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SLA5800 Mass Flow Controller
with EtherNet/IP

Using Digital MFC Diagnostic Capabilities to Improve Bioprocessing Results

Ken Clapp, Sr. Bioreactor Technology, Application & Integration Leader, Cytiva
Joe Sipka, Global Business Development, Brooks Instrument

Introduction

Biomanufacturing relies on numerous pieces of equipment working in concert to produce life-altering therapeutics. The equipment relies on various subsystems to achieve the desired results. In a bioreactor, one of the most essential subsystems provides gas management for the gases necessary for cellular metabolism. At the heart of the gas management subsystem is the thermal mass flow controller (MFC), a component that precisely measures and controls the delivery of gases to the bioprocess.

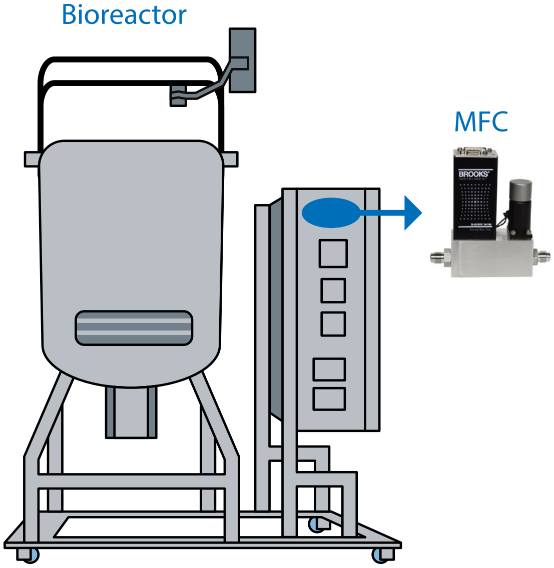

Figure 1. XDR Single-use Bioreactor depicting the location of an MFC associated with process gas management.

Proper mass flow controller performance is critical to the performance of the bioprocess. Fortunately, modern day mass flow control devices, with their highly integrated microprocessor-based electronics, are extraordinarily robust and reliable. The capabilities of these devices, due both to their electronic hardware and the supporting firmware, offer more than just gas delivery. These devices now possess native "intelligent" functionality associated with the industrial internet of things (IIOT), namely, data management and connectivity. This functionality can be used to improve or enhance biomanufacturing operational efficiency.

Properly applied, specified, and configured, intelligent mass flow control devices are able to gather, generate, and communicate a variety of data. These devices along with other typical bioprocess equipment data sources (e.g., sensors, probes) have the capacity to generate enormous amounts of data. It should be kept in mind, not all data is useful. Sufficient contextual data can provide information necessary to gain insight and make appropriate decisions.

This article discusses mass flow controller data capabilities in relation to a broader biomanufacturing capital asset management. Data categories will be defined and used to discuss relevance to various stakeholders. The focus will be on practical aspects of device data utilization, including what data is available and which data contributes to context, with examples and recommendations.

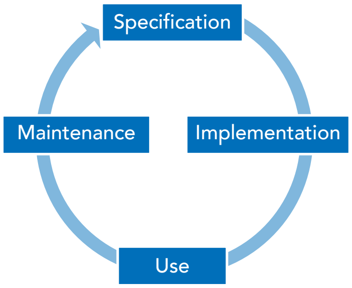

Figure 2. MFC Lifecycle, a framework for collaboration to meet customer needs: Specification aligns the design with application and capabilities; Implementation ensures data availability; Use enables meaningful data utility to the drug maker; Maintenance offers alternate asset management methods.

Components, machines, process and stakeholders

The process train is made up of machines, the machines of components. For reliable bioproduction, the machines must be properly designed and operational down to the component level, especially process instrumentation. Equipment suppliers design and build their machines, to be highly functional, robust and reliable. To meet these objectives, equipment suppliers rely on component capabilities and specifications to select and incorporate the most suitable components. Application, mechanical and electrical design considerations have been the most common, prevailing collaboration areas between equipment and component suppliers. The intelligence in a device, such as mass flow controller (MFC), along with the data it can generate impose new design considerations. Beyond simple considerations like tag names and analog signal (e.g., 4-20mA) routing, are more complex considerations associated with device identification, configuration and diagnostics, as well as built-in alarm handling. Intelligent devices offer the potential to enhance equipment functionality and improve reliability. Consequently, incorporating intelligent devices requires a new level of equipment design collaboration. To help guide the collaboration between process instrument suppliers, equipment manufacturers and end users, a lifecycle framework is useful *(Figure 2)*. Using this framework, the equipment and component suppliers can create designs that align the data, information and diagnostics around the end customers' needs.

