

ProCellics™ Raman Analyzer with Bio4C® PAT Raman Software

An Easy-to-Use Process Analytical Technology (PAT) Platform to Monitor Cell Cultures In-Line and in Real-Time, from Process Development to Manufacturing

Cell culture processes are complex and highly variable in nature and yet only a handful of key parameters such as temperature, pH, and dissolved oxygen (DO) are typically controlled in real-time. While the measurement and control of these parameters are necessary for successful bioprocessing monitoring, they only provide indirect information which offers limited insights into actual culture content. Critical process parameters (CPP) and critical quality attributes (CQA) provide a direct indication of the culture's content and state but are generally measured off-line and therefore, not in real-time.

Specifically designed for the bioprocessing industry, ProCellics™ Raman Analyzer with Bio4C® PAT Raman Software enables you to perform in-line and real-time measurement of CPPs and CQAs (Table 1), from process development to manufacturing.

Benefits

Process improvement: Real-time monitoring of process parameters and quality attributes enables greater process understanding and optimization and increases control and reproducibility during process development phases.

Process automation: This PAT solution can reduce off-line sampling and manual feeding via an automated nutrient control loop strategy. It prevents the risk of contamination and minimizes the risk of batch failures.

The Raman PAT Platform ensures better process understanding and enables the ability to implement an automated process control strategy. In addition, the platform contributes to time-savings, provides operator flexibility, and reduces contamination risk and batch failures compared to manual sampling.

Table 1

Examples of CPPs and CQAs monitored by the Raman PAT Platform.

Critical process parameters (CPP)	Critical quality attributes (CQA)
Glucose	Protein titer
Lactate	Glycosylation
Glutamate	Aggregates
Glutamine	HCP
Ammonium	DNA
VCD	
TCD	
Amino acids	

Easy-to-use: The analyzer and software, specifically designed for the bioprocessing industry, are easy to use for both Raman experts and team members unfamiliar with Raman technology and multivariate analytics.

Easy-to-implement: The technology is supported by comprehensive technical support and services from our experienced engineers and chemometric bioprocessing experts ensuring successful implementation and use, from process development to manufacturing.

ProCellics™ Raman Analyzer

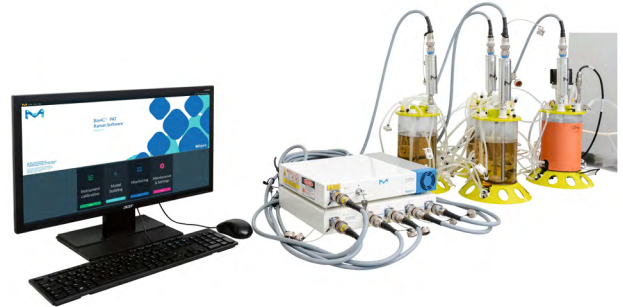
The analyzer is available in two configurations, fully adaptable to manufacturing requirements, to address a range of monitoring needs, from process development to manufacturing.

