

# Real-time bioprocess insights and control for downstream

Precise high-speed, low-volume sample measurement with the Raman flow assembly



## Raman flow assembly

Optimized for downstream unit operations

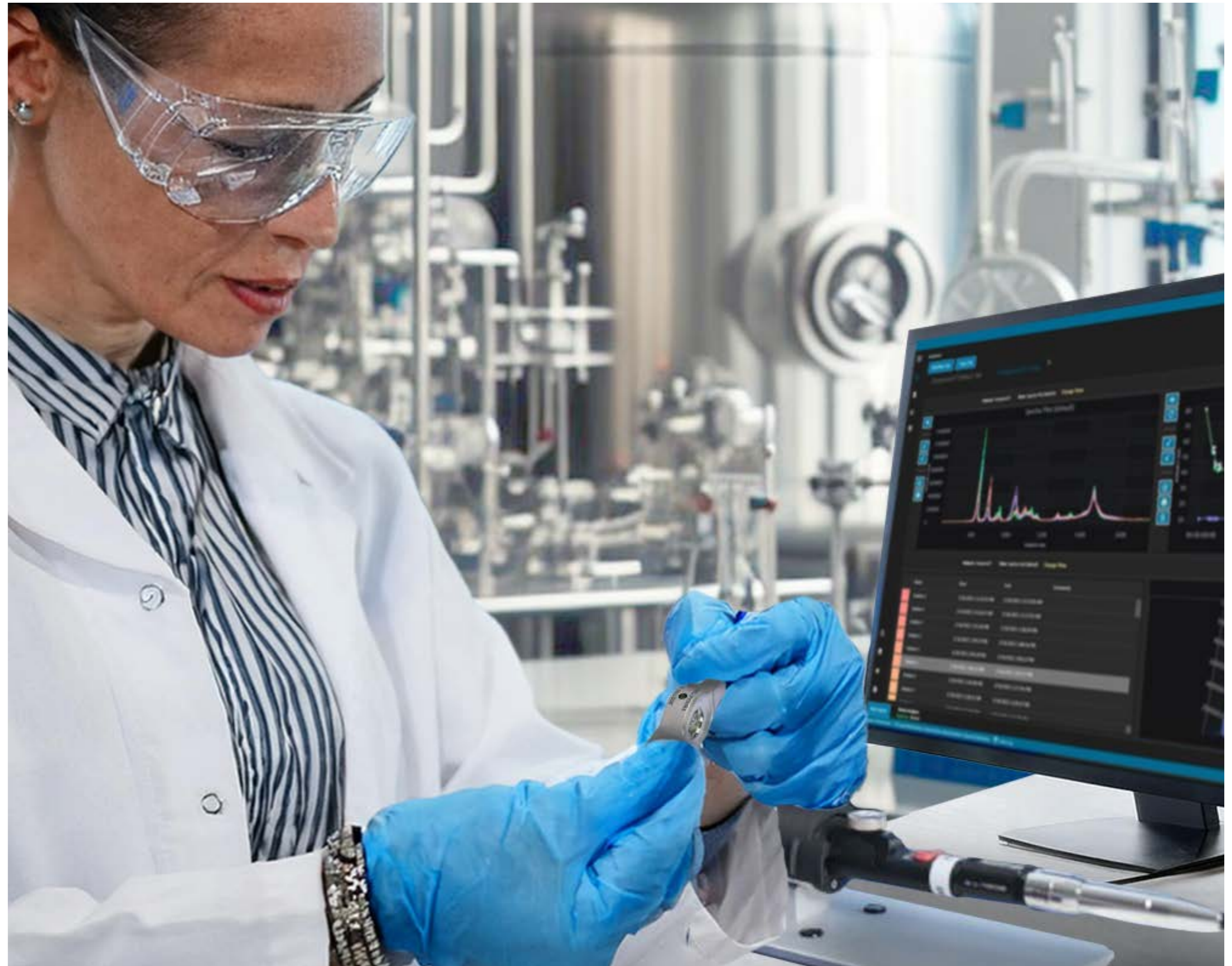
The Raman flow assembly brings in-line Raman spectroscopy measurement to downstream unit operations in bioprocessing.

