremely reliable product — Mean Time Between Failure > 80 years

Free software communicates directly with devices in-situ to confirm accurate MFC performance

Externally accessible service port and calibration software supports in-situ verification or recalibration

Local technical support and equipment service across the globe

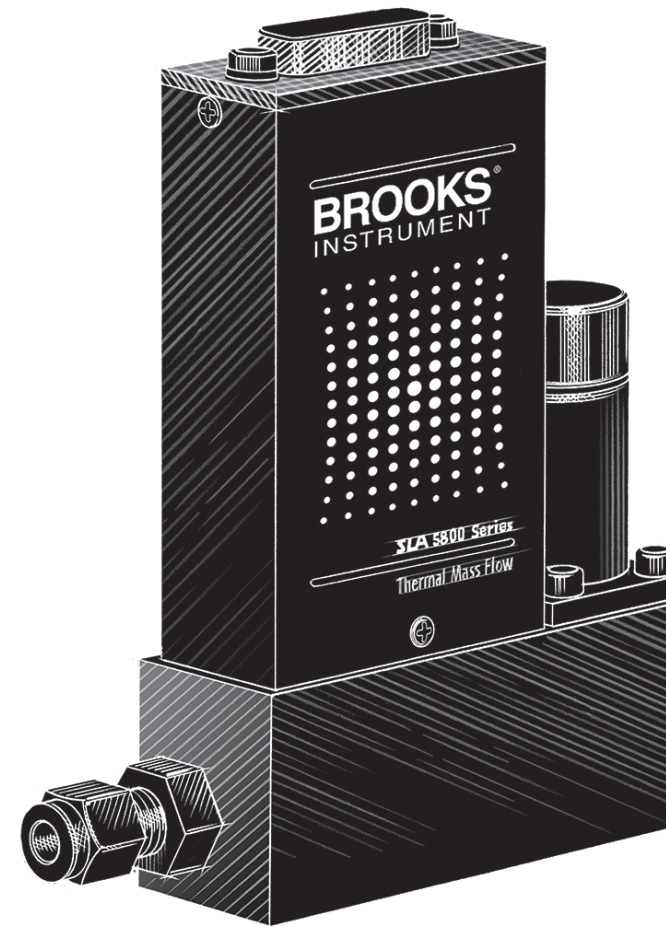
MFCs in bioreactors: Controlling critical flows

Two of the most critical factors governing cell culture yield are the levels of dissolved oxygen (DO) and the pH of the fermentation broth.

Tight control of dissolved oxygen by enriching the airflow with oxygen, or depleting it with nitrogen, regulates cell growth, reduces production of toxic cell by-products and, thus, increases reactor yields.

Tight control of pH with carbon dioxide flow is also critical for creating the proper growth environment. And while some bioreactor processes introduce acids and bases to achieve pH control, this approach can be 'harsh' on delicate mammalian cells; using CO₂ has been found to be an effective approach.

The MFC controls the delivery of the critical gasses that maintain the proper levels of both factors – and because typical bioreactor process runs can last up to 15 days, precise accuracy and continuous stable performance of the MFC are absolutely vital.





Just how accurate is accurate?

Imagine your process for producing a new cancer treatment calls for keeping the DO at a constant 35% of air saturation.

And one of the four bioreactors shows a significantly lower yield than the other three – yet all four MFCs recorded consistent totalized volumes of oxygen delivered to the bioreactor.

There could be many reasons why the yield dropped in the one system – what you need to do is be certain the MFC is actually delivering the flow rate stated in its technical documentation.

Three elements of MFC accuracy

CMC

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

This element is required because all Mass Flow Controllers are inherently nonlinear to some degree. To account for this, a curve-fit correction is applied to the devices. This is accomplished by collecting multiple data points during a calibration process and determining a curve fit equation. Linearity indicates how well the curve-fit correction worked.

+ Repeatability

This represents the device's ability to repeat a flow measurement under the same conditions in a short period of time. If an MFC was used to create a specific flow rate over and over again in rapid succession without changing conditions, the distribution of the flow measurement data points (in excess of the variation in the CMC) would indicate the repeatability of the MFC.

= 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.

By understanding these elements of MFC accuracy and how they relate to the device specifications, you can make informed decisions about the gas flow control technology for the bioreactors you choose.