ProCellics™ Raman Analyzer single channel

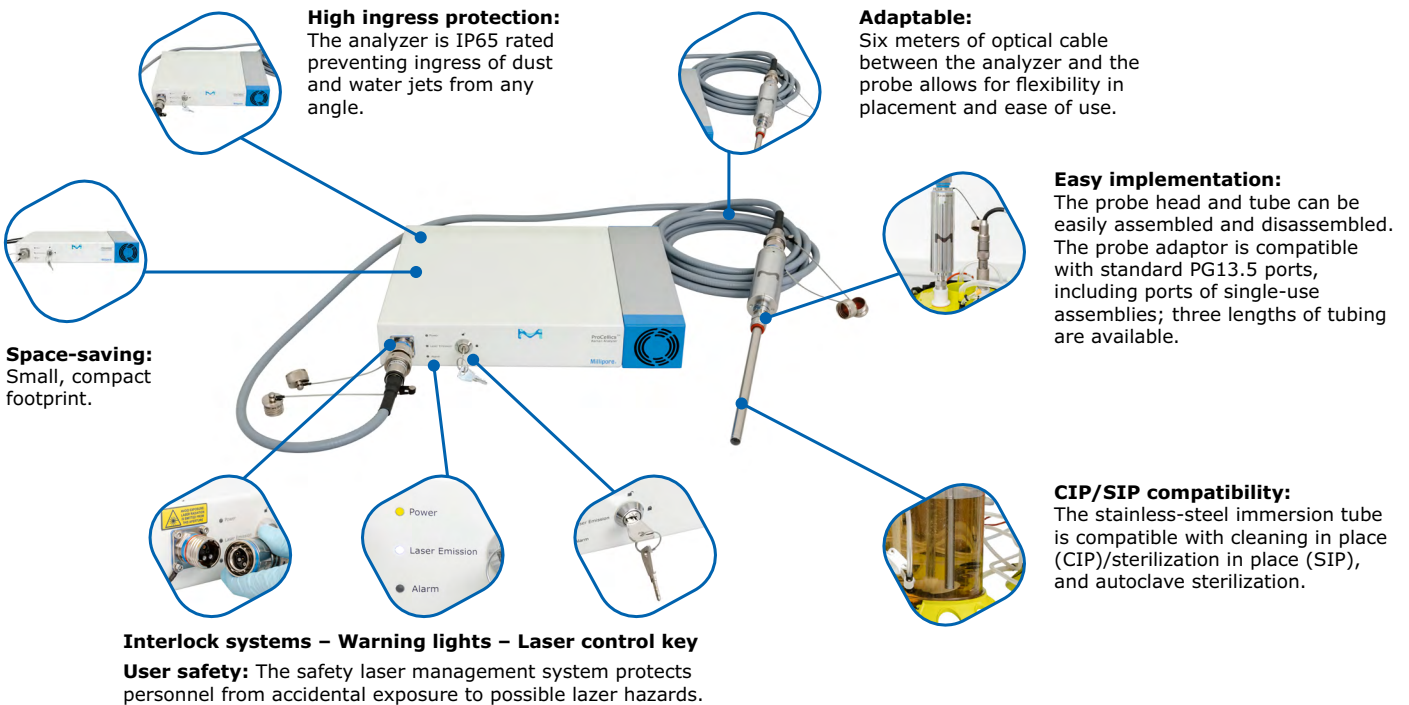
The single channel unit enables monitoring of cultures with a single probe. The package includes a base unit with a 785 nm laser, one probe, accessories and an all-in-one computer including Bio4C® PAT Raman Software.

ProCellics™ Raman Analyzer multi-channel

The multi-channel unit enables monitoring of up to four cultures in parallel within the same system footprint. This package includes a base unit with a 785 nm laser, a multi-channel unit with four probes, accessories and an all-in-one computer including Bio4C® PAT Raman Software.



System components



System Specifications

ProCellics™ Raman Analyzer	
General Specifications	
Laser wavelength	785 nm
Laser power	0–600 mW maximum, 0–100% adjustable
Spectral coverage	+150 to +4,000 cm ⁻¹
Spectral sampling	3 cm ⁻¹
Operating Temperature Range	+10 to +30 °C
Storage temperature	-10 to +60 °C
Relative humidity	20–80%, non-condensing
Warm-up time	<60 min
Power supply	100–240 VAC, 1.9 A, 47–63 Hz
Electrical power consumption	45 W typical, 65 W maximum
Base Unit	
Number of probes	1
Enclosure material	316L stainless steel, aluminum, silicon, antimicrobial white powder coating
Enclosure rating	IP65
Weight	7 kg (15.5 lbs.)
Dimensions (width × depth × height)	37.6 cm × 33.2 cm × 7.2 cm (15 in. × 13 in. × 3 in.)
External communication protocol	Ethernet (CAT6)
Multi-Channel Unit	
Number of probes	4
Enclosure material	316L stainless steel, aluminum, silicon, antimicrobial white powder coating
Enclosure rating	IP65
Weight	6 kg (13 lbs.)
Dimensions (width × depth × height)	37.4 cm × 33.0 cm × 7.2 cm (15 in. × 13 in. × 3 in.)