It is a highly adaptable, *in situ* downstream sample interrogation system that integrates directly into process streams, reducing the need for offline measurements.

The Raman flow assembly also provides enhanced signal generation while accurately monitoring material in a flow path.

Components include:

- **Micro flow bench:** The flow bench features a reusable optic connected to an Rxn-10 probe, which has no product contact and is tuned for specific flow cell and sample conditions.
- **Micro flow cell:** The flow cell interfaces with the flow bench and allows the sample to flow within it. The flow cell may be sterilized by approved methods and can be either reused or discarded after use.





## Micro flow bench

A robust sampling platform for rapid composition measurement in downstream processes

The micro flow bench is the non-wetted component of the Raman flow assembly system which serves as an optimized Raman interface for downstream bioprocessing. It houses the micro flow cell and attaches to the multi-purpose Raman Rxn-10 probe, offering flexibility during process development.

The flow bench provides essential signal amplification and noise reduction, achieving lower limit of detection (LOD) and quantification (LOQ). This enhancement enables faster Raman data collection, ensuring the rapid response times needed for downstream composition analysis.



Raman micro flow bench

**The micro flow bench provides a secure interface for the micro flow cell and serves as the non-wetted portion of the Raman flow assembly.**

### Highlights:

- Delivered ready to connect to the Rxn-10 probe in benchtop position (other mounting options available)
- Designed for perfusion and downstream applications to allow liquid material to be analyzed without interrupting the flow
- Features an amplification option which delivers 3-4 times signal improvement over traditional immersion optics in non-turbid material\*
- Leverages the internal geometries of the micro flow cell to enhance the total signal-to-noise, allowing for faster sampling time or lower LOD
- Arrives factory tuned for the unique micro flow cell and application based on the fluid-path thickness and/or the refractive index of the samples

\* System-specific variables ultimately determine the level of enhancement

## Micro flow cell

Optimized for downstream volumes and flow rates with a sterilizable, versatile design

The Raman micro flow cell was designed to meet the unique requirements of downstream bioprocessing by delivering reliable *in situ* composition measurements in real time.

This innovative device seamlessly integrates into the Raman flow assembly's flow bench component, utilizing bio-compatible materials optimized for lab-scale bioprocess development. Its sealed, fixed focus design ensures long-term measurement stability and superior signal performance without any movable parts.

The micro flow cell accommodates a wide range of dynamic process parameters and sample changes in lab-scale bioprocess development. Offering both flexibility and efficiency, it can be easily cleaned, sterilized, and reused or discarded after each use.



Raman micro flow cell

**The innovative micro flow cell serves as the wetted portion of the Raman flow assembly, compatible with the micro flow bench. It provides long term measurement stability and superior signal performance.**

### Highlights:

- Features a sealed, fixed focus design with no movable parts for long-term measurement stability and superior signal performance
- Integrates directly into applications where static samples are not preferred, accommodating dynamic process parameters and sample changes (such as fluorescence decay or heating)
- Designed to produce laminar flow within a wide range of volumetric flowrates, pressures, tubing diameters, and fitting options
- Comes standard as ASME BPE SF4 Bio-Compatible, and may be cleaned and sterilized for re-use or discarded after each use

# Benefits at a glance

Optimized monitoring and control of downstream unit operations

Our Raman flow assembly is designed for development process analytical technology (PAT) scientists and engineers in biopharmaceutical development laboratories.

It provides multi-attribute composition measurements with significant Raman signal amplification for speed enhancements and lower limits of detection.

As a result, the system optimizes process efficiency and yield by integrating real-time Raman measurements into a wide variety of downstream operations.

