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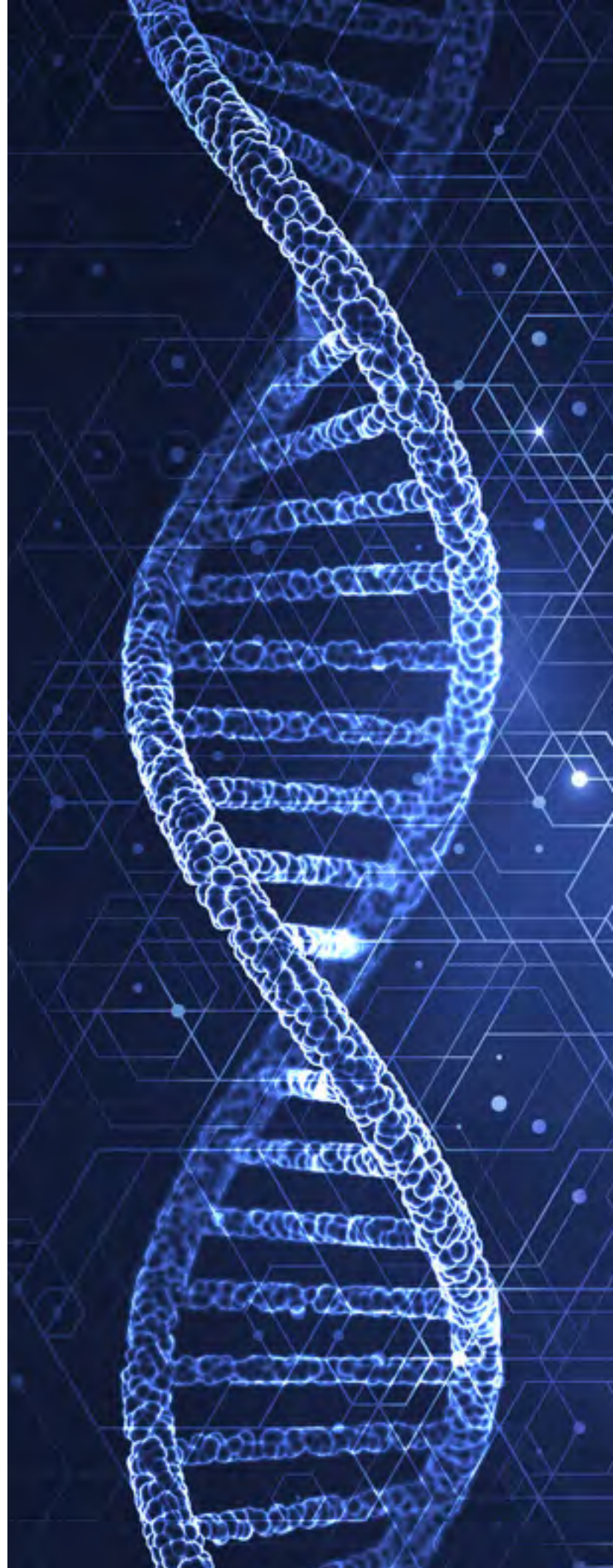
Beyond Measure

Satisfying the Increasing Need for Flexibility in Bioprocess Equipment

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INTRODUCTION: The Shifting Biotherapeutics Landscape Requires Flexibility Beyond Single-Use Systems – Looking to Bioreactor and Gas Delivery Systems



Bioreactors are a critical “tool” in biological process development, as well as an essential piece of equipment in the production of biotherapeutics. Productivity and efficiency depend on effective measurement and control of process variables, using a variety of sensors and control devices. Dissolved oxygen (DO) and pH are two critical process parameters, the control of which relies on the DO and pH sensors in control loops with mass flow controllers (MFCs).

MFCs used in bioreactors have historically been specified for accurate control in specific process-relevant gas flow ranges. Each MFC is then configured for the specific gas and range, and, as a result the process and equipment flexibility are limited. The lack of flexibility has, historically, not been a significant issue because multi-use bioreactors were routinely designed and specified to address a single product or process.

With diverse and ever-broadening biotherapeutic product development pipelines and the entrenchment of multi-product manufacturing facilities...**adaptability...flexibility are essential for competitive success**. Bioprocess equipment must keep pace with this industry requirement for flexibility down to the components and devices used in building them. To a certain extent, this is already evident by the wide-ranging adoption and implementation of single-use based equipment, in particular, single-use bioreactors. In many cases, **a properly designed and configured single-use bioreactor platform has the flexibility to adapt to a variety of processes**: “change the process, change the single-use bioreactor bag”. To achieve this at the equipment level, however, there have been limitations associated with how bioprocess gas flow control requirements have been specified and, how mass flow controllers have been designed and documented.

