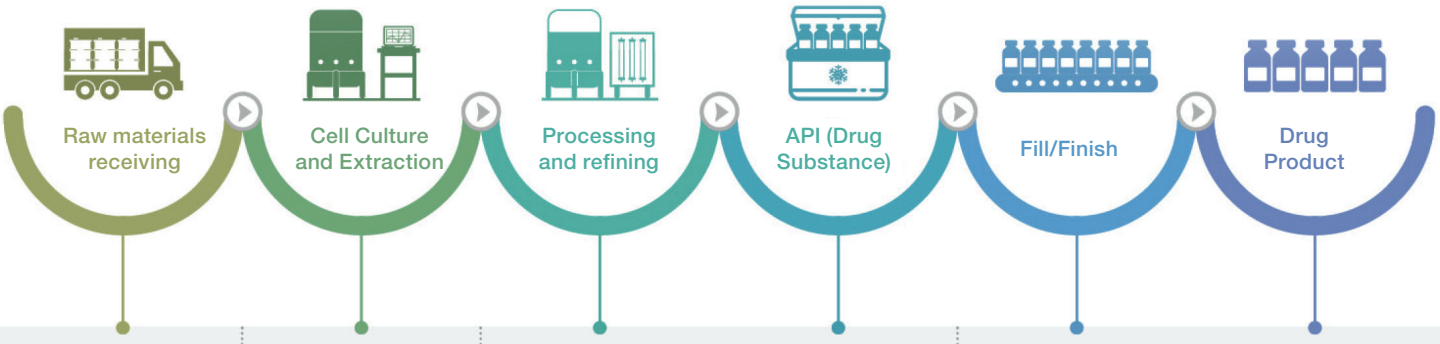
Process analytical technology

Process monitoring from raw materials to finished products in biopharmaceutical industry

thermo scientific

Process monitoring analyzers

As part of current good manufacturing practice (cGMP), many pharmaceutical manufacturers are adopting Process Analytical Technologies (PAT), Quality by Design (QbD), or Process Validation (PV) to provide continuous process verification and analysis. Analytical instruments may be used for at-line and in-process monitoring to bring the technology to the sample to speed up the analysis process and enable more flexibility from a smaller footprint.



Raw-material Identification	Process Monitoring	API, Excipient Identification		Finished Product Testing	
 Thermo Scientific™ TruScan™ RM Analyzer	 Thermo Scientific™ Prima™ BT Mass Spectrometer	 Thermo Scientific™ TruScan™ RM Analyzer	 Thermo Scientific™ TruScan™ RM Analyzer	 Thermo Scientific™ TruScan™ RM Analyzer	 Thermo Scientific™ TruScan™ RM Analyzer
 Thermo Scientific™ microPHAZIR RX Analyzer	 Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer	 Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer		 Thermo Scientific™ microPHAZIR RX Analyzer	

Nutrient & metabolite monitoring workflow

Sparge Gas
- Oxygen, Carbon Dioxide, Nitrogen, Argon

Outlet Gas
- Oxygen, Carbon Dioxide, Nitrogen, Argon
- Derived Values (RQ, CER, OUR)
- Methanol, Ethanol, Water, Hydrogen, Ammonia, Hydrogen Sulfide

Prima BT Mass Spectrometer

Outlet Gas

Sparge Gas

Analysis of the respiratory gases being fed into and produced from the cell culture is an ideal way of characterizing the behavior and productivity of the cells during the process.

Hyperforma™ Bioreactor

HyPerforma™ G3 Controler

An innovative, open-architecture, cost-effective controller offering a compact design—enabling users to easily scale-up and adapt to suit specific process and application goals. It can control most bench-scale single-use bioreactors and fermentors up to 15 L.

- Glucose, Glutamine, Glutamate, Lactate, Ammonia etc
- Protein purification
- Analyte ID

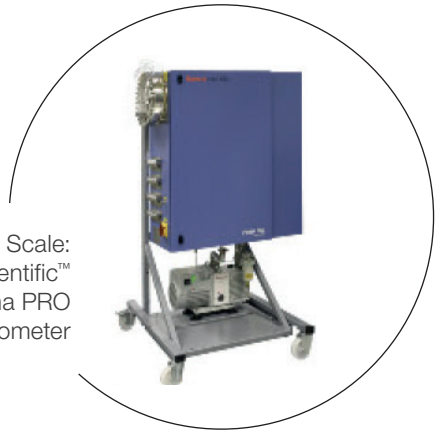
MarqMetrix All-In-One Process Raman Analyzer

In biopharmaceutical production, cells require a feeding cycle of glucose to enable cell reproduction. The MarqMetrix All-In-One Process Raman Analyzer leverages compact and simplified hardware along with data science tools to model the glucose content of a bioprocess and tell you exactly when to add more glucose to ensure cell production at a precise rate.