Understanding available device data allows definition of meaningful data categories. Benefits of consensus categorization include: (a) creation of a common language with which stakeholders can communicate, (b) prioritization of design activities, and (c) simplification of lifecycle management. As an intelligent component, or device, three specific MFC data categories can be defined: pedigree, performance and reliability. Specific data within each category may be used to create new ways in which the capital asset (bioprocess equipment) is managed. Pedigree covers static configuration and installation attributes, like serial number, network address and calibration.

Calibration-related data includes gas type, flow range and calibration date. The performance category addresses dynamic operational attributes such as gas flow rate, temperature and pressure. Reliability category data may be used for troubleshooting and maintenance of the MFCs and bioreactors. Relevant data combined from each of these categories can contribute to bioprocess analytics.

MFC Anatomy

Thermal mass flow controller sub-systems:

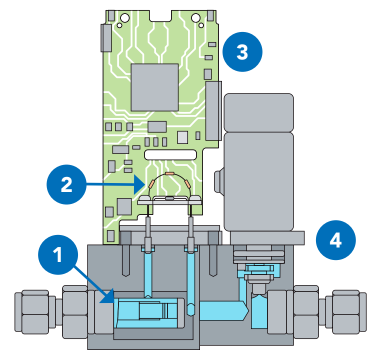

Figure 3.

1. **Body/Flow Restrictor (bypass):**
   - Mechanically sets the maximum flow rate.
   - Conditions flow (turbulent to laminar).
   - Diverts a precise sample of gas to the sensor to be measured.

2. **Flow Sensor:** Precisely measures the thermal conductivity of the gas to obtain the mass flow rate.

3. **Digital Electronics (firmware):** Processes flow sensor data, compares to customer set point and drives valve to control flow.

4. **Control Valve (orifice):**
   - Jet size based on max flow rate.
   - Electromagnetic valve modulates to increase or decrease spacing between plunger and jet to control the flow rate.
   - Control valves not designed for positive shut-off (<1% of FS leak-by).

Body/Restrictor:

The body and restrictor manage gas flow through the mass flow controller. The restrictor diverts a small sample of incoming gas to a thermal sensor. Restrictor design is critical for creating and maintaining a constant bypass, or split ratio — the gas flow ratio between sensor and restrictor. A well-designed restrictor creates a constant flow ratio across the full operating range with different gases.

Sensor:

The thermal sensor is the heart of the MFC. The three-wire sensor accurately detects temperature differences to determine the mass flow rate considering the gas properties. Sensor design and production processes have an impact on MFC repeatability and long-term stability.

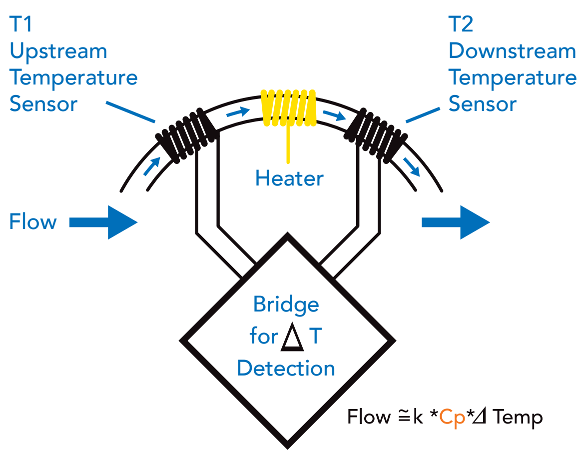

Figure 4. Thermal mass sensor measurement detail

Electronics/Firmware:

The electronics process and scale the sensor signal, compares the sensor signal to the setpoint signal, modulates the gas flow control valve, and provides a flow signal output. There is an increasing demand for intelligent diagnostics, digital protocols and process flexibility which requires highly integrated functionality.

