Brochure

ThermoFisher SCIENTIFIC

Process monitoring

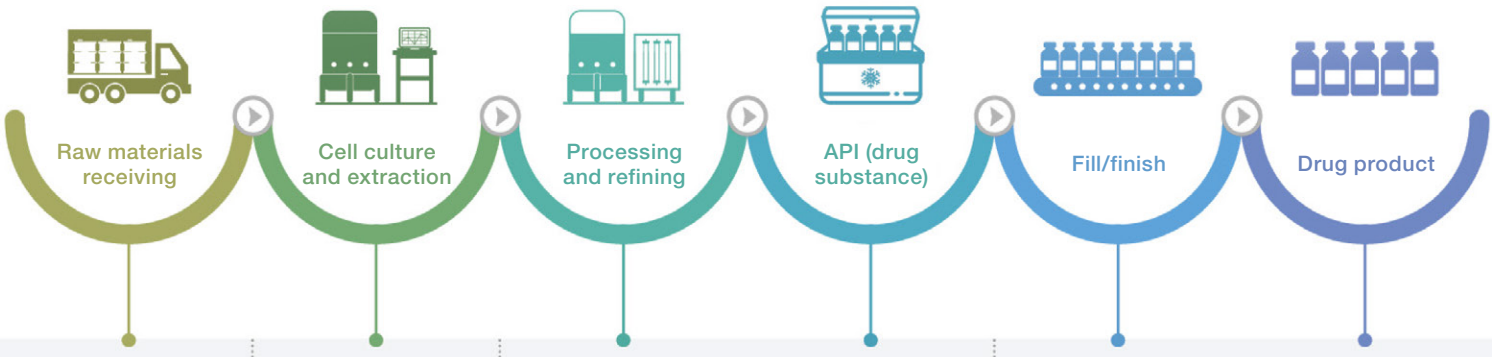
Process analytical technology

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

Thermo Scientific™ TruScan™ RM Analyzer

Process monitoring

Thermo Scientific™ Prima™ BT Mass Spectrometer

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

API, excipient identification

Thermo Scientific™ TruScan™ RM Analyzer

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

Thermo Scientific™ TruScan™ RM Analyzer

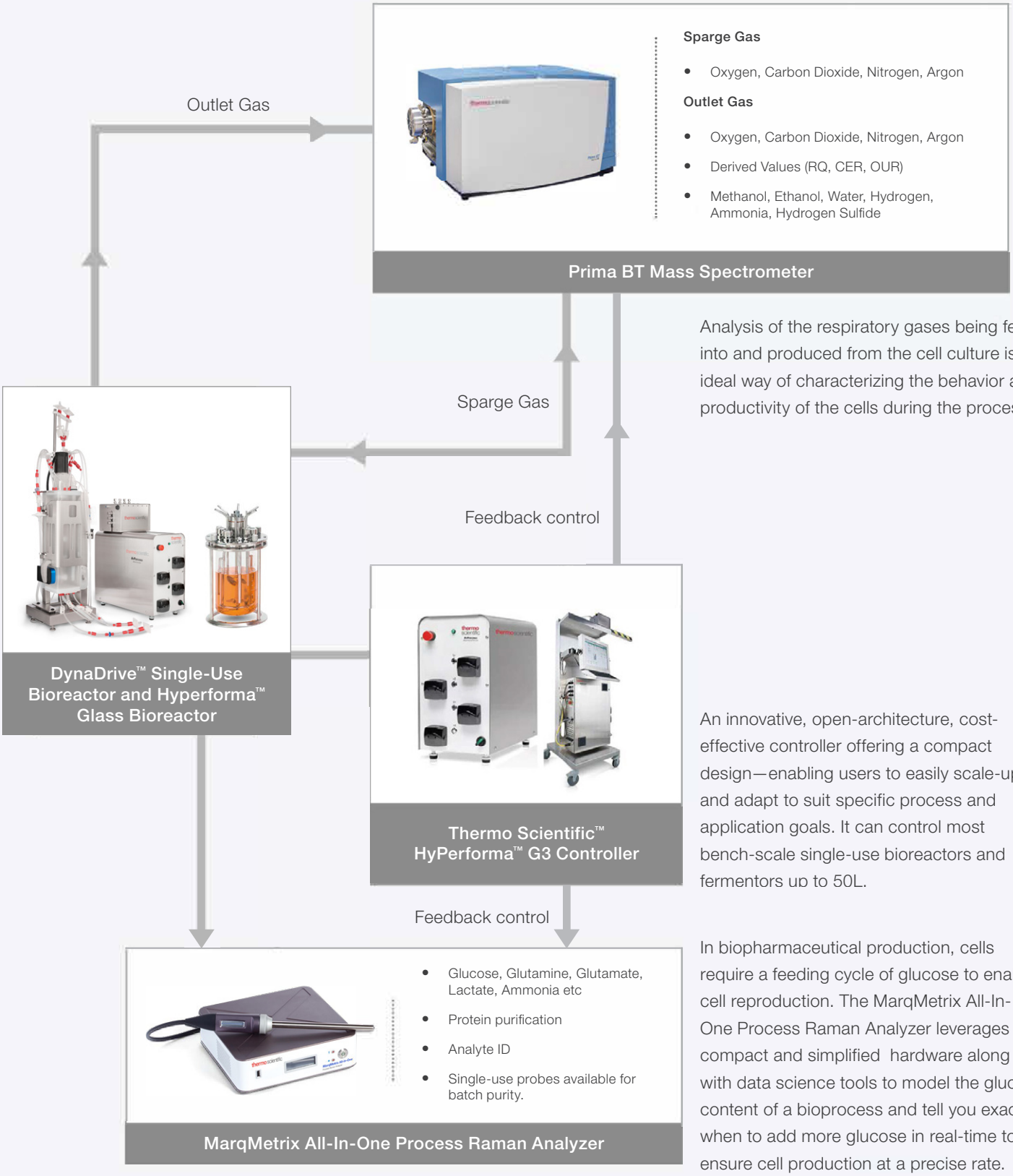
Thermo Scientific™ Prima PRO 710 Process Mass Spectrometer

