Kaiser Raman in Bioprocessing
Scalable *in situ* bioprocess monitoring enabling advanced process control
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Discover the benefits of Kaiser Raman in bioprocessing:
A partnership for success

Kaiser Optical Systems, Inc.: a global partner who is driven for your success

Deliver consistent product quality from the beginning  Kaiser Raman provides in situ, real-time analysis of nutrients, metabolites, product quality, and cell viability with a single probe. Our equipment helps you deliver higher yield and improved product quality with reduced contamination risk and improved efficiency.

Getting it right the first time  We understand continuous improvement is key in a dynamic business and regulatory environment. The trusted scalability and performance of Kaiser Raman simplifies your process equipment complexity and eases method transferability. Our training, advanced analytics, support, and data modeling services allow you to focus on your core business while benefiting from our experience to ensure a rapid return on investment.

Complexity, simplified  We put our experience in instrument manufacturing, process analytics, data analysis, and life sciences into the design and manufacturing of our bioprocessing products so you can easily integrate Kaiser Raman for bioprocess advancement with full confidence in our robust and reliable analytical solutions.

Successes from process innovation to process automation  Kaiser has an established installation base throughout the world in GMP manufacturing environments. Our installation base of >1500 units worldwide speaks to how industry leaders trust their products to Kaiser Raman.
**Ensure process and product quality**

Benefit from our leading bioprocess analytical solutions and comprehensive compliance offerings to get your lab-to-process analysis right the first time.

**Kaiser Raman provides in situ, real-time sensing** of multiple parameters for cell culture, fermentation, or downstream bioprocesses. Our offerings for in situ bioprocess analytics enables advanced bioprocess control. Our technology scales with you so that you can use Raman for traditional of single-use bioreactors, in batch or continuous mode, from lab to cGMP.

We capitalize on our experience in the life sciences and working closely with industry leaders to provide a wide selection of bioprocessing analytical solutions. Ask Kaiser’s team of Raman experts about:

- Method development services
- Advanced training
- Service plans to help you reduce downtime, avoid instrument requalification and protect your process’s investment

**Kaiser’s compliance services** helps you to improve your process and ensure quality while maintaining cGMP. We carry a ISO9001:2015 certification, ensuring quality to our customers. Kaiser has over 10 years experience in building ATEX or North America (NA) certified equipment for hazardous area installations. We extend this experience in ATEX/NA to provide NEMA 4x enclosures for wash-down plant environments. Kaiser is a Drug Master File holder with the U.S. Food and Drug Administration pertaining to reusable and single-use bioprocess Raman probes.

We provide a comprehensive portfolio of compliance services for cGMP applications including:

- Questionnaire and audit support
- Standard and customized IQ/OQ
- Factory acceptance testing
- In-house audits
- Supplier qualification
- cGMP trained service personnel
Through our 30+ years in process Raman, we understand the value of being a trusted partner. Kaiser has an established history in the life sciences, from its first feasibility studies in the 1990’s to our first GMP installation in 2000. We worked with industry early to help solve their challenges and we continue though our analysis products, compliance offerings, services, and support.

Our experience in life sciences, from research to manufacturing, is one reason why Kaiser has been a leading bioprocess monitoring and control solution for over 10 years. Our customers have shown that Kaiser Raman can provide:

- Improved product quality
- Increased titer
- Higher volumetric productivity
- Closed-loop feedback control
- Cross-scale and cross-platform method transferability
- Automated feed control
- High density culture monitoring

Kaiser’s parent company, Endress+Hauser, is committed to the life sciences through its offerings in process automation, physical properties sensors, cGxP expertise and services.

Our strong support of the life sciences means that you can rely on Kaiser and Endress+Hauser for your upstream and downstream bioprocess needs.