## Simplified workflow and greater process efficiency

Flexibility to swap out flow cells any time without impacting the process or sterility



## Accurate and reliable downstream measurement

Achieves lower limits of detection through enhancement of the Raman signal



## Downstream process transparency

Gain valuable process insights and control for downstream bioprocessing unit operations



## Continuous, real-time measurements

Delivers 24/7 instant readings with high sensitivity for development-scale flow rates



## Lower costs and better outcomes

Reduces downstream bioprocessing costs and leads to safer patient outcomes



## Seamless scalability

Easily connects to a Raman Rxn analyzer and Rxn-10 probe, and ensures transferability when used with its calibration and verification kit



# Challenges in Life Sciences

## Overcoming analytical challenges in downstream bioprocessing

In the downstream phase of bioprocessing, isolating and purifying the target molecule from the reaction mixture is crucial to maintaining product quality. Each step in this phase must be meticulously managed to ensure the final product meets stringent quality standards. However, downstream bioprocessing faces unique challenges that complicate this task.

While upstream applications have widely adopted PAT solutions, downstream unit operations have lagged behind. The increasing complexity of purification steps, driven by intensified upstream processes, underscores the need for innovative solutions in downstream bioprocessing.

This complexity has not only increased processing time but also dramatically escalated costs, making it a significant hurdle for the industry.

### Issues with current downstream analytics

- Extractive
- Slow response time
- Insufficient nominal range
- Background interference
- Accuracy issues / non-linear effects
- Lack of stability
- Lack of specificity
- Hardware complexity for cGMP
- Lack of automation support



### Downstream analysis requirements:

- High-sensitivity measurement of small volumes
- Enhanced signal generation while accurately monitoring samples in a flow path
- Real-time monitoring for quality control
- Compatibility with standard sterilization protocols
- Non-invasive procedures to maintain sterility
- Quick and easy calibration and verification
- Compliance with regulations and cGMP standards
- Reliable technology transfer from lab to manufacturing

### Our answer

The **Raman flow assembly** addresses downstream bioprocess measurement challenges by handling reduced volumes and shorter cycle times efficiently. It optimizes Raman collection for low-turbidity, low-volume samples, ensuring high-sensitivity measurements and real-time monitoring. The Raman flow assembly supports non-invasive applications, maintaining sterility and compliance with cGMP standards. It is also designed to facilitate seamless lab-to-manufacturing transfer.

# Applications in Life Sciences

Raman-based process insights and control for downstream bioprocessing unit operations

Ideally suited for development-scale flow rates, the Raman flow assembly system allows real-time monitoring, rapid process optimization, and tight process control for chromatography and other downstream unit operations in bioprocessing.

This system is also suited for use in midstream applications for analyte monitoring in permeate.

## Downstream applications include:

- Aggregation
- Protein crystallization
- Formula stability
- Product critical quality attributes (COAs)
- Protein concentration
- Buffer excipients



## Your task

Real-time chemical composition measurement of downstream bioprocesses, such as:

- Chromatography
- Ultrafiltration/diafiltration
- Buffer preparation
- Final product

Plus, additional flow-based applications, such as:

- Perfusion permeate
- High-throughput sample screening

## Our answer

The **Raman flow assembly** precisely measures a critical downstream process parameter—chemical composition—in real time to ensure target protein quality while effectively monitoring aggregates. By combining practical techniques with fast, precise analysis, the Raman flow assembly helps scientists safely formulate biologics in the downstream phase more quickly, leading to effective patient outcomes.

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# Raman spectroscopy

Illuminating molecular secrets

## Technology overview

Utilizing visible or near-infrared light, Raman spectroscopy reveals intricate details about molecular vibrations. As light interacts with these vibrations, it undergoes inelastic scattering, resulting in a unique “molecular fingerprint.” This powerful technique enables identification, quantification, and monitoring of specific chemistries.