Probe Specifications

ProCellics™ Probe tube	
Standard	
Operating temperature	+5 to +140 °C
Tube length	225, 320, or 420 mm (custom on demand)
Tube outside diameter	12 mm
Port connection	PG13.5
Enclosure material	316L stainless steel (housing) and FDA-compatible sapphire (window)
Cleaning and sterilization	Clean-in-place/steam-in-place (2.2 bars max (32 psi)), autoclavable (30 cycles at 134 °C)
Fiber-optical cable	6-meter length; industrial robust design with laser safety interlock
Advanced probe tube (with light-reduction feature)	
Operating temperature	+5 to +140 °C
Tube length	110 or 225 mm (custom on demand)
Cap length	15 mm
Tube outside diameter (Tube & Cap)	12 mm
Port connection	PG13.5 (captive nut)
Enclosure material	316L stainless steel (housing) and FDA-compatible sapphire (window)
Cleaning and sterilization (Tube & Cap)	Clean-in-place/steam-in-place (2.2 bars max (32 psi)), autoclavable (30 cycles at 134 °C)
Fiber-optical cable	6-meter length; industrial robust design with laser safety interlock

International Regulatory Requirements

EU declaration of conformity – UL safety marking

The ProCellics™ Raman Analyzer and the ProCellics™ Raman Analyzer Multi-Channel Unit have been designed and manufactured in accordance with the international standard and test method defined by the IECCE organization according to CB Scheme process. CB Scheme process was applied for electromagnetic compatibility and safety compliance.

The ProCellics™ Raman Analyzer and the ProCellics™ Raman Analyzer Multi-Channel Unit are also subject to the UL listing Marking Program and meets the following marking and registration requirements:

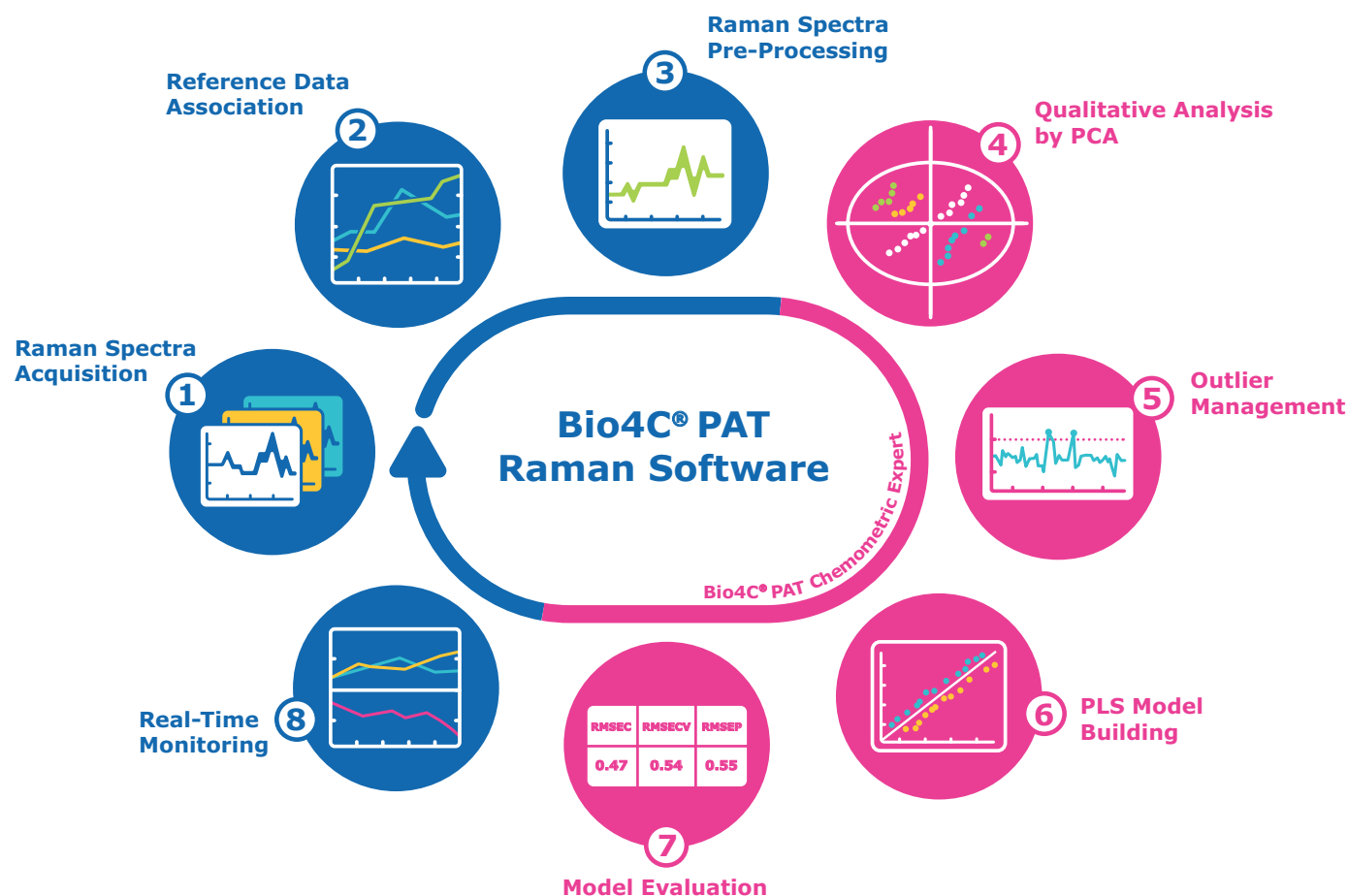
- UL registration can be verified on the UL website: www.ul.com
- Access to CB certificate: www.iecee.org/members