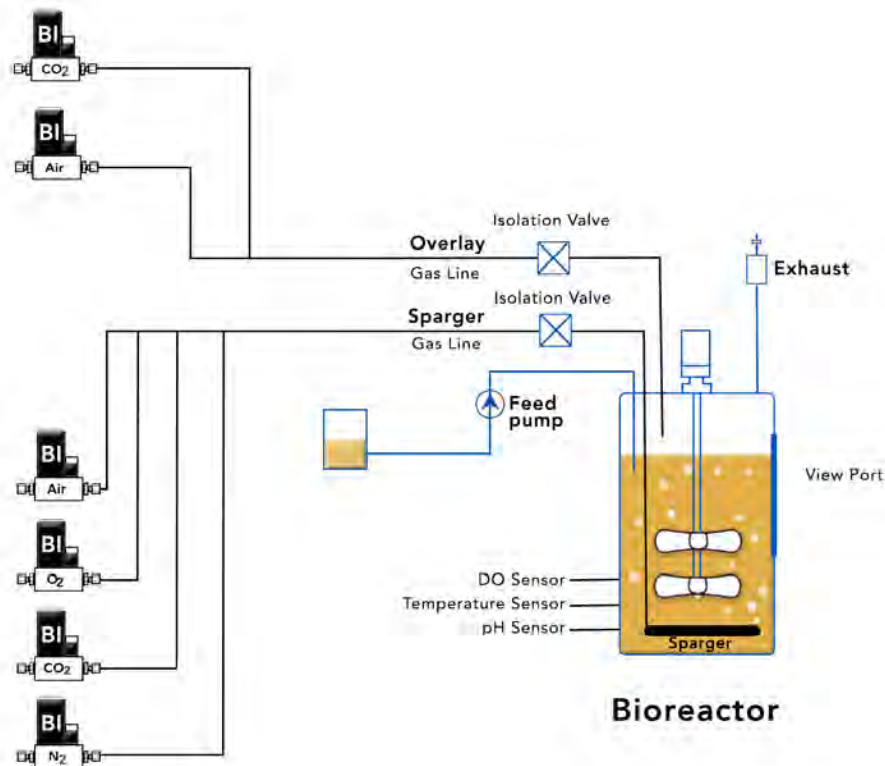


Figure 1: Representative Bioreactor

This paper presents a mass flow controller design and performance level that supports enhanced bioprocess equipment flexibility (See Figure 1). The concepts of MFC cardinal ranges and range slices will be introduced and explained. Also explained will be how the device’s capabilities and supporting documentation overcome limits to adaptability introduced above.

1 Mass Flow Controller Flexibility

Mass Flow Controller Flexibility

Mass flow controller flexibility is facilitated by a **wide usable flow range or turndown ratio and the capability for multiple gases and multiple ranges (MG-MR)**. The usable range spans from the maximum measurable flow rate to the minimum flow rate, where a meaningful, accurate, repeatable measurement signal is achieved (See Equation below). MG-MR capability allows an MFC to be set up for, or easily adapted to a variety of gases and flow ranges.

$$\text{TURNDOWN RATIO} = \frac{\text{Full Scale Flow}}{\text{Minimum Flow}}$$

To better understand wide usable range and MG-MR, it helps to understand the functional elements that establish MFC performance. Mass flow controllers combine a flow sensor, control valve and on-board control, to automatically measure and control the flow rate of a given gas at the user's specified setpoint.