Off-gas analysis

Lab Scale:
Thermo Scientific™ Prima BT Mass Spectrometer

Production Scale:
Thermo Scientific™
Prima PRO
Mass Spectrometer



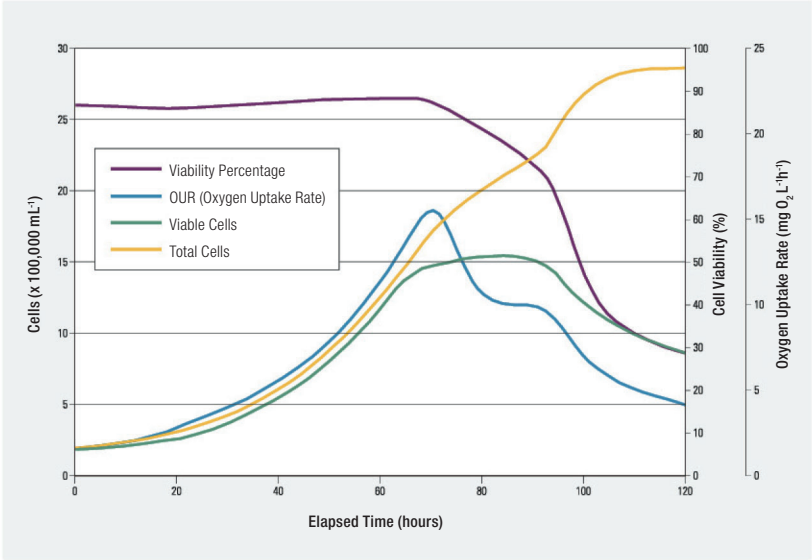
Prima BT I Prima Pro Mass Spectrometers

In mammalian cell cultures, the sparge gas composition is a frequently changing mixture of several compounds. The implementation of real-time, off-gas analysis using Mass Spectrometry in mammalian cell culture can help identify process deviations during bioreactor runs and evaluate batch to batch variation, within predefined specifications, for robust manufacturing.

Features • Application fields

- Tracking growth factor and enzyme substrate consumption by analyzing exhaust gas
- Identification of end point for maximum production yield
- Accurate Oxygen Uptake Rate (OUR), Carbon dioxide Evolution Rate (CER), Respiratory Quotient (RQ) measurements
- Precise multi-component analysis with high reliability
- 16, 32, or 64-port Rapid Multistream Sampler (RMS) enables reliable monitoring of multiple fermentors and bioreactors
- 21 CFR Part 11 regulation observance, GasWorks software included

CER/OUR/RQ real-time monitoring



10-liter Hybridoma plot generated by the Prima process mass spectrometer

	Inlet Air	Fermentor Outlet
Time	12:01:01	12:01:11
Nitrogen	78.0935%	78.1566%
Carbon Dioxide	0.0394%	0.9774%
Oxygen	20.9271%	19.9246%
Argon	0.9400%	0.9414%
CO_2 evolution rate (CER)		0.9372
O_2 uptake rate (OUR)		1.0186
Respiratory Quotient (RQ)		0.9201

Prima BT process mass spectrometer data

Metabolite monitoring with Raman spectroscopy

Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer

HyPerforma™ glass bioreactor with MarqMetrix All-In-One Process Raman Analyzer

MarqMetrix All-In-One Process Raman Analyzer

Raman Spectroscopy is used for in-line, real-time monitoring of biopharmaceutical production processes. Cell culture processes are very labor intensive due to frequent sample analysis required to estimate cell feed amounts (glucose) The Thermo Scientific™ MarqMetrix™ All-In-One Process Raman Analyzer connects to the bioreactor to perform in-line measurements of TCD, VCD, and the concentrations of glucose, & lactate.

The MarqMetrix All-In-One Process Raman Analyzer is designed for out-of-the-box use, enabling you to take highly accurate Raman measurements in less than 15 minutes. Pack this analyzer in a protective case and take it to the point of need, as its factory calibration ensures continuous and precise analysis on the go. The MarqMetrix All-In-One Process Raman Analyzer can be easily integrated into your existing process and eliminates the need for costly technical expertise.

Features • Application fields

- Analysis without sample preparation, delivering Raman spectral results in real time
- Easy setup and deployment by non–Raman spectroscopists
- Nondestructive workflows to protect precious samples
- Noninvasive handling to minimize contamination of samples
- Small footprint for convenient deployment
- Factory calibration for hardware stability and portability

Metabolite parameters and high measurement precision

Metabolite Predicted	R^2 Predicted	RMSEC	RMSECV	RMSEP
Viability (%)	0.9	2.92	3.12	2.50
TCD (106 TC/mL)	0.97	2.63	3.45	1.77
VCD (106 VC/mL)	0.97	2.83	3.59	1.80
TCD (106 TC/mL)	0.9	1.83	2.11	1.72
VCD (106 VC/mL)	0.9	1.73	2.43	1.62
Viability (%)	0.94	2.55	3.48	2.17
Diameter (pm)	0.91	0.41	0.47	0.41
Gin (mmol/L)	0.96	0.23	0.28	0.25
Glu (mmol/L)	0.97	0.38	0.4	0.40
Glue (g/L)	0.97	0.42	0.64	0.38
Lac (g/L)	0.93	0.16	0.2	0.16
NH4+ (mmol/L)	0.95	1.04	1.27	0.79

Correlation of model prediction with offline data analysis

Various parameters (Lactate, glutamine, glutamate, viable cell density [VCD], total cell density [TCD]) during the cell culture process can be analyzed with high accuracy using the MarqMetrix All-In-One Process Raman Analyzer.