We also meet the regulatory requirements of the following organizations:



Bio4C® PAT Raman Software

The Bio4C® PAT Raman Software, including the Bio4C® PAT Chemometric Expert module, was developed by bio-process experts to provide an easy-to-use platform for expert and new users. The software provides end-to-end capabilities including spectral acquisition, reference data association, spectral pre-processing, chemometric model building, and real-time monitoring. The software suite was developed to facilitate 21 CFR Part 11 compliance.



Bio4C® PAT Raman Software

The Bio4C® PAT Raman Software interface is divided into four distinct modules for easy operation:

- **Instrument Calibration** guides the user on periodic verification of the analyzer and probe. It helps users through recalibration to ensure the best quality spectral acquisition for model building and monitoring.
- **Model Building** empowers the user to record, manage, pre-process and export processed data. This module helps users to build calibration datasets for model building.
- **Monitoring** allows the user to monitor process parameters and quality attributes in real-time and displays graphs showing the batch kinetic over time. Sending data through an OPC protocol, this module enables the configuration of a feedback control loop.
- **Maintenance and Settings** enable user management and house all software settings. Through this module, you can manage user access, electronic signatures, back-up/restore the database and access a complete audit trail.

Bio4C® PAT Chemometric Expert

Bio4C® PAT Chemometric Expert provides a robust and easy-to-use Raman model building platform for qualitative and quantitative analysis which can be seamlessly integrated into Bio4C® PAT Raman Software to enable real-time monitoring. Bio4C® PAT Chemometric Expert enables:

- Qualitative analysis with Principal Component Analysis (PCA) and quantitative analysis with Partial Least Squares (PLS).
- Ease-of-use through built-in autofit functions, interactive plots, summary tables to interpret modeling performances with relevant metrics such as Root Mean Square Error of Calibration (RMSEC), Cross-Validation (RMSECV) and Prediction (RMSEP).
- Outlier detection through the Hotelling's T^2 and dModX criteria.
- Full audit trail of all actions within the software.
- Remote communication via data connection through TCP/IP. Easy-to-configure Open Platform Communications Unified Architecture (OPC-UA) protocol.



Figure 1

Bio4C® PAT Chemometric Expert interface (a) PCA score plot view (b) Model performance evaluation view (c) Model criteria selection view (d) Outlier detection view.