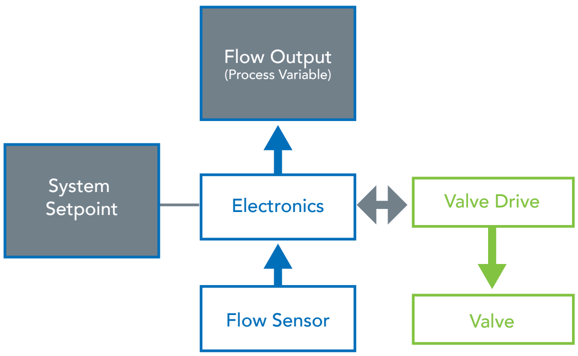

Figure 5. MFC circuit board data flow

Control Valve and Drive:

The integral gas flow control valve ensures accurate control throughout the full gas flow range. The valve is designed to allow a wide, usable control range. The valve drive supports diagnostics and can be indicative of device performance and reliability.

MFC Output Signal: The Brooks Ethernet/IP MFC provides the capability to output over 500 attributes, or data points that can be categorized by device pedigree, performance and reliability. By comparison, a typical analog input/output (I/O) MFC outputs one or two process variables, for example, a 4-20mA flow output signal.

Output: Measurement and control devices with digital I/O, regardless of the protocol used, can provide a myriad of information that is not available from a basic analog I/O device. A typical analog I/O MFC outputs one or two process variables, for example, a 4-20mA flow output signal. A digital MFC provides the capability to output over 500 attributes, or data points that are associated with device pedigree, performance and reliability.

Use in Bioprocess

Bioreactors include several functional subsystems to create and control the proper process environment for growing cells. Numerous process parameters are measured, including temperature, agitation speed, dissolved oxygen (DO), pH and pressure. The gas management subsystem is used to control both dissolved oxygen and pH levels. Essential for this control are thermal mass flow controllers (MFC). Typically, air and oxygen MFCs are used for dissolved oxygen control while a carbon dioxide mass flow controller is used for one side of pH control (the other side uses liquid base addition). MFC response, stability, and reproducibility are critical in maintaining proper dissolved oxygen and pH levels.

MFC performance is verified across a wide flow range assuring MFC product repeatability and reliability. Mass flow controller response and repeatability have direct impact on DO and pH control loops, therefore, system performance. A typical dissolved oxygen graph *(Figure 6)* demonstrates the gas flow influences on a typical single-use bioreactor process run.

Drug maker personnel validate and calibrate mass flow controllers on a regular basis using primary reference standards. During regularly scheduled, periodic checks, any "Out of Tolerance" (OoT) condition represents a deviation. This may have implications for prior batch or batches. The ability to diagnosis, predict and potentially correct component-, subsystem- or bioreactor-related issues in real-time requires collaboration and coordination between equipment manufacturers and process instrument suppliers. Brooks Ethernet/IP protocol enables the latest diagnostics and predictive functions. For example, if upstream gas inlet pressure becomes restricted, the overall MFC accuracy could change. Using the MFC's built-in choked flow alarm, the alarm data could be presented to an operator on the bioreactor HMI, to prompt action.

Data Values

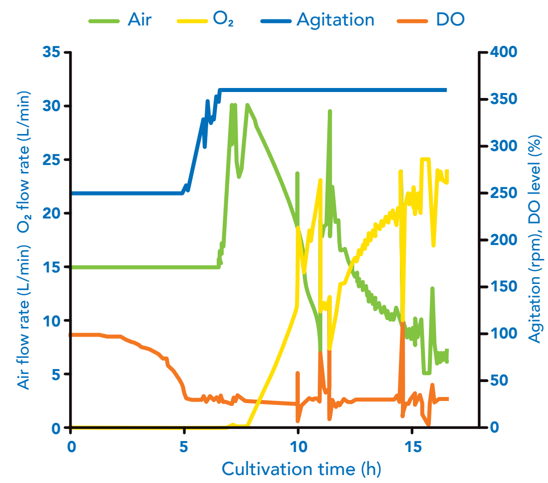

Figure 6. Typical process data from a single-use bioreactor system with DO%, gas flow rates and agitation.

When incorporating intelligent devices, equipment suppliers (OEM) must evaluate which and how much data, to read, analyze and retain. For example, considering only MFC flow setpoint and output may overlook critical device, equipment or process issues. The Brooks Instrument EtherNet/IP MFCs are intelligent and data-rich devices that can facilitate improvement in operational efficiency in areas of equipment automation, metrology and maintenance. Understanding each data type requires upfront and on-going collaboration between the OEM and supplier engagement. Global Life Sciences Solutions USA and Brooks Instrument are collaborating on how to define, implement and use data generated by or available from the MFC in the bioreactor unit operation. Listed below are important questions to raise during supplier discussions:

– What is the process benefit?