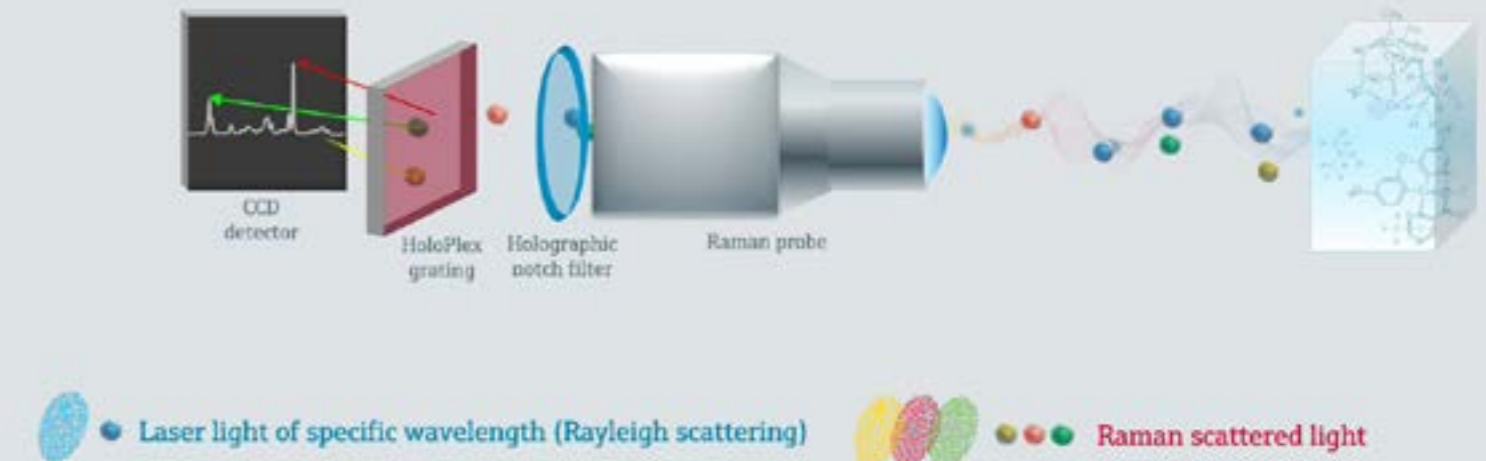
Raman spectroscopy, traditionally used in laboratory settings, has now become a crucial PAT solution in biopharmaceutical process development and commercial manufacturing.

Here is why:

- **Real-time measurement** – Raman provides real-time, *in situ* measurements during various bioprocessing operations.
- **Insensitivity to water** – unlike other techniques, Raman measurements remain accurate even in aqueous environments, making it ideal for bioprocessing applications.
- **Specificity** – Raman can distinguish between different molecules, even those with similar structures, enabling precise analysis of complex mixtures in biopharmaceutical processes.
- **Inline sampling** – directly inserted into bioreactors or flow paths, a single probe can simultaneously measure multiple parameters and quality indicators without disrupting the process.

## Raman technology illustrated

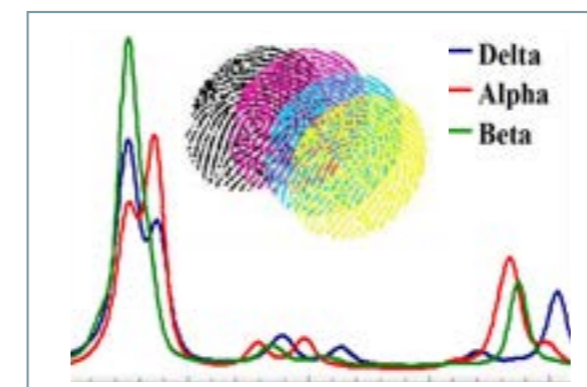
- Laser light of specific wavelength interacts with molecules which causes scattering
- 1 out of  $10^8$  photons is frequency-shifted due to specific energy transfer (Raman shift)
- Result: specific photons allow identification and quantification of materials (solvent, products, substrate)