Software Specifications

Bio4C® PAT Raman Software & Bio4C® PAT Chemometric Expert	
General	
Computer	Workstation, Dell OptiPlex All-In-One
Operating system	Microsoft Windows 10 Pro
CPU	Intel® Core™ i7-12700 CPU 2.10 GHz
Memory	16 GB (RAM)
Hard drive	400 MB available disk space
Graphics screen (recommended)	1,920 × 1,080 pixels
Computer Dimension	34.4 cm × 54.0 cm × 5.26 cm (H × W × D) 13.54 in. × 21.26 in. × 2.07 in. (H × W × D)
Weight	6.83 kg (15.1 lbs.)
Communication Protocol	
Connectivity	Ethernet (10-meter cable length, IP65 rating)
Remote communication	Data connection through TCP/IP
OPC communication	OPC-UA (Open Platform Communications Unified Architecture)
Regulatory compliance (main features)	
21 CFR part 11	✓
Data integrity	✓
Audit trail	✓
Database Back up & Retrieval	✓
User access control	✓
Electronic signatures	✓
Software security	✓ ISA/IEC-62443-3-3:2013 (security for industrial automation and control systems Part 3-3: System security requirements and security for control systems)

ProCellics™ Raman Analyzer accessories

External Measurement Unit (EMU)

The External Measurement Unit is an add-on system to the ProCellics™ Raman Analyzer to allow the bioreactor probe to perform measurement in an external cuvette. It is designed on a stable opto-mechanical assembly coupled with an interlock circuit for laser safety.



Figure 2

External Measurement Unit with a cyclohexane sealed cell to perform instrument recalibration (note: the cyclohexane cuvette is a spare part and is not included by default).



Figure 3

External Measurement Unit components in their transportation box.

The EMU can address two different user situations:

Calibration with cyclohexane

Cyclohexane is an ASTM reference standard recommended for the calibration of spectroscopic systems. However, because of the substance's toxicity, it requires specific handling procedures to ensure user safety. To facilitate safe cyclohexane use, the EMU has been designed to accommodate the measurement of cyclohexane in a sealed cuvette allowing measurements without any contact with the substance. The non-invasive measurement guarantees a reproducible calibration of the analyzer.

Off-line analytics

ProCellics™ Raman Analyzer can be also used in off-line mode to perform preliminary work or verification. The EMU provides the user with the possibility to fill a quartz cuvette and perform a measurement in a dark environment to ensure reproducible measurements. In addition, the user safety is ensured by adding a interlock safety element directly connected to ProCellics™ Raman Analyzer. If the EMU is not properly closed prior to measurement, the laser emission is not possible.

Adaptation Kit for Mobius® 3L Single-Use Bioreactor

The adaptation kit secures a correct and reproducible setup for immersion of the probe into the Mobius® 3L Bioreactor. It minimizes the risk of Raman signal variability due to the probe position, ensures stability of the assembly and reduces the risk of contamination related to potential leaks at the port/probe connection.



Figure 4
PG13.5 port adaptor.



Figure 5
Probe holder.

The kit is composed of a PG13.5 port adaptor and a probe holder to be associated with the motor adapter of the bioreactor. The port adaptor is made of stainless steel 316L material and is autoclavable (30 cycles). Specific tools are provided to ensure easy installation of the adaptation kit.

Services and Support

To ensure smooth and efficient implementation of ProCellics™ Raman Analyzer with Bio4C® PAT Raman Software, we offer comprehensive services to help you save time, lower costs, and comply with regulations. All our services are delivered by our global experts who have extensive experience with this technology.

Applications Assessment Services

Our presales service program allows users to experience the benefits of the ProCellics™ Raman Analyzer with Bio4C® PAT Raman Software prior to purchase.