Finished product testing

Thermo Scientific™ TruScan™ RM Analyzer

Thermo Scientific™ TruScan™ RM Analyzer

Automated feedback control workflow



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.

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 50L.

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 in real-time to ensure cell production at a precise rate.

Off-gas analysis

Lab Scale:
Thermo Scientific™ Prima BT Mass Spectrometer

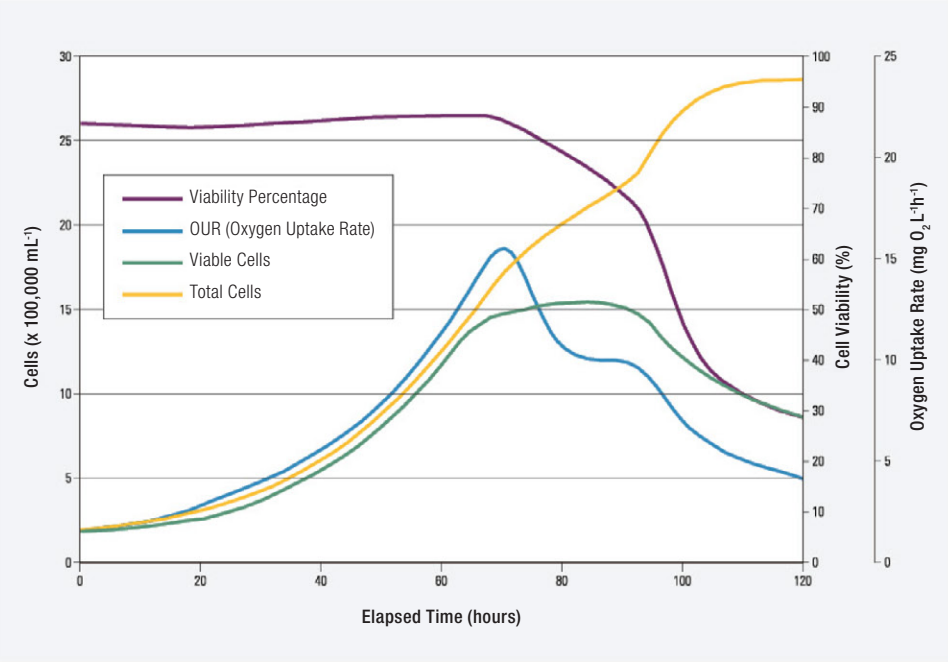
Prima BT & Prima PRO Mass Spectrometers

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

Solvent Drying

Production Scale:
Thermo Scientific™
Prima PRO 710
Mass Spectrometer

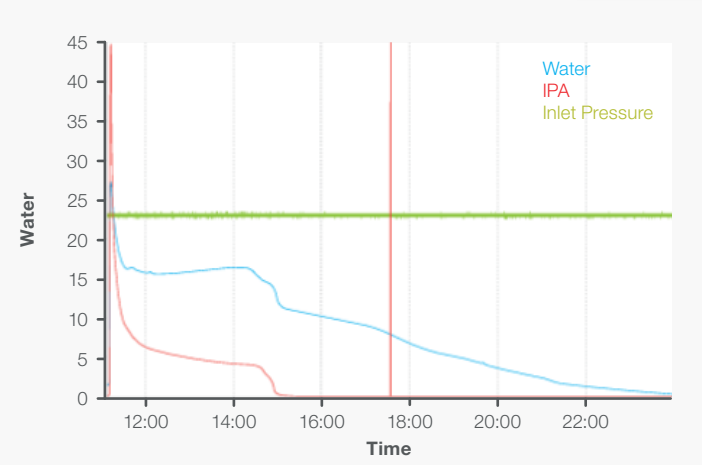


Figure 1. Two-solvent vacuum drying curve indicating the removal of water (blue line) and isopropanol (red line) as the pressure drops from atmospheric to 2 mbar while the inlet pressure (green line) remains constant at 0.1 mbar.