Accuracy: The role of calibration

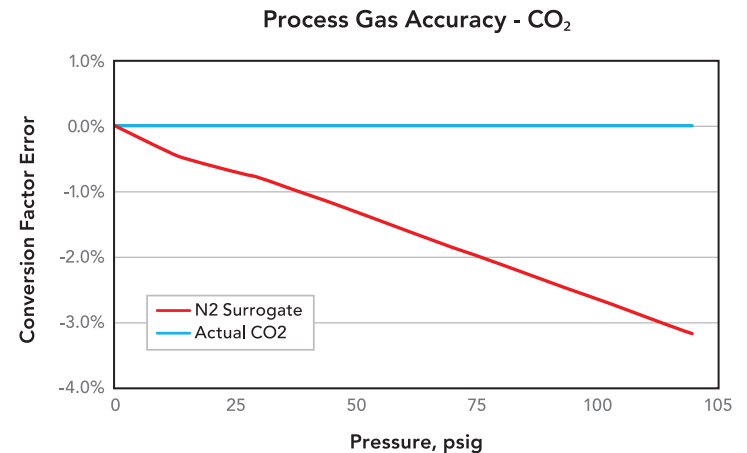
It's crucial to understand the role calibration plays in establishing the actual process gas accuracy of MFCs in bioreactors and other process equipment.

How calibrations work

MFC calibrations are typically done against a reference device or calibration standard using a surrogate calibration gas such as nitrogen or air. Surrogate gasses are used because it can be difficult and expensive to test and calibrate a device on the actual process gas.

When a surrogate gas is used, a conversion factor or conversion function is applied to that surrogate gas calibration to set up the device for the specified process gas.

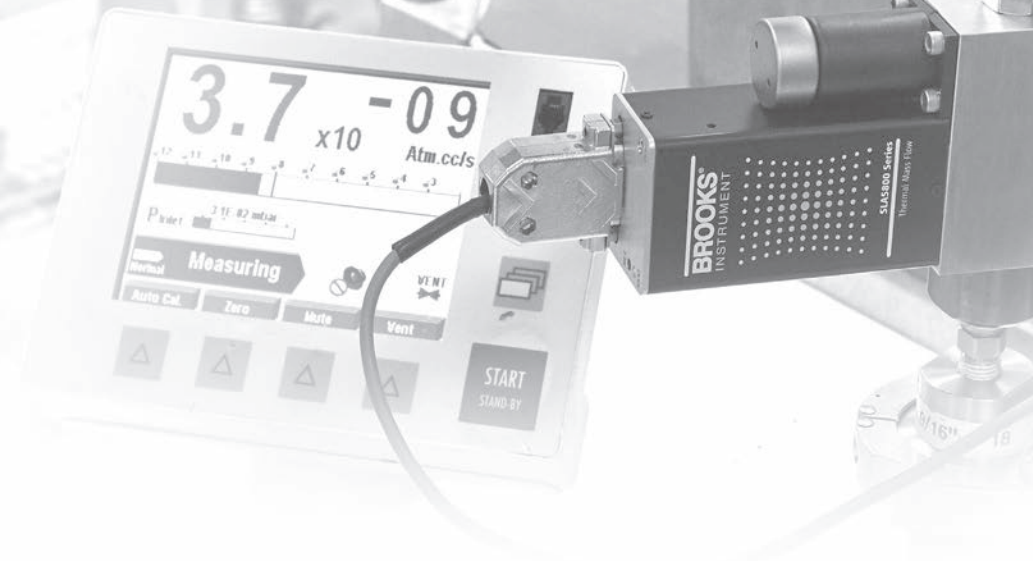
This conversion factor may introduce additional inaccuracy. For example, when calibrating an MFC for carbon dioxide delivery, using a surrogate gas can cause divergence in the actual gas flow.



Accuracy: The role of calibration

Nothing like the real thing

The best possible accuracy is delivered when the device is calibrated directly on the bioreactor's specified process gas - nitrogen, air, carbon dioxide - and at the process conditions for cell cultures undergoing production.