Preliminary study

- Test conducted on customer samples (1 cell culture type, up to 5 samples)
- Test executed at our facilities
- Report provided to customer
- Debriefing call with technical support team

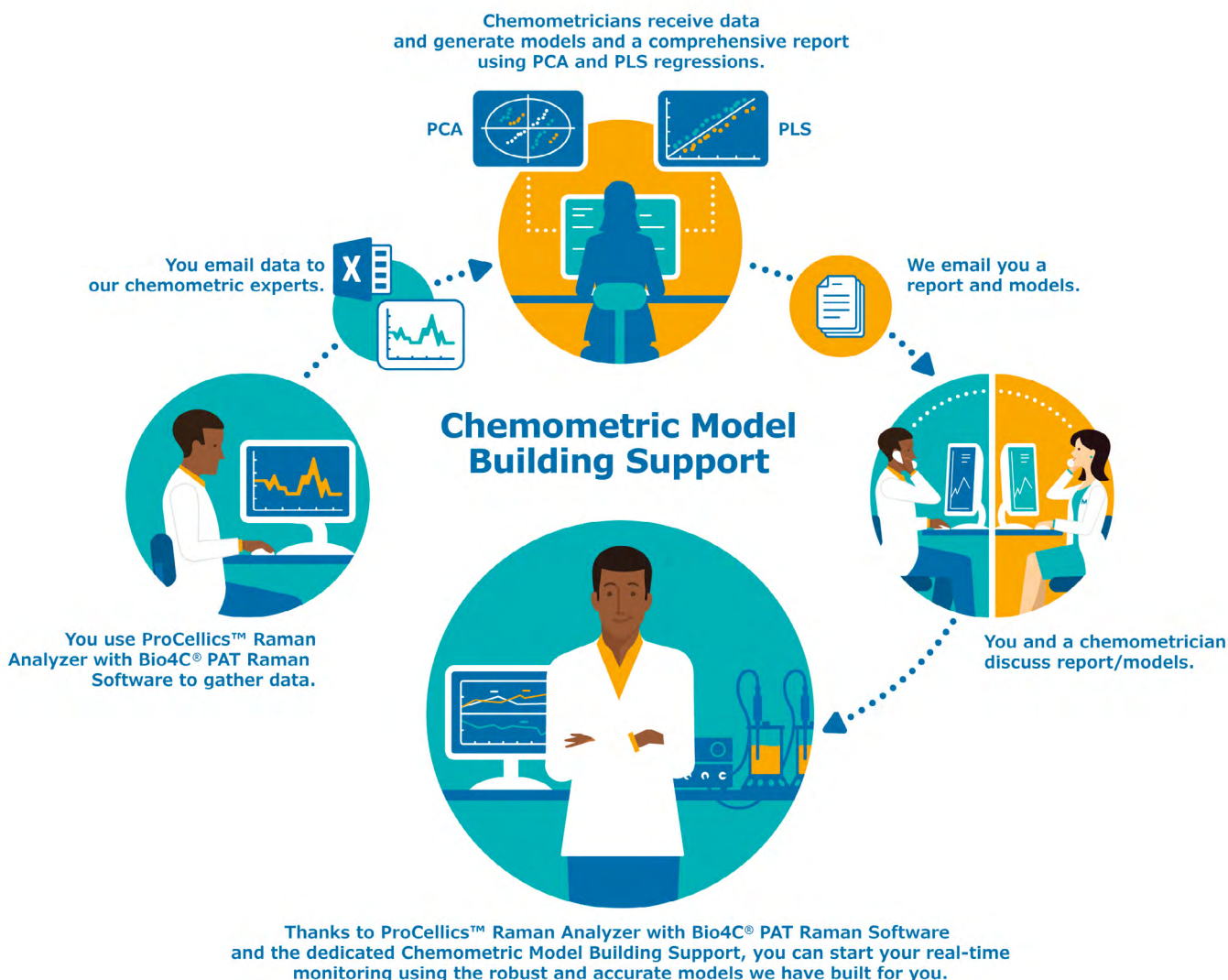
Evaluation package (including system rental and support)

- Duration: one month
- System shipped to customer's location
- Installation, qualification, and training at customer site
- Two-day support including evaluation and chemometric models for five parameters of interest (glucose, lactate, total cell density (TCD), viable cell density (VCD) and titer)

Software Services

Chemometric Model Building Support and Training Package

To assist in building robust chemometric models, our chemometric experts provide guidance on chemometric foundations, best practices in reference data collection and association, spectra analysis and model building using state-of-the-art algorithms.