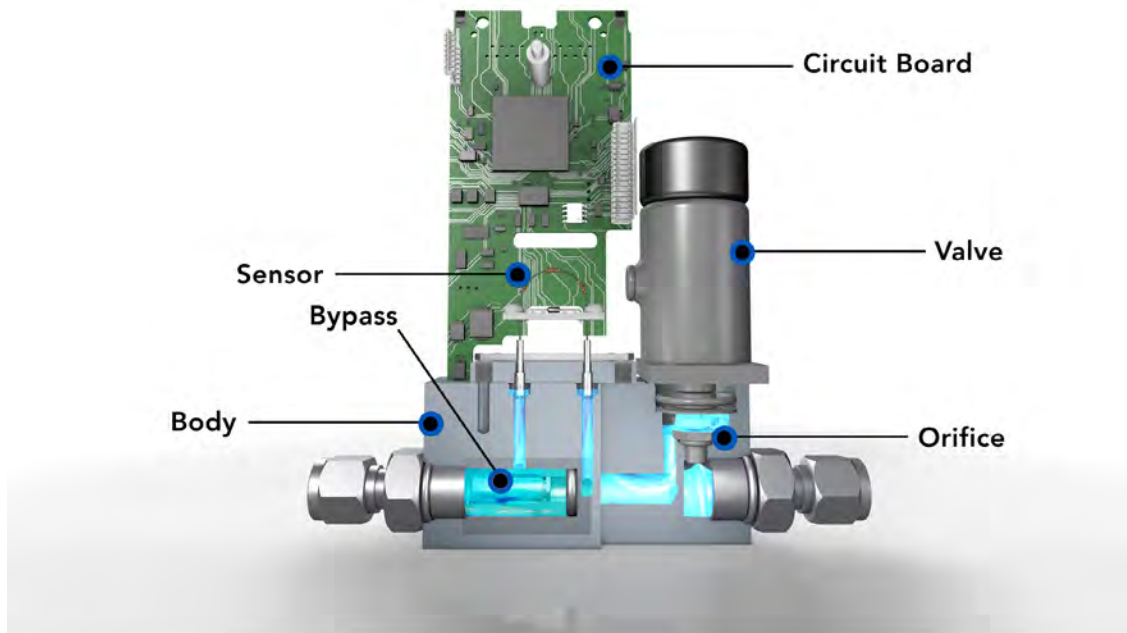


Figure 2: Basic Anatomy, Brooks Instrument SLA Series *Biotech* Mass Flow Controller

Let's look at these functional elements and review how they impact usable range as shown in Figure 2.

Sensor: The thermal flow sensor is the heart of the device and is key to measuring the mass flow. Aspects of a well-designed sensor include exceptional signal-to-noise ratio (SNR), electromagnetic interference and radio-frequency interference (EMI/RFI) noise immunity and low long-term drift characteristics. The lower the SNR, the better the low flow performance. SNR and noise immunity help establish a wide usable range. A poorly designed and produced sensor will exhibit a change in flow accuracy over time. In some models, SNR and zero drift may be available as advanced diagnostics within the device's data stream.

Printed Circuit Board (PCB): Electronics and firmware constitute the brain of the device, taking in sensor data, performing calculations, and making control decisions. Various device data, such as flow, temperature, and valve position (drive), among others, provide information upon which the MFC brain may take action. The same data establishes the foundation for sophisticated notifications, alarming, and diagnostics. Demand for this level of sophistication and intelligence is growing as the “industrial internet of things” (IIoT) becomes commonplace and may eventually become “table-stakes” for MFCs and other sensors and instrumentation.

Control Valve: The control valve is responsible for achieving and maintaining stable flow control, especially at the extreme low end of the usable range. Not classified as a positive shut-off valve, low end control and stability is governed by the maximum leakage rate across the valve seat. Several factors influence leakage rate, including valve seat material of construction, valve seat integrity, MFC configuration and testing, full-scale range and process gas conditions.

Mass flow controllers combine a flow sensor, control valve and on-board control, to automatically measure and control the flow rate of a given gas at the user’s specified setpoint.

		Brooks SLA Series MFC	Competitive MFC	Typical Mid/Low Tier MFC	Typical Purge Variable Area Flow Meter
	Accuracy Specification	0.9% of rate 20-100% FS, 0.18% of FS below 20%	±0.8% of rate, +0.2% of FS	1.0% FS	5.0% FS
% Full Scale Flow	Turndown	error % of rate	error % of rate	error % of rate	error % of rate
0.05 %	2000 to 1	360	401	2000	10000
0.10%	1000 to 1	180	201	1000	5000
0.20%	500 to 1	90	101	500	2500
0.40%	250 to 1	45	51	250	1250
0.50%	200 to 1	36	41	200	1000
1%	100 to 1	18	21	100	500
2%	50 to 1	9	10.8	50	250
5%	20 to 1	3.6	4.8	20	100
10%	10 to 1	1.8	2.8	10	50
20%	5.0 to 1	0.9	1.8	5.0	25
30%	3.3 to 1	0.9	1.5	3.3	17
40%	2.5 to 1	0.9	1.3	2.5	13
50%	2.0 to 1	0.9	1.2	2.0	10
60%	1.7 to 1	0.9	1.1	1.7	8.3
70%	1.4 to 1	0.9	1.1	1.4	7.1
80%	1.3 to 1	0.9	1.1	1.3	6.3
90%	1.1 to 1	0.9	1.0	1.1	5.6
100%	1.0 to 1	0.9	1.0	1.0	5.0

Device Full Scale	2000
Operating Point	100
Table Increment	100

White	<=1% of rate
Yellow	1-2% of rate
Orange	2-50% of rate
Red	>50% of rate

Table 1. Typical Gas Flow Control Device Comparison - Usable Range Based on Accuracy

Usable Range

The practical limits of an instrument and the application requirements define the instrument’s usable range. Applications, or processes with high accuracy requirements narrow the usable range.