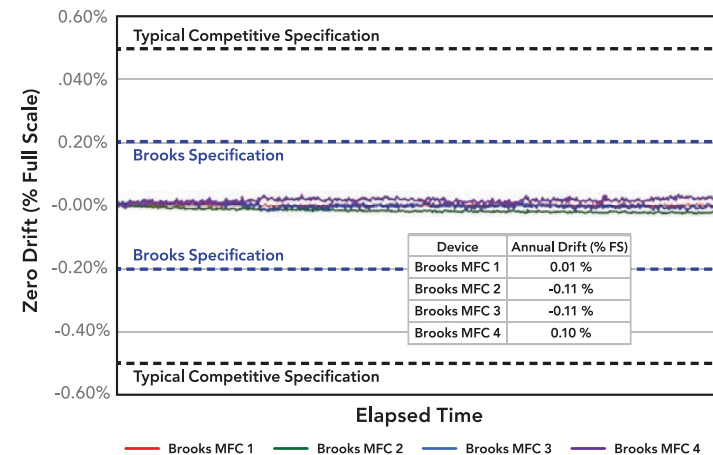
**At Brooks Instrument,
we use traceable
calibration standards for all
our mass flow calibrations
to ensure that we
consistently meet our
published specification.**

Stable MFCs are accurate MFCs

Bioreactor processes can run non-stop for up to 15 days – so stable gas control is essential to maintain critical process parameters, combined with maximum uptime to reach target yields. MFCs engineered to deliver both superior long-term drift stability and the best mean-time between-failures (MTBF) help ensure accurate, on-target process gas delivery.

When a MFC has poor long-term stability, bioreactor operators and metrology technicians must spend more time verifying and then recalibrating the device. This results in lost time, money and the opportunity to operate bioreactors at their fullest potential.

Long-Term Zero Stability of Brooks MFCs





Brooks Instrument MFCs are engineered for ultra-high levels of stability. Our long-term zero stability means device recalibration or replacement is less frequent.

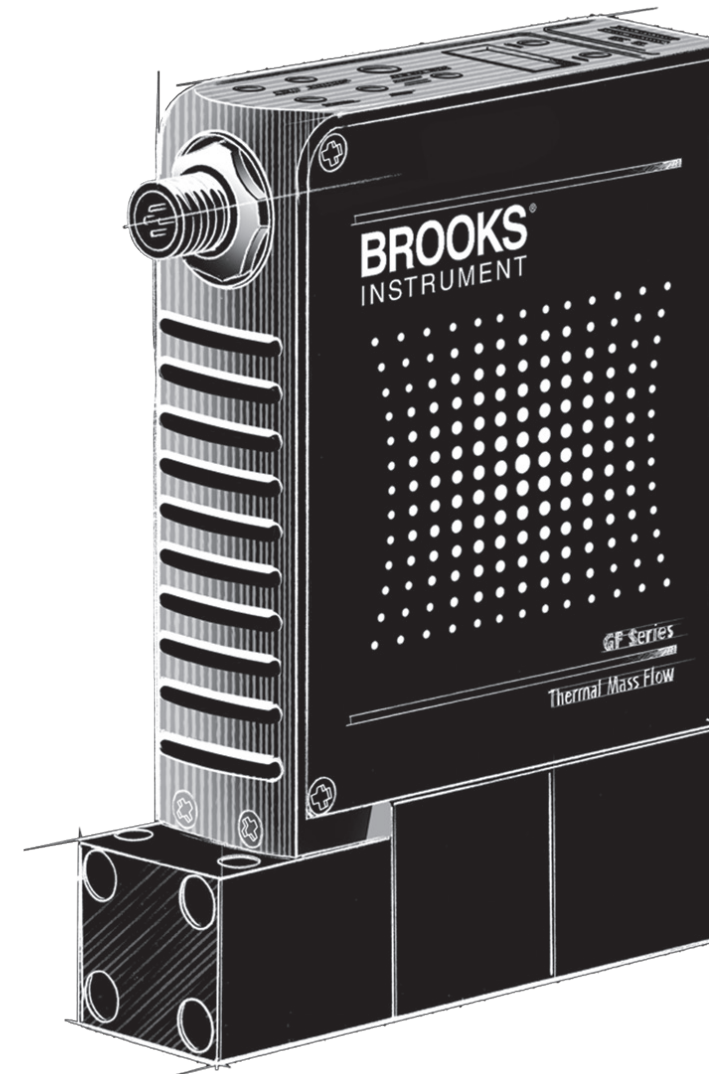
This helps ensure highly accurate research results and consistent biopharmaceutical production, during each batch run and from batch to batch.