Monitoring pharmaceutical solvent drying processes

A key stage in many pharmaceutical processes is the complete or partial removal of a solvent, or solvents, from a product or intermediate. The drying process can occur in various process vessels, including vacuum dryers, tray dryers, and rotary dryers.

In the past, the success of the drying process was measured upon conclusion by simply taking a sample for laboratory analysis. Organic solvent concentrations in the active pharmaceutical ingredient (API) or intermediate were measured by gas chromatography; residual water levels were typically checked by performing a Karl Fischer titration. The amount of residual solvent was defined by the loss on drying (LOD). If the sample failed the LOD test for one or more solvents, the drying process had to be restarted. If the drying took place under a vacuum, additional complications in terms of both sampling the API and restarting the dryer were likely to occur.

Gas analysis using process mass spectrometry offers the advantages of simplicity in both sampling and data manipulation.

Advantages of mass spectrometry

- Sampling from the headspace above the product for effective bulk measurement and avoiding homogeneity issues.
- Collecting samples at the dryer outlet via vacuum suction or outlet air line.
- Operating at high vacuum (10–5 to 10–6 mbar) for practical sampling from vacuum drying processes.
- Confirming vacuum integrity by detecting air or helium leaks.
- Using molecular fragmentation patterns as ‘fingerprints’ for simplifying complex mixture analysis.

Figure 1 shows an example of a typical two-solvent drying curve. It depicts removing water and isopropanol as the pressure drops from atmospheric to 2 mbar. The MS analyzer inlet pressure remains constant at 0.1 mbar throughout the process.

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 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

- In-line analysis without sample preparation, delivering Raman spectral results in real time
- Easy setup and deployment by non-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
- Single-use (disposable) Raman probes available for high-value batches

Metabolite parameters and high measurement precision

Metabolite Predicted	R^2 Predicted	RMSEC	RMSECV	RMSEP
TCD (106 TC/mL)	0.9	1.83	2.11	1.72
VCD (106 VC/mL)	0.9	1.73	2.43	1.62
Gln(mmol/L)	0.96	0.23	0.28	0.25
Glu (mmol/L)	0.97	0.38	0.4	0.40
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

DynaDrive and HyPerforma Single-Use Bioreactor systems

Thermo Scientific Single-Use Bioreactor systems (S.U.B.). Enable superior performance and automation. Available from 1L to 5,000L, this versatile portfolio of S.U.B.s support robust production across scales and have the flexibility to accommodate a variety of cell lines and processing modalities.

Single-use bioreactors

Thermo Scientific™ DynaDrive and HyPerforma Single-Use Bioreactor (S.U.B.), are 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. Available from 1L to 5,000L vessels sizes.

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.

50L DynaDrive and HyPerforma Single-Use Bioreactors

300L HyPerforma Enhanced Single-Use Fermentor

DynaDrive™ Single-Use Bioreactor and HyPerforma™ Glass Bioreactor

Single-Use Bioreactor probes

The MarqMetrix Single-Use BioReactor BallProbe Sampling Optic is specifically designed to monitor common bioreactor processes. This probe includes a standard Pg 13.5 threaded adapter for universal integration into bioreactor platforms such as the Thermo Scientific HyPerforma and DyndaDrive bioreactor platforms.

Built from 316L stainless steel, this probe allows for easy and reproducible Raman measurements across all sizes of bioreactors in your workflow in an easy to use single-use setup. The probe is available in multiple lengths for analysis in any bioreactor system from benchtop to production volumes.

Material identification

Material identification is vital for cGMP for several reasons. It ensures product quality by verifying raw materials before use, maintaining the integrity and efficacy of pharmaceutical products. It is also essential for regulatory compliance, as mandated by the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR Parts 210 and 211.

Proper material identification prevents contamination and mix-ups, avoiding product recalls, safety issues, and financial losses. Techniques like Raman spectroscopy offer rapid, non-destructive results, enhancing manufacturing efficiency.

Additionally, using the correct materials protects the brand's reputation by preventing the release of substandard products. Overall, material identification is critical to cGMP, ensuring pharmaceutical products are safe, effective, and high-quality while complying with regulations and improving efficiency.

Handheld Raman Analyzer

Thermo Scientific™ TruScan™ RM Handheld Raman Analyzer with Thermo Scientific™ TruTools™

The Thermo Scientific TruTools is embedded chemometric software that runs on the TruScan RM analyzer and allows users to build customized qualitative and quantitative methods for complex material analysis problems.

TruScan RM and TruTools methods can:

- Support quantification of up to 10 chemicals
- Discriminate between materials with similar chemical compounds such as magnesium stearate, zinc stearate, and calcium stearate
- Run qualitative and quantitative methods at line
- Expand TruScan RM's raw materials verification capabilities – allows for finer discrimination of materials

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

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