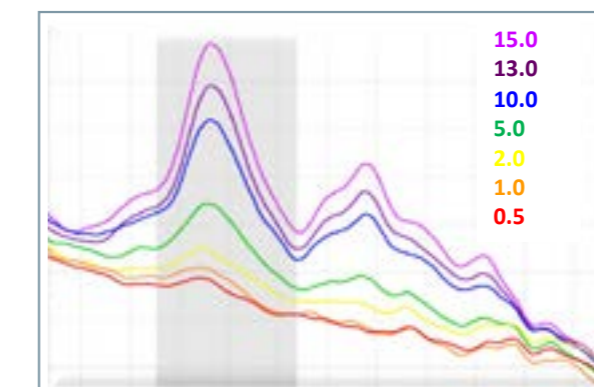
The collected light is interpreted as a spectrum by the camera, creating a “molecular fingerprint” of the material being sampled.

## Raman spectra from a lab sample or process can tell us...

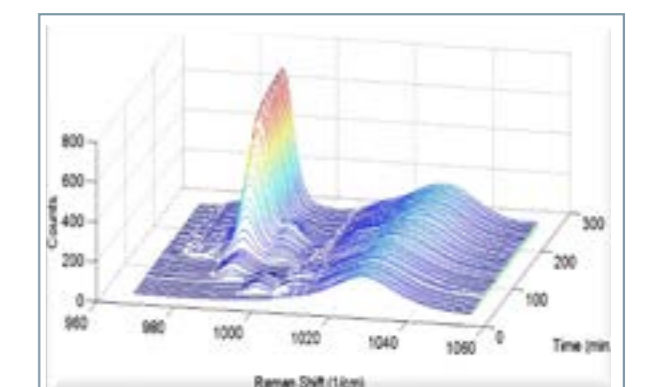
What is it?



How much?



Has it changed?



# Technical data

Explore the operational and technical details

The Raman flow assembly is part of our bioprocessing probe portfolio, known for having the highest quality of contact materials and the most flexible sampling capabilities in the market. Its components can be quickly configured thanks to its modular design.

- The Rxn-10 probe slides easily onto the micro flow bench
- After pulling back and twisting the light shield, the micro flow cell can be placed into the center cavity of the micro flow bench
- Once the micro flow cell is in place, the light shield should be returned to the closed position to secure the micro flow cell and offer added safety to the user
- The system has been designed to ensure maximum transferability, so replacing the micro flow cell on the micro flow bench will not affect the integrity of the resulting spectrum

## Quick & easy operation



Connecting the Raman Rxn-10 probe to the micro flow bench



Inserting the micro flow cell into the micro flow bench

## Technical specifications

### Micro flow bench

Non-wetted component



Sampling probe compatibility	■ Rxn-10 probe
Laser wavelength	■ 785 nm
Sample interface	<ul style="list-style-type: none"> <li>■ <b>Temperature (operating):</b> 0 to 40 °C (32 to 104 °F)</li> <li>■ <b>Temperature (storage):</b> -10 to 50 °C (14 to 122 °F)</li> </ul>
Wetted materials	■ n/a
Process connection	■ n/a
Fluid path thickness	■ 1.0 to 5.0 mm (flow cell driven)
Flow conditions / maximum volumetric flow rate	■ n/a
Dimensions (width x height x depth)	■ 254 x 102 x 66 mm (10.0 x 4.0 x 2.6 in)
Cleaning & sterilization	■ n/a
Calibration method	■ Micro flow bench calibration cell
Verification method	■ Micro flow bench verification cell with 70 % IPA