MultiFlo™

Adding flexibility to accuracy

In the past decade, the availability of MFCs that incorporate multi-range and multi-gas programmability has redefined the flow control industry. Programmable MFCs have made it possible to use one MFC in process equipment and have it handle multiple gasses and gas flow rates.

Programmable MFCs have also provided a platform for improving MFC accuracy and stability. For example, Brooks Instrument's MultiFlo™ technology provides superior process gas accuracy with the help of data generated by over thousands of different data points over the course of 10 years.



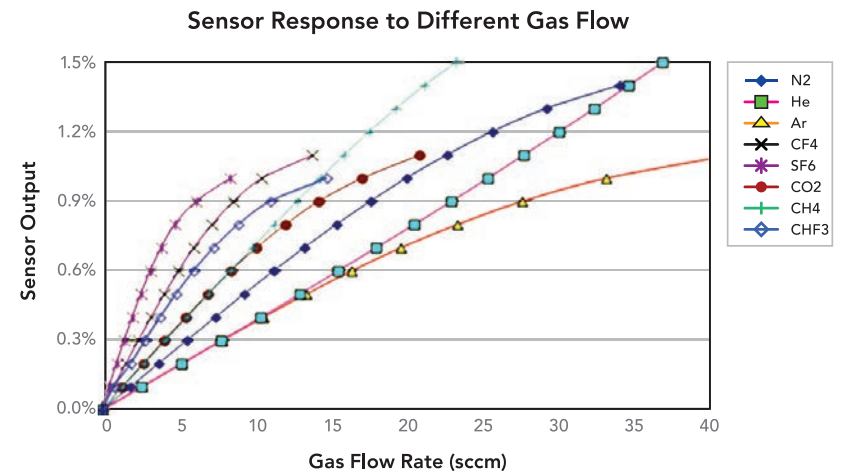
MultiFlo™

Adding flexibility to accuracy

Better actual process gas accuracy

MultiFlo technology significantly improves actual process gas accuracy. Advanced gas modeling is optimized through actual gas testing, which compensates for non-linear gases.

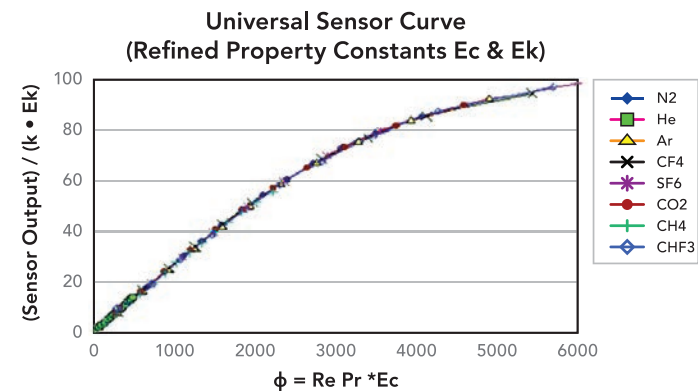
As can be seen here, MFC flow sensors respond very differently with different gases. While gas conversion factors may work better for some gases, most do not have a linear relationship between the flow rate and the sensor output, which causes inaccurate readings.