– What is the attribute key?

– What can be changed/altered with the data?

– Where should the data be stored?

– Does it add value to current methodology?

– Can this data be different for existing PV?

– When (in the process) should the attribute be collected?

– Is it possible to integrate into automation?

– Is it possible to link to service or metrology functions?

– Can it be utilized for predictive modeling or analytics?

– What are the typical conditions and limits?

– Can it be utilized for alarm and diagnostic feedback?

As previously mentioned, MFC attributes are segregated into the following main categories — pedigree, performance, and reliability. Pedigree is defined as configuration or unique MFC device information such as full-scale range, device serial number or last date of calibration. Performance category is defined as key variables required to complete process run — examples are MFC flow rate and MFC setpoint. The reliability category is defined as variables providing a predictive function to the users — examples are zero trending or valve drive trending functions. The valve and zero drift trending functions are unique to Brooks Ethernet/IP protocol.

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Preventive maintenance and process quality are also enhanced by having a broad array of thresholds and alarms that can be set and monitored by digital MFCs. A few examples of alarms are: high flow alarm; no flow alarm; and device calibration due. The alarms and diagnostic functions are available both in the performance and reliability categories. Interpreting and automating these alarms can improve overall equipment effectiveness and flexibility.

Not every MFC variable/data should be recorded or analyzed. Often the outputs are only helpful when analyzed as part of a multivariable scenario. The table below represents 35 MFC process variables, segregated into **seven sub-categories**, considered to be useful to operational efficiency improvements. Utilizing the correct MFC data to proactively predict events or process shifts is an evolving effort requiring communication and coordination between all stakeholders.

Data Category	Parameter Identity (type, class, instance, attribute)	Device Attribute	Description	Data Use	Stakeholder
Pedigree	*TC-IP (3,245,1,101)*	*IP Address*	*TCP/IP Address*	*Configuration*	*OEM*
Pedigree	*TC-IP (3,245,1,102)*	*Network Mask*	*TCP/IP Network Mask*	*Configuration*	*OEM*
Pedigree	*Identity (3,1,1,1)*	*Vendor_ID*	*ODVA Vendor ID*	*Configuration*	*OEM*
Pedigree	*Identity (3,1,1,2)*	*Device_Type*	*General Product Type*	*Configuration*	*OEM*
Pedigree	*Flow Meter (3,169,1,4)*	*Flow_Units*	*Flow Meter Units*	*Configuration*	*OEM/Metrology*
Pedigree	*Produce Assembly Output (1,202,n/a,n/a)*	*Full_Scale_Process Gas*	*Full scale range of the selected process gas page*	*Configuration*	*OEM*
Pedigree	*Produce Assembly Output (1,202,n/a,n/a)*	*Process Gas ID*	*Numeric identifier of the process gas*	*Configuration*	*OEM*
Pedigree	*Process Page (3,102,1,40)*	*pgGasStandardNumber*	*Configured gas type*	*Configuration*	*OEM*
Pedigree	*Identity (3,1,1,6)*	*Serial_Number*	*Device Serial Number*	*Configuration*	*OEM*
Pedigree	*Flow Meter (3,169,1,227)*	*Calibration_Due*	*Recommended recalibrated time for MFC*	*Metrology check*	*Metrology/Automation*
Pedigree	*Process Page (3,102,1,37)*	*ReferenceTemperature*	*Calibration reference temperature*	*Metrology check*	*Metrology*
Pedigree	*Process Page (3,102,1,38)*	*ReferencePressure*	*Calibration reference pressure*	*Metrology check*	*Metrology*
Performance	*Process Control Monitoring (1,201,n/a,n/a)*	*Flow Output*	*Flow Sensor Value*	*Active monitoring*	*Automation/Process*
Performance	*Process Control Monitoring (1,201,n/a,n/a)*	*MFC_Setpoint*	*Current setpoint value*	*Active monitoring*	*Automation/Process*
Performance	*Process Control Monitoring (1,202,n/a,n/a)*	*Temperature*	*Temperature sensor value*	*Active monitoring*	*Automation/Process*
Performance	*Process Control Monitoring (1,201,n/a,n/a)*	*Active Alarms*	*Active Alarms*	*Active monitoring*	*Automation/Maintenance*
Performance	*Process Control Monitoring (1,201,n/a,n/a)*	*Device_Status*	*Device Status*	*Active monitoring*	*Automation/Maintenance*
Performance	*TC-IP (3,245,1,1)*	*tcpStatus*	*EtherNet Communication Status*	*Communication*	*OEM*
Performance	*Flow Controller (3,158,1,15)*	*WarningSettlingTime*	*MFC allowed controlled time*	*Configuration*	*OEM*
Performance	*Process Control Monitoring (1,202,n/a,n/a)*	*Valve_Override*	*Current valve override setting*	*Maintenance check*	*Maintenance/Metrology*
Performance	*Flow Meter (3,169,1,112)*	*Device Zero Enabled*	*Starts the device zero operation*	*Metrology check*	*Metrology/Automation*
Performance	*Flow Meter (3,169,1,21)*	*Flow_Alarm_TP_High*	*High Flow Alarm Trip Point*	*Process recipe change*	*Process/Automation*
Performance	*Flow Meter (3,169,1,22)*	*Flow_Alarm_TP_Low*	*Low Flow Alarm Trip Point*	*Process recipe change*	*Process/Automation*
Performance	*Temperature Meter((3,164,1,21)*	*tmWarningTripPointHigh*	*High Temperature Alarm Trip Point*	*Process recipe change*	*Process/Automation*
Performance	*Status (3,184,1,4,Bit2)*	*No_Flow_Limit*	*No Flow Limit Threshold*	*Service/Trouble shooting*	*Automation/Process*
Performance	*Status (3,184,1,3,Bit2)*	*Backstreaming*	*Reports when a gas/liquid flows backward thru MFC*	*Service/Trouble shooting*	*Process/Automation*
Performance	*Status (3,184,1,5,Bit26)*	*Input Power Supply*	*Reports input system power supply*	*Service/Trouble shooting*	*Maintenance/Automation*