Table 1 above compares error, as a percentage of (flow) rate, relative to % full-scale flow and turndown ratio for typical gas flow measurement and control devices. The red, orange and yellow colors highlight error ranges with which to evaluate the suitability of the particular instrument in a given application. An application requiring a usable range of 0.4-100% without crossing into the unusable red zone would be best addressed with a Brooks Instrument SLA Series *Biotech* MFC. In this example the turndown ratio is 250-to-1. By comparison, a conventional MFC can only achieve a usable range of 2-100% and turndown ratio of 50-to-1. The device with a larger turndown ratio at the acceptable error value can be used in a broader set of applications throughout the entire usable range, including sub-ranges (referred to as range slices) below the maximum.

These table accuracy specifications include calibration system uncertainty. When comparing such device specifications, it should be clear whether or not calibration uncertainty is included.

Multiple Gases – Multiple Ranges (MG-MR)

An MFC feature affecting bioprocess equipment flexibility is MG-MR capability. MG-MR can be delivered in a variety of ways with varying degrees of flexibility. **The bottom line: proper MG-MR functionality allows a single device to satisfy multiple applications.** MFC software tools or other inherent, dynamic programming interfaces allow setup or configuration for alternate flow ranges from within the device’s original pedigree (gas and range). Each MFC has internal elements (e.g., valve orifice and flow restrictor) that are sized based on the primary application (gas, range, pressure, pressure drop). Within the limits of those internal elements the device can be repurposed for other gases and flow ranges. Many MFCs support multiple gas pages, in particular, the Brooks Instrument SLA Series *Biotech* MFC, with its internal index that includes gas specific tuning and calibration attributes. This facilitates the ability to easily change gases, ranges or both. Active gas page changes can be made through digital commands over EtherNet/IP, BEST field service software from Brooks Instrument or by using the MFC’s on-board web server (MFC resident browser-based service capability). Changing the gas page on the Brooks Instrument SLA Series *Biotech* MFC enables an adaptable bioreactor platform, enhanced process control and maximum utility from the MFC. The device software manual and this article detail practical methods on how to take advantage of the various MFC attributes to maximize flexibility, reliability and performance of the bioreactor system.

Changing gas pages (better asset utilization) is typical under the 3 below scenarios:

User Type	Process	Gas Page Selection State	Gas Page Selection Tool
OEM Bioreactor Supplier	During first installation and commissioning	Static	Utilize BEST* software or MFC on-board web server
OEM Bioreactor Supplier	Equipment design to automatically change based on application using available MFC commands in conjunction with machine controller	Dynamic	PLC, DCS
End-User Drug Maker	Application specific configuration	Situational	Utilize BEST* software or MFC on-board web server

*Brooks Expert Support Tool (BEST)

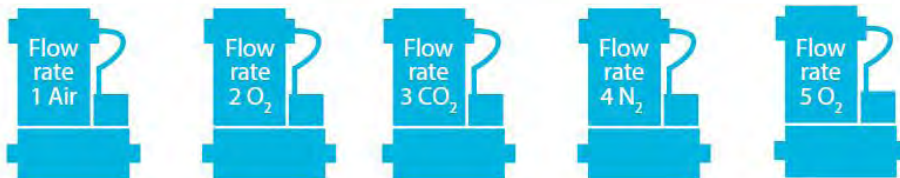
Table 2. Gas Page Change Scenarios Based on User Type (with selection state and method)

The primary benefits of MG-MR and multiple gas pages are:

- Part number reduction for OEMs
- Reduction of spares inventory for the end-user (See Figure 3). This MG-MR capability has been widely accepted in the semiconductor industry for many years because of a range of benefits and is now gaining acceptance in bioprocess applications.

Traditional MFC

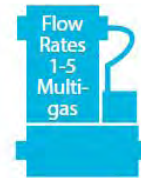
Each MFC Pre-configured



Spares
Inventory
=
5 Devices

Brooks Instrument SLA Series *Biotech* MFC

MFC Field Configured



Spares
Inventory
=
1 Device

Figure 3. Spares Inventory Reduction with MG-MR and Gas Page Capable MFCs

2 Practical Implementation of Wide Usable Range MFCs with MG-MR Capability in Bioprocess Equipment

Practical Implementation of Wide Usable Range MFCs with MG-MR Capability in Bioprocess Equipment

In this section we introduce and explain two concepts associated with maximizing MFC and, therefore, bioprocess flexibility:

- (1) Cardinal range, defined as the full-scale gas flow range necessary to support one or more processes or bioreactor vessel sizes with one or more mass flow controllers. Defining cardinal ranges offers an approach to minimizing the number of discrete MFCs for a maximum number of bioprocesses, based on gas flow rate(s).
- (2) Range slice, defined as the selected subset of an MFC cardinal range. The range slice must fall between the full scale and minimum controllable flow for that MFC.

MFC Part Number Reduction (MFC Ranges)

By taking advantage of wide usable ranges, MG-MR and gas page capable MFCs, Original Equipment Manufacturers (OEMs) and System Integrators (SIs) can minimize the number of unique MFCs (i.e., MFC cardinal ranges) required to satisfy their broad range of requirements. This reduces multiple, unique part inventory in the equipment manufacturing stage. For the end-user, there is a reduction in spare parts required to maintain their mass flow controllers across bioreactors of varying size, e.g., a process train.

Examples of MFC cardinal ranges are provided in Tables 3 and 4 (See Page 12). Table 3, associates MFC cardinal ranges versus the bioreactor total gas requirements, in VVM. The cardinal ranges are color-coded to match the vessel and process requirements. Each cardinal range provides flexibility with in-situ configuration and by allowing full-scale range changes. In Table 4, the Minimum Controllable Flow Rate column reflects the turndown and is the lowest flow setpoint where the MFC provides repeatable closed-loop control. By selecting appropriate cardinal ranges, the OEM can implement equipment flexibility in support of process change flexibility. For example, an MFC with cardinal range of 50 SLPM (see Table 4, blue cell: 500L vessel size, oxygen), leveraging MG-MR and multiple gas pages, can be switched to 40 SLPM (Air). The switch can be made using digital commands without the need to remove, replace or recalibrate the MFC.

Table 3 includes the lowest configurable range which, for this 50L MFC example, is 28 SLPM. This means this MFC's minimum full-scale range 28 SLPM, without physically altering or recalibrating the device.

Consider a multiproduct biomanufacturing facility utilizing 500L seed and 2000L terminal production bioreactors incorporating Brooks SLA Series *Biotech* MFCs, with its high turndown ratio and the multiple gas page capabilities. Table 3 indicates only three MFC configurations (green, orange and blue colors from the table below) are required to support ten gas flow paths and the associated ranges, across both vessels.

Function	Gas	VVM	Vessel Size (L)			
			50	100	500	2000
DO Control	Air	0.1	5.0	10.0	50.0	200.0
DO Control	Oxygen	0.2	10.0	20.0	100.0	400.0
DO Control	Oxygen	0.1	5.0	10.0	50.0	200.0
pH Control	CO ₂	0.15	7.5	15.0	75.0	300.0
Headspace	Air	0.15	7.5	15.0	75.0	300.0

Table 3. Maximum Flow Rate Requirements by Function vs Vessel Size
Note: VVM, is defined as vessel volume flow rate per unit time (minute)

OEM Configuration				
Vessel Size (L)	MFC Cardinal Range (SLPM)	Lowest Configurable Range Upper Limit (SLPM)	Minimum Controllable Flow Rate (SLPM)	MFC Body Size
2k	400	186.0	2.67	C
500L	100	75.0	0.40	B
500L	50	28.0	0.20	A
100L	20	17.0	0.08	A
100 & 50L	15	10.0	0.06	A
50L	7.5	5.0	0.03	A

Table 4. MFC Cardinal Range and Range Capability by Vessel Size

Utilizing the same cardinal range MFC for multiple recipes and functions:

- Improves system reliability
- Reduces cost
- Minimizes contamination risk
- Decreases system turn-over time
- Reduces spares requirements
- Reduces calibration verification and recalibration costs and
- Provides maximum process flexibility

Process Flexibility (Range Slices)

Figure 4 (See Page 15) depicts the concept of ranges slices within the cardinal range and turndown ratio, using three slices (A-E, B-D and A-C) corresponding to three different processes (1-3), respectively. Configured range is the MFC active gas page full scale setting to address the range slice. The tabular information provides MFC's configured range, flow accuracy at the minimum of the range slice range and chosen gas page. This range slice approach allows one (1) MFC with a cardinal range of 50 slpm, large turndown ratio and three gas pages to satisfy flow requirements for three (3) distinct processes, all within a user-defined accuracy window. Process 1 requires between 0.2 and 50 SLPM of O₂ flow (range slice A-E). The 250:1 turndown and device accuracy ensures stable, accurate repeatable flow at the low end. The same MFC can be configured to 30 SLPM, in-situ, by digitally selecting the appropriate pre-defined gas page. This enables process 3 to be run at 0.2 SLPM – 30 SLPM without removing and recalibrating the MFC. Process 2 has a narrower range, highlighted by minimum flow rate well within the MFC's capabilities.

Biotech MFC Range Scenarios Using Single MFC with 50 SLPM Range, O₂

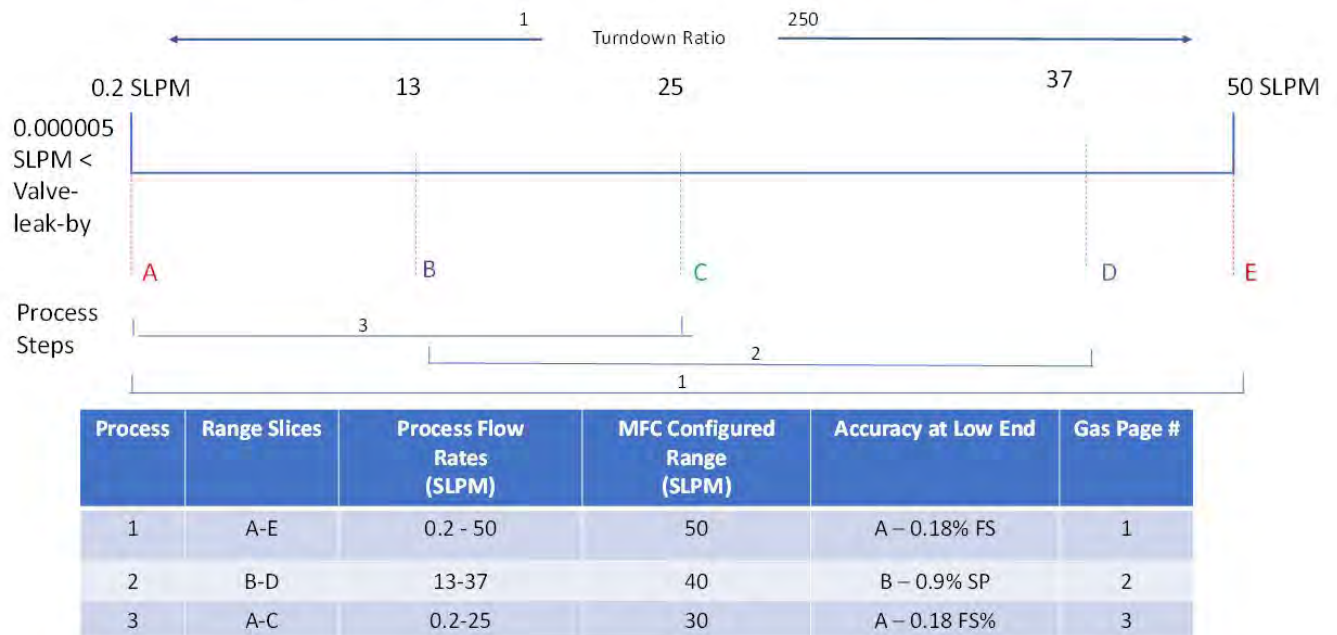


Figure 4. Range Slice Example for 50 SLMP O₂ MFC

Again, the capabilities of the Brooks SLA Series *Biotech* MFC support process 2 without the need for removal and recalibration. Countless other process scenarios can make use of the range slice approach, taking full advantage of the Brooks SLA Series *Biotech* MFC. Understanding the process requirements, especially in operating scenarios, where flexibility is imperative to defining cardinal ranges and applying range slices.

Stakeholder	Benefit
Engineering Company	Design flexibility in flow capacities for URS definition
Original Equipment Manufacturer	Bioreactor configuration flexibility using a common, reduced set of mass flow controllers
End-User Process	Multiple products or processes supported without hardware change-out
End-User Metrology	Improved System reliability with fewer assets/devices to manage

Table 5. Benefit by Stakeholder

Examples

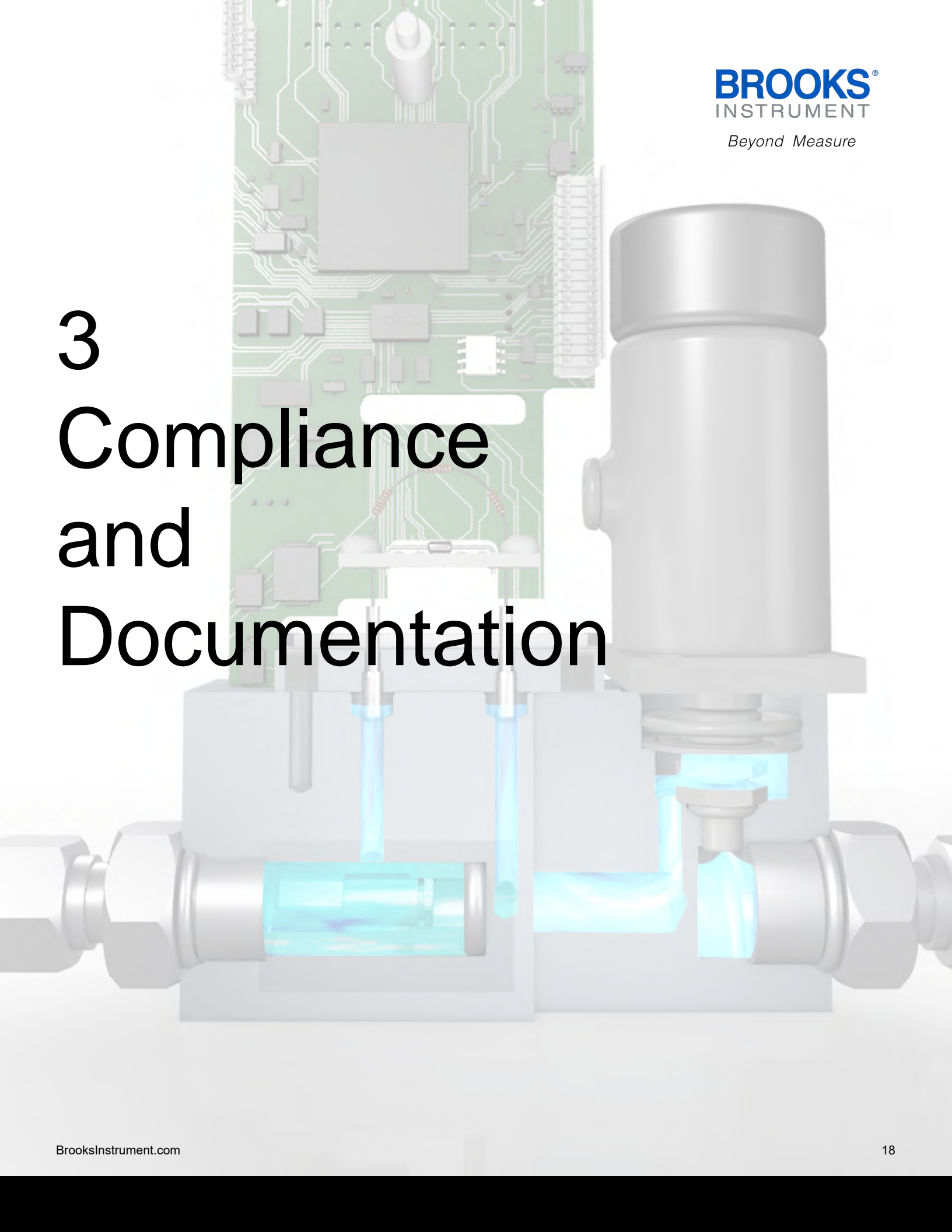
A multi-product biologics plant could require a 200L seed bioreactor operating within a VVM range of 0.1 to 0.25. For oxygen, this equates to 20 SLPM to 50 SLPM gas flow. The high turndown 50L MFC ensures control within the process requirements. The multi-gas page approach allows a single MFC to address multiple functions within the same gas management subsystem.

Consider a bioprocess development example, with a 50L or 100L bioreactor, in which a variety of cell lines may be used to develop a portfolio of potential biotherapeutics. One process, run as a fed-batch, may have a low cell density and correspondingly low gas flow rate to meet metabolic oxygen demand. Conversely, a higher cell density perfusion process may have a much greater need for metabolic oxygen, requiring correspondingly higher gas flow rate. From within the flow range established by the 250-to-1 turndown ratio of the Brooks SLA Series *Biotech* MFC, the fed-batch process would have a range slice of 0.2-10 SLPM compared to the perfusion process with a range slice of 1-50 SLPM. The same mass flow controller in the same bioreactor could be used, for both processes, without needing to be removed or recalibrated.

As another example, in some two-sided dissolved oxygen control applications, a nitrogen mass flow controller is used to reduce the oxygen concentration level when above setpoint. Using the gas page capability of a Brooks SLA Series *Biotech* MFC, an MFC with air and nitrogen gas pages could be switched dynamically between the two gases to support this type of control without the need for a dedicated nitrogen MFC.

In these examples, the technology and design of the Brooks SLA Series *Biotech* MFC enables this flexible bioprocess functionality. To properly take advantage of this flexibility, coordination and planning between OEM and end-user as well as between the OEM and MFC supplier are key to maximizing the functions inherent in the Brooks SLA Series *Biotech* MFC (See Table 5).

3 Compliance and Documentation



Compliance and Documentation

The Brooks SLA Series *Biotech* MFCs are designed, produced, and documented, to support regulated and non-regulated industries alike. Each Brooks SLA Series *Biotech* MFC is provided with NIST traceable compliance certificates for four gases and can be supplied with optional compliance documents listed in Table 6 and Figure 5.

Compliance Documents	Included with SLA Series <i>Biotech</i> MFC
USP and 21CFR177.2600 elastomeric certification	Yes
Calibration certificates, one for each of 4 gases	Yes
NIST and ICC standard traceability	Yes
3.1 Material certification (ISO 10474/EN-10204)	Option
Oxygen service cleaning	Option

Table 6. Available Supporting Documentation

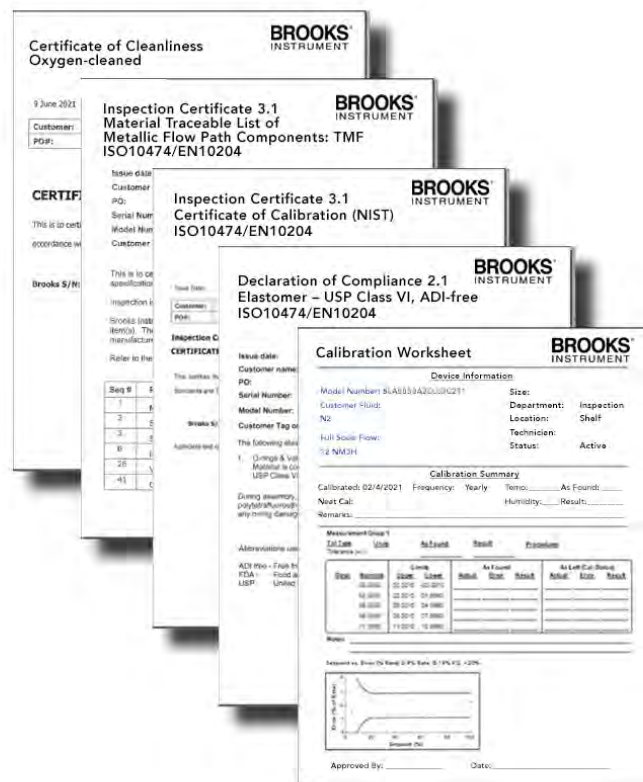


Figure 5. Sample of Quality Certificates Delivered with SLA Series *Biotech* MFCs

Conclusion

Maintaining market competitiveness requires flexible, efficient and reliable manufacturing processes. Achieving flexibility may require challenging established conventions. The type and extent of flexibility can be influenced by available technologies. Biopharmaceutical manufacturing is a good example of an industry where flexibility keeps the competition keen but, more importantly, gets more drugs, of higher quality, to patients faster. **Using bioreactors as an example, flexible biomanufacturing (and process development) has benefitted substantially since the advent and widespread adoption of single-use bioreactors.** Single-use bioreactors offer drug makers a tool for challenging the conventional approaches to biomanufacturing: one product, one plant. Multi-product biologics manufacturing facilities have become more practical and have gained greater flexibility with adoption of single-use technology; in this discussion, single-use bioreactors. Using single-use bioreactors supports the “change the process, change the single-use bioreactor bag” approach to flexibility. The bioreactor equipment, mostly limited by process instrumentation, has not been as flexible, often requiring capital expenditures (CAPEX) or downtime to replace or reconfigure the equipment to accommodate a new process...and, new bag. With the Brooks SLA Series *Biotech* MFC, a new level of device flexibility substantially improves the flexibility of the entire bioreactor unit operation – essential for process development and biomanufacturing, alike. Available documentation, including the calibration material, supports relevant range slices from within a given cardinal range. Combined, the MFC capabilities and supporting documentation, establish a foundation for specifying, integrating and maintaining MFCs in a new, more efficient way. Perhaps the final step to achieving maximum flexibility, is rethinking how MFCs are specified in user requirements. Applying the concepts of MFC cardinal ranges and range slices, in conjunction with the dynamic gas ranges and large turndown ratios found in these mass flow controllers allows the bioreactor hardware to be “reconfigured instead of being replaced or enduring the downtime associated with removing and recalibrating MFCs to address a different process. Incorporating this MFC into the single-use bioreactor approach to flexibility, it could be said, “change the process, change the single-use bioreactor bag, reconfigure the MFC.” Adoption and implementation of this approach to flexibility requires the acceptance of the beneficial capabilities of these advanced MFCs, by all stakeholders. This flexibility, coupled with the expanding wealth of information provided by the MFC alarms and diagnostics, offers significant opportunities for improvements in asset utilization, efficiency, and reliability.

For more information, please email Brooks-Mktg@BrooksInstrument.com or call 888-554-3569.