Qualification Services

Our qualification services are designed to make the integration of the ProCellics™ Raman Analyzer with Bio4C® PAT Raman Software into your process as seamless as possible and ensure it is properly installed and functioning per your predefined requirements.

Installation Qualification and Operational Qualification (IQ/OQ)






- Completion of as-built system documentation
- Visual inspection
- Instrumentation verification
- Performance verification
- Safety verification
- Functional tests
- Full qualification report


Training


Comprehensive training ensures users have the expertise to properly implement the ProCellics™ Raman Analyzer with Bio4C® PAT Raman Software as part of their development projects.

Service Reliance Plans

System Service Reliance Plans offer priority access to a wide range of services and support ensuring your equipment is properly maintained.

Services	Details	Protection Level			Risk Level
		Total Reliance Plan	Advanced Reliance Plan	Essential Reliance Plan	
System Eligibility		<10 years	<15 years	All ages	
Preventive Maintenance (PM) visit	1 PM visit (labor & travel included) ^(a)	✓	✓	✓	
Preventive Maintenance (PM) spare parts kit	Yearly preventive maintenance spare parts kit	✗	✗	✗	
Traceable and auditable documentation	Full service report	✓	✓	✓	
Spare parts storage assessment	Spare part advisory service (first year only)	✓	✓	✓	
Asset tagging solution	QR code sticker and cards	 ✓	 ✓	 ✓	
Remote troubleshooting	Priority remote support on system and software ^(b) – phone and email	24 h ^(e)	24 h ^(e)	✓	
	Priority remote support on system and software ^(b) – remote connection ^(c)	 ✓	 ✓	✗	
On-site troubleshooting	On-site support – response time	Within 48 h ^(f)	Within 5 days ^(f)	No engagement on response time	
	Troubleshooting/repair visit (labor and travel included)	Unlimited	1 per year (no carry over)	Billable services	
Spare parts	Spare parts for repair ^(d)	Included	15% discount ^(g)	10% discount ^(g)	
Software update	Minor software update execution ^(h)	✓	✓	✓	

 = Remote connection

 = Asset Tagging

(a) Maintenance kit to be purchased separately prior to service.

(b) Support provided via phone and email and limited to 10 cases per year and 30 hours of investigation.

(c) Only for suitable systems and if the connection is tested upfront with customer.

(d) Best effort is aimed at supplying spare parts and/or find equivalent over the system's lifetime, but no guarantee of availability over time.

(e) 24 h from the customer's requests, to our service team returning the call. May vary depending on customer's location.

(f) Five business days for Advanced, or 48 business hours for Total, from the time when it is agreed that a troubleshooting visit was necessary.

(g) Discount on list price.

(h) For Software developed by Merck only. Included if performed during the yearly PM visit. Post update qualification not included.

Introduction to Raman technology and chemometric analysis covers:

- Overview of the analyzer components and functions
- Laser safety information and recommendations
- Installation of the Raman analyzer
- Software settings and user management
- Guidance on instrument calibration
- Data acquisition, management, and export to a chemometric model building support software
- Use of the analyzer and software for batch monitoring

Spare Parts & Repair Services

Repair services

In the unlikely event your system experiences a problem, our worldwide network of engineers will provide onsite technical support to get the system back up and running as quickly as possible.

Spare parts

Purchasing spare parts directly from us guarantees receipt of the correct part.

Please refer to the complete spare part list document MK_CA7273EN.

For additional details, please refer to the System Service Reliance Plans Data Sheet MK_DS7881EN.