*The root mean square error of calibration (RMSEC), root mean square error of cross-validation (RMSECV), and root mean square error of prediction was calculated for each parameter (RMSEP)

Single-use technology

Hyperforma™ Bioreactor Systems

The Hyperforma™ Bioreactor Systems, developed based on a robust industrial controller, can analyze various data measured in gas and liquid during cultivation in real-time and automatically reflect them in the culture process by linking multiple sensors and process monitoring equipment.

Hyperforma™ single-use bioreactor

The most extensive single use product, Thermo Scientific™ DynaDrive Single-Use Bioreactor (S.U.B.), is used in a variety of applications, including biosimilars, vaccines, viral vectors, and anaerobic microbial cultures. The 10:1 turn down powertrain minimizes the N culture's foot print. At least 50L, 500L, 3000L, and 5000L of products are provided.

Hyperforma™ single-use fermentor

Hyperforma™ single-use fermentor, which can supply up to 2 VVM (vessel volume/minute) of gas by adopting a dedicated vessel design, achieves the convenience of single-use and productivity of stainless in aerobic microorganisms at the same time. Products in sizes 30L to 300L are available.

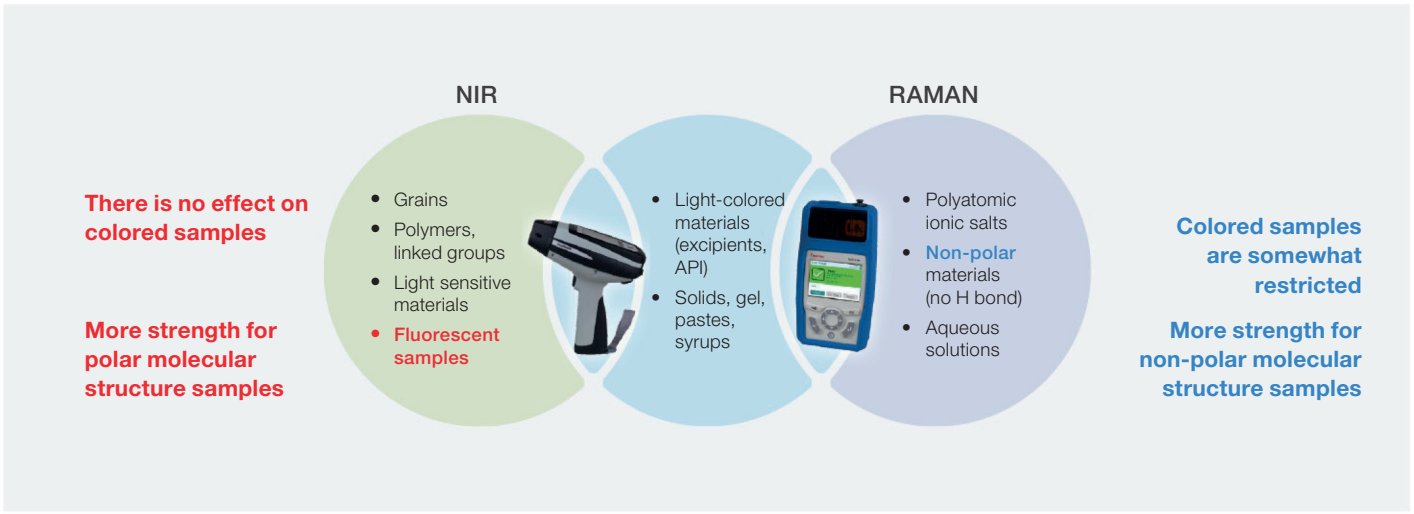
5000L DynaDrive™ Single-Use Bioreactor

300L HyPerforma™ Enhanced Single-Use Fermentor

3L HyPerforma™ Glass Bioreactor

Material identification

The divide between NIR and Raman



Handheld Raman Analyzer

Thermo Scientific™ TruScan™ RM Handheld Raman Analyzer

- Ensure the quality of materials from incoming raw material through finished product
- Reliable material identity verification through sealed packaging in seconds
- Users can build advanced, customized qualitative and quantitative methods for complex material analysis problem
- Compliance of USP 1120, EP 2.2.48

Handheld NIR Analyzer

Thermo Scientific™ microPHAZIR™ RX Analyzer

- Used for total inspection from pharmaceutical/bio raw material warehousing to finished products
- Microcrystalline Cellulose. It is optimized for analyzing colored samples, herbal medicines, HCl, etc.
- Ability to analyze moisture content in seconds
- Compliance of USP1119, EP 2.2.40

Thermo Fisher SCIENTIFIC

Learn more at **Thermofisher.com/pharmamanufacturing**

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