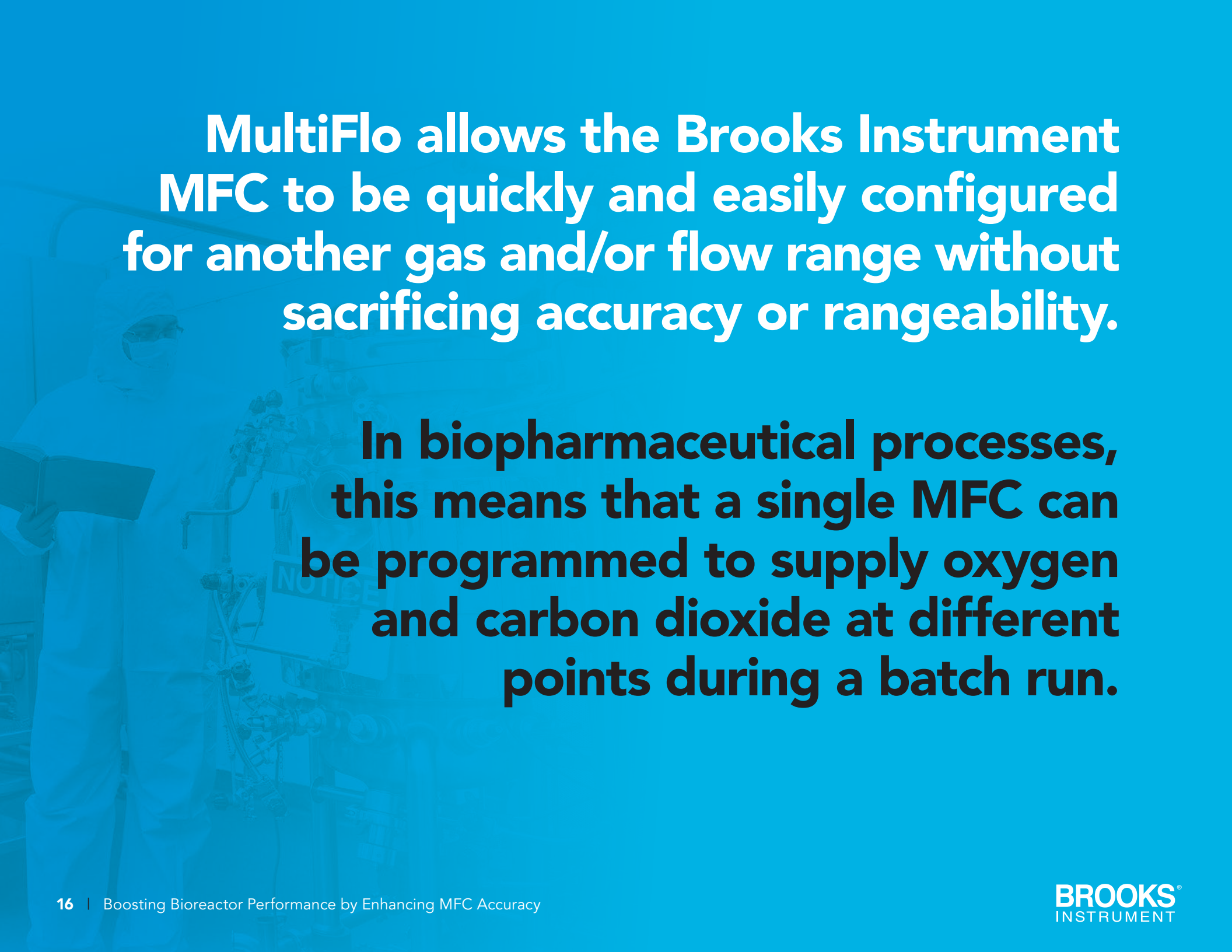


MultiFlo™

Adding flexibility to accuracy

Brooks Instrument developed its MultiFlo technology to much tighter calibrations for each major process gas type. Each sensor is nitrogen-calibrated. Then a universal sensor calibration curve based on a similarity theory was applied to create an accurate MultiFlo process gas calibration curve.





MultiFlo allows the Brooks Instrument MFC to be quickly and easily configured for another gas and/or flow range without sacrificing accuracy or rangeability.

In biopharmaceutical processes, this means that a single MFC can be programmed to supply oxygen and carbon dioxide at different points during a batch run.



Accurate flow control for bioreactors

Brooks Instrument has been innovating thermal mass flow technology for decades. Bioreactor systems equipped with our MFCs deliver the accuracy, reliability and long-term ease of use today's advanced life sciences researchers and biopharmaceutical producers need.

THE RESULT: You will maximize your bioreactor's value and sustain the return on investment your operations require.

How can we help?

Today's MFC technology is highly reliable – but if you have concerns about the long-term stability of your bioreactor's MFCs, or you would like to explore ways to use the latest Brooks Instrument MFCs in your system, we're ready to help.

CONTACT US TODAY.

T: 215-362-3527
Brooks.Mktg@BrooksInstrument.com

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

BROOKS[®]
INSTRUMENT

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



© Copyright 2017 Brooks Instrument, LLC All rights reserved.