### Micro flow cell

Wetted component



Sampling probe compatibility	■ Rxn-10 probe
Laser wavelength	■ 785 nm
Sample interface	<ul style="list-style-type: none"> <li>■ <b>Temperature (operating):</b> 0 to 40 °C (32 to 104 °F)</li> <li>■ <b>Temperature (storage):</b> -20 to 60 °C (-4 to 140 °F)</li> <li>■ <b>Maximum pressure:</b> 4.8 barg (70 psig)</li> <li>■ <b>Relative humidity:</b> &lt;90 % non-condensing</li> </ul>
Wetted materials	<ul style="list-style-type: none"> <li>■ <b>Body:</b> 316 stainless steel</li> <li>■ <b>Surface finish:</b> Ra 15 with Electropolish to ASME BPE SF4 finish</li> <li>■ <b>Adhesive:</b> USP Class VI and ISO 10993 compatible</li> <li>■ <b>Window:</b> Proprietary material, optimized for bioprocesses</li> </ul>
Process connection	■ 5/16-24 flat bottom ferrules; up to 3/16 inch OD tubing
Fluid path thickness	■ 2.5 mm
Flow conditions / maximum volumetric flow rate	■ 50 mL / min for laminar flow, 100 mL / min max
Dimensions (width x height x depth)	■ 46 x 25 x 11 mm (1.8 x 1.0 x 0.4 in)
Cleaning & sterilization	■ CIP, SIP
Calibration method	■ n/a
Verification method	■ n/a



# Calibration and verification kit

Everything needed to standardize your Raman system for lab-to-process scalability

The Raman flow assembly calibration and verification kit contains all the necessary hardware for calibrating and verifying the calibration of the flow bench when it is connected to an Rxn-10 probe, paired with a Raman Rxn embedded analyzer.

Requiring no external power, these tools boost efficiency and reduce downtime via easy field deployment. The kit contains non-wetted parts which offers flexibility to be used any time without impacting sterilization.



Raman flow assembly calibration and verification kit

## Conveniently packaged within a durable case, each Raman flow assembly calibration and verification kit includes:

- A stainless-steel micro flow bench verification cell
- A temperature display that plugs into the calibration cell (the temperature is entered into the analyzer software)
- A USB flash drive containing the necessary calibration files
- A calibration certificate
- A syringe used to refill the verification cell if needed
- Two (2) syringe tips to refill the verification cell if needed
- Three (3) lens cleaning wipes to clean the optical surfaces of the calibration and verification cells



A verification cell being inserted into a micro flow bench connected to an Rxn-10 probe



An Rxn-10 probe with a micro flow bench and a calibration cell connected to a temperature display

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## Why partner with Endress+Hauser?

30+ years of Life Sciences innovation, expertise, and customer success

Endress+Hauser is the global leader in Raman instrumentation for laboratory, process, and manufacturing environments in the Life Sciences industry. In particular, biopharmaceutical manufacturers rely on our Raman analyzers and probes to help drive lab-to-process optimization.

Our Raman bioprocessing technology stands apart from other alternatives in the market because we offer:

- 30+ years of lab-to-process Raman leadership, expertise, innovation, and reliability
- 20+ years of cGMP expertise (10+ years leading the bioprocess PAT journey), with proven compliance, method transfer, and up time
- Proven successes documented in countless biopharmaceutical customer publications and other industry publications
- ISO 9001:2015 certification and experience hosting many successful audits by leading pharma/biopharma companies and suppliers
- The security of partnering with the Endress+Hauser Group and its network of global and local support process automation experts
- The most trusted, robust, scalable, and reliable Raman analyzer systems on the market
- Superior bioprocessing probes known for having the highest quality of contact materials and the most flexible sampling capabilities
- A demonstrated ability to simplify process equipment complexity and ease method transferability from lab-to-manufacturing
- Experience, training, support, data modeling, and advanced analytics services to allow companies to achieve rapid ROI
- Pharma Manufacturing's 2020 Pharma Innovation Award for the Rxn-46 bioprocessing probe



# People for Process Automation



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