Proven Kaiser Raman Applications in Bioprocessing

<table>
<thead>
<tr>
<th>Cell Culture</th>
<th>Fermentation</th>
<th>Downstream</th>
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<tr>
<td>Glucose</td>
<td>Glycerol</td>
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<tr>
<td>Lactate</td>
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<td>Cell Density</td>
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<td>Protein concentration</td>
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<tr>
<td>Titer</td>
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<td>Buffer excipients</td>
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Additional product and process related CQAs possible

“I need full application and development support”

Our response:

- We are your solution from technology to implementation
- Kaiser’s modeling, training, and advanced analytics services provide an opportunity for you to benefit from our experience in life sciences and expert application support so that you can focus on your core business

Kaiser Raman in laboratory and process development

Kaiser Raman has the widest selection of offerings with proven lab to cGMP scalability that is trusted by industry leaders.

The Raman Rxn2™ family is Kaiser’s laboratory Raman analyzer. When combined with Kaiser’s phase-optimized sampling probes, the Raman Rxn2™ offers high-resolution performance for in situ, real-time measurement and control.

Raman RunTime™ ensures reliability and seamless connectivity. Raman RunTime’s embedded controller technology combines with Kaiser Raman to support the needs of Industry 4.0. Raman RunTime™ integrates the spectrometer functions into the analyzer electronics without needing a separate PC running proprietary software. Raman RunTime™ exports raw data and diagnostics using standard communication protocols to support data integrity assurance.

Available as a benchtop or cart mounted analyzer, the Raman Rxn2™ offers location flexibility for process development laboratories. With up to four probes per analyzer, measurement from four different bioreactors or sampling points is possible with a single system. The Raman Rxn2™ has a unique analyzer self-monitoring system and is available in 785nm or 1000nm wavelengths.

In-process Kaiser Raman in laboratory and process development applications

Laboratory-scale bioreactors (glass or SUB)
**bIO-LAB Raman probe**

- Compatible with bioprocess industry standard ports
- Pg 13.5 threaded connector
- 120, 220, 320 or 420 mm length
- Autoclavable

**SUB-Optic System**

- Developed according to industry standards for single use sensors
- Materials of construction tested at an independent agency
- FDA-compatible window
- Gamma sterilizable

**Kaiser Raman RunTime™**

*Lab-to-cGMP software for bioprocess monitoring and control*

Benefits for lab and PD

- Intuitive touch screen interface
- Auto-calibration
- SIMCA (Sartorius Stedim) and other MVA compatible
- OPC enabled for integration with 3rd party control systems
Kaiser Raman in process and cGMP

Ensure your manufacturing project’s success with our comprehensive package of process analytical solutions

The Raman Rxn4™ family is Kaiser’s process Raman analyzer, delivering 24/7/365 performance and high precision that is essential for seamless calibration transfer.

Raman RunTime™ ensures reliability and seamless connectivity. Raman RunTime’s embedded controller technology combines with Kaiser Raman to support the needs of Industry 4.0. Raman RunTime™ integrates the spectrometer functions into the analyzer electronics without needing a separate PC running proprietary software. Raman RunTime™ exports raw data and diagnostics using standard communication protocols to support data integrity assurance.

Available as a 785 nm or 1000 nm rack-mounted analyzer for control room installations, or in a NEMA 4x enclosure for production floor installations, The Raman Rxn4™ has a unique analyzer self-monitoring system to ensure the validity of each measurement. The analyzer is capable of self-calibration and utilizes self-diagnostics and self-correction methods.
**SUB-Optic probe system**
- Developed according to industry standards for single use sensors
- Materials of construction tested at an independent agency
- FDA-compatible window
- cGMP qualified
- Gamma sterilizable

**biO-PRO Raman probe**
- Compatible with bioprocess industry standard housings for 25mm side ports
- Pg 13.5 threaded connector with 120 mm probe length
- RA 32 or better for pilot, RA 15 or better for cGMP
- CIP, SIP compatible

**Kaiser Raman RunTime™**
**Lab-to-cGMP software for bioprocess monitoring and control**

**Benefits for process and cGMP**
- cGMP compliant ready
- Intuitive touch screen interface
- Auto-calibration
- SIMCA (Sartorius Stedim) and other MVA compatible
- OPC enabled for integration with 3rd party control systems
- Integrated to leading PAT management systems
Application successes in upstream

Increased titer up to 85% and improved product quality with Kaiser Raman-based glucose or lactate control in a mammalian cell bioprocess

Production of protein therapeutics by mammalian cells is the most widely used bioprocess because of its ability to properly produce and fold a recombinant protein. 60-70% of biopharmaceuticals are produced by this bioprocess. Bioreactor parameters affect cell metabolic processes and detailed bioreactor knowledge is needed to achieve a balanced and consistent metabolic state of cultured cells.