Available at SigmaAldrich.com/services-plans

Ordering information

Product Description	Catalog Number
System	
ProCellics™ Raman Analyzer 785 Single Channel with 1 probe and a tube of 225 mm	RAM785PSC225
ProCellics™ Raman Analyzer 785 Single Channel with 1 probe and a tube of 320 mm	RAM785PSC320
ProCellics™ Raman Analyzer 785 Single Channel with 1 probe and a tube of 420 mm	RAM785PSC420
ProCellics™ Raman Analyzer 785 Multi-Channel with 4 probes and tubes of 225 mm	RAM785PMC225
ProCellics™ Raman Analyzer 785 Multi-Channel with 4 probes and tubes of 320 mm	RAM785PMC320
ProCellics™ Raman Analyzer 785 Multi-Channel with 4 probes and tubes of 420 mm	RAM785PMC420
ProCellics™ Raman Analyzer 785 Additional Module to complete the item RAM785PSC225	RAM785PAM225
ProCellics™ Raman Analyzer 785 Additional Module to complete the item RAM785PSC320	RAM785PAM320
ProCellics™ Raman Analyzer 785 Additional Module to complete the item RAM785PSC420	RAM785PAM420
ProCellics™ Raman Analyzer 785 Single Channel with 1 probe and an advanced tube of 225 mm for light-reduction	RAM785PSC225LR
ProCellics™ Raman Analyzer 785 Multi-Channel with 4 probes and advanced tubes of 225 mm for light-reduction	RAM785PMC225LR
ProCellics™ Raman Analyzer 785 Additional Module to complete the item RAM785PSC225LR	RAM785PAM225LR
ProCellics™ Raman Analyzer 785 Single Channel with 1 probe and an advanced tube of 110 mm for light-reduction	RAM785PSC110LR
ProCellics™ Raman Analyzer 785 Multi-Channel with 4 probes and advanced tubes of 110 mm for light-reduction	RAM785PMC110LR
ProCellics™ Raman Analyzer 785 Additional Module to complete the item RAM785PSC110LR	RAM785PAM110LR
Power Cord 230V (Austria, Belgium, Bulgaria, Cyprus, Estonia, Finland, France, Germany, Greece, Lithuania, Luxemburg, Portugal, Rumania, Slovenia, Spain, Sweden, The Netherlands, Turkey, Korea, Indonesia, Russia, Kazakhstan)	FTPF01866
Cord Line 115V (United States, Canada, Puerto Rico, Taiwan, Thailand, Mexico, Columbia)	FTPF02471
Simplicity Line Cord UK (Ireland, Malta, United Kingdom, Hong Kong, Singapore, Vietnam)	SIMCABLE1
Simplicity Line Cord DENMK (Denmark)	SIMCABLE2
Simplicity Line Cord SAF (South Africa)	SIMCABLE3
Cable IEC(F) to SZ Plug (M) (Liechtenstein, Switzerland)	SIMCABLE4
Cable IEC(F) to Plug CHINA (M) (Argentina, China)	SIMCABLE5
Cable IEC(F) to Plug INDIA (M) (India)	SIMCABLE6
Cable IEC(F) to JAPAN Plug (M) (Japan)	SIMCABLE7
Cable IEC(F) to AUSTRALIA Plug (M) (Australia, New Zealand)	SIMCABLE8
Cable IEC(F) to Plug BRAZIL (M) (Brazil)	SIMCABLE11
Accessories	
ProCellics™ Raman Analyzer 785 External Measurement Unit	RAM785EMU
ProCellics™ Raman Analyzer 785 Adaptation kit for Mobius® 3L Single-Use Bioreactor	RAM785MCR3LADAPT
Software	
Bio4C® PAT Raman Software – Annual License 1 Single Channel	BIO4CRSPSC1
Bio4C® PAT Raman Software – Annual License 1 Multi-Channel	BIO4CRSPMC1
Bio4C® PAT Raman Software – 10 days Chemometric model building support and training package	BIO4CRSCHEM010
Bio4C® PAT Raman Software – OPC Connect Support	BIO4CRS0PC
Services & Support	
Pre-study, quantity 1 sample set	SSVPREPCL
Evaluation package (including system rental and support), 1-month	SSVRENPCCL
IQ/OQ execution protocol and travel	SSVQUAPCL
Essential Service Reliance Plan	SSVESSPCL
Advanced Service Reliance Plan (Essential Service Plan + Advanced Coverage)	SSVESSPCL + SSVADPPCL
ProCellics™ Raman Analyzer with Bio4C® PAT Raman Software Training	TRPCSHWSW

Merck KGaA

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For additional information, please visit www.sigmaaldrich.com/PAT

To place an order or receive technical assistance, please visit www.sigmaaldrich.com/offices

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose