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Data Category	Parameter Identity (type, class, instance, attribute)	Device Attribute	Description	Data Use	Stakeholder
Performance	*Temperature Meter (3,164,1,24)*	*WarningSettlingTime*	*Time before triggering or clearing temperature alarm.*	*Service/Trouble shooting*	*Maintenance/Automation*
Reliability	*Process Control Monitoring (1,201,n/a,n/a)*	*Valve Position*	*Valve Drive*	*Active Monitoring*	*Automation/Process*
Reliability	*Process Control Monitoring (1,202,n/a,n/a)*	*Flow_Totalizer*	*Flow Sensor totalizer*	*Active Monitoring*	*Process*
Reliability	*Process Control Monitoring (1,202,n/a,n/a)*	*Total_Flow_Hours*	*Total hours of flow through flow sensor*	*Active Monitoring*	*Metrology/Process*
Reliability	*Flow Controller (3,158,1,19)*	*Ramp_Time*	*MFC response time adjustment*	*Configuration*	*Process/Automation*
Reliability	*Flow Controller (3,158,1,16)*	*ControlErrorBand*	*Flow deviation allowed during steady state control*	*Configuration*	*OEM*
Reliability	*Flow Meter(3,169,1,149)*	*Power On Hours*	*Total power on hours at the time of the zero operation*	*Maintenance Check*	*Maintenance/Metrology*

Table 1. MFC data categories

Data Category: Performance, reliability or pedigree classification

Stakeholder: Key groups that will benefit from the attribute

Parameter Identity: Digital protocol class

Type: Communication method—implicit (1) or explicit (3)

Device Attribute: MFC Process Variable definition

Class: Categorization or grouping within the device

Description: Brief attribute explanation

Instance: Grouping or classification within each class

Data Use: Recommended utilization of variable

Attribute: Specific parameter location within each instance

Recommended Categories and Data

The parameters below are available as implicit, or cyclic (class 1) or explicit (class 3) from Brooks Ethernet/IP mass flow controllers. Cyclic attribute data is grouped and generated based on criticality process control and diagnostics. These represent specific examples within the three primary categories: pedigree, performance and reliability.

Pedigree

Device Serial Number: Each MFC will have a unique serial number that can be used for process tool reporting. The serial number alone can be used to associate devices to specific equipment inherently within the automation platform.

Process Page Instance: Some MFCs can be configured for multiple gases, different flow rates and operating pressures. MFC Process pages are used to switch from among the pre-programmed choices. This can reduce equipment downtime (keeping the same hardware on the system) and enables equipment manufacturing flexibility.

Performance

Flow Output: MFC gas flow output is a typical or standard process value. Commonly, the data is available for real-time trending along with other relevant process parameters such as DO, pH, Temperature, RPM and others; all of which are stored in a data historian. Continuously monitored, used for control and in a variety of alarms, gas flow rate data can be indicative of process performance. Alone or together with several other process variables, the flow output data may also provide insight for component- or machine-health and useful for troubleshooting. Flow output is an example of MFC data that can be used in trouble-shooting batch cell growth inconsistencies.

Flow Totalizer: The gas flow totalizer continuously accumulates the total gas flowing through an MFC, during a process run. Whereas Total Flow Hours, a separate parameter related flow to time, the Flow Totalizer provides process information associated with mass balance and material use. Although the gas flow totalizer can be set-up to provide data only when polled, it is more commonly used as continuous data source.

Active Alarms: These intelligent MFCs include a number of internal alarms that may be associated with one or more of the defined data categories. Within digital data, streaming from the MFC, an Active Alarm Bit, is set whenever any MFC alarm is active.

No Flow Limit Threshold: No gas flow when the cells need it, will likely result in their death and the loss of the batch. This threshold initiates a "No flow" MFC alarm, when exceeded which can be used to alert the bioreactor operator to take action — open an upstream valve, check the inlet pressure conditions, verify MFC configuration and flow setpoint.

Reliability

Total Flow Hours: A rarely used function but potentially valuable is total flow hours through the sensor. This for maintenance or service, providing a link between actual usage time, maintenance intervals and metrology schedules. Can be used to change the way the equipment is managed, such as maintenance scheduling.

Flow deviation (Alarm) during steady state control: This alarm parameter is available for configuration and use in understanding the source of unexpected variations in dissolved oxygen level This parameter can be aligned with the bioreactor operating limits or be applied to tighter on-board MFC gas control. This function can be utilized to alert and potentially prevent flow hunting or oscillation conditions. This is helpful in trouble shooting and understanding the system limits.

Summary and Conclusion

The foregoing discussion used a bioreactor and a mass flow controller to highlight the impact intelligent, data-rich devices can have on bioprocess equipment design. Incorporation of an intelligent mass flow controller focused on the primary stakeholders needs. These devices significantly change the extent to which these stakeholders interact. A lifecycle framework was developed to help structure collaboration. To make appropriate use of available data, relevant categories were defined. A subset of device data elements introduced new design considerations enabled by such data, fostered by a new level of collaboration.

From among 500 or so available MFC data elements, a much smaller subset of 35 were identified and categorized under pedigree, performance and reliability. Collaboration and categorization served to reduce the generation, recording and management of excessive data. Table 1 aligned data use with the categories and expanded stakeholders to include drug maker personnel in metrology, process sciences, automation and quality. Relevant to these stakeholders, data subsets and their categories may be useful for device or equipment health, process analytics, maintenance, reliability and qualification. The data elements not only affect the design and realization of the bioreactor, data availability will also change how the equipment is specified, managed and serviced.

Change is a constant force, as pervasive in the biopharmaceutical industry as in any other industry. As biopharmaceutical manufacturers adopt technologies to create value and sustain competitiveness, so too, will equipment and component suppliers. Industry 4.0 principles will define a new, more agile biopharmaceutical industry. Fortunately, the path to achieving such goals is facilitated by myriad devices, capable of generating huge volumes of data. Incremental change is expected, with some increments being more far-reaching than others.

Incorporation of intelligent devices and, the appropriate integration and use, of their data is just beginning. As capabilities and requirements change over time, included among possible incremental changes may be a shift in subject matter expertise, perhaps, ultimately leading to enough machine intelligence to supplant the bioreactor and device suppliers' subject matter expertise, placing device, equipment and process troubleshooting, and maintenance fully in the hands of the drug maker. In any case, data and digitization, regardless of how and when it is leveraged, will create new opportunities for efficient, reliable drug supply.

Global Headquarters
Brooks Instrument
407 West Vine Street
P.O. Box 903
Hatfield, PA 19440-0903

T 215-362-3500
Toll Free (USA): 888-544-FLOW
Brooks-Mktg@BrooksInstrument.com