Glucose is a critical process parameter because it affects the cell’s metabolic profile, production of waste products and post-translational non-enzymatic glycation of proteins. Continuous glucose measurements using Kaiser Raman equipment offer important bioprocess information for process understanding and enables feedback control feed conditions from process development (PD) to manufacturing. Spectra of the process contents were acquired using Raman Rxn2™ analyzer equipped with a 785-nm Invictus™ laser and a stainless-steel bIO-LAB in situ probe head. The data were exported automatically to a PLS model in the SIMCA software package.

Studies by Berry et al and Matthews et al [1] [2], a Kaiser Raman-driven feedback control system was rapidly implemented and shown to not only improve a biopharmaceutical protein product’s quality and but also increase yield up to 85% over the historical process. Significant automated control was achieved after only two calibration steps and quickly integrated into process development work. Raman was able to support a targeted concentration condition or a stepwise condition, demonstrating Raman as a robust method to integrate into a controller of an industrially relevant bioprocess. Kaiser Raman is easily integrated into bioreactor controllers, and is a proven PAT solution able to provide real-time process control and ensure biopharmaceutical product quality.

References:

Kaiser Raman customers’ application successes

Cell culture and fermentation
- Real-time CPP and CQA monitoring and control
- Increased productivity
- Improved product quality
- Cross-scale and cross-platform model transfer
- Automated feed control
- Advanced process control
- Raw material qualification
- Cell and gene therapies

Contact Kaiser for technical references.

Schematic of Kaiser Raman-based feedback control
Application successes in downstream

Rapid optimization of protein crystallization conditions

Raman spectroscopy is an established PAT for understanding crystallization in small molecule active pharmaceutical ingredients and protein therapeutics. Similar to small molecules, protein crystallization may be affected by temperature, pH, solvent, and concentration of species in the system. Raman spectroscopy was used to monitor a laboratory scale batch crystallization of lysozyme. In situ Raman spectroscopy was used to investigate the effect of temperature, concentration of precipitating agent, time of crystallization, and possible interactions between these factors.

The Raman spectrum of proteins contains spectral contributions from the protein backbone and side chains. The amide III envelope at ~1240 cm$^{-1}$ and the amide I envelope at ~1650 cm$^{-1}$ provide higher order structure information such as the presence of a-helix, $\beta$-sheet or random coil. In the example by Mercado et al, bands at 750, 760 and 2950 cm$^{-1}$ yielded useful protein structure information, reporting on the chemical environment of tryptophan (750, 760 cm$^{-1}$) and CH$_3$ groups in aliphatic residues (2940 cm$^{-1}$). Intensities of these bands, and the 760:750-cm$^{-1}$ band area ratio, were sensitive to the effects of NaCl concentration, temperature and time on lysozyme crystallization.

Raman-derived surface plots indicated that optimal conditions for lysozyme crystallization were within 35–40 °C and 5–9% (w/w) NaCl. These data could form the basis of a crystallization design space for scale-up and process development studies. In situ Raman spectroscopy was effective in monitoring the effects of temperature, time and NaCl concentration on the crystallization of a model protein. Raman spectra provided information on the protein backbone and side chains, which was used to generate quantitative process knowledge and determine optimal crystallization conditions. Extension of the technique to biopharmaceutical laboratory or process development environments can be achieved using Kaiser’s Raman Rxn2™ analyzer platform, and in cGMP manufacturing environments using Kaiser’s Raman Rxn4™ analyzer platform.

References:

[2] Protein structure: 10.2210/pdb253L/pdb