Non-Invasive Raman Spectroscopy – Ready for In-Situ Monitoring of Standard Upstream Bioprocesses

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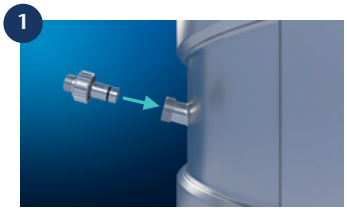
1. | Introduction

- Real-time control of key biopharmaceutical process parameters under sterile conditions in-situ (i.e., directly within the reactor) can increase resource efficiency and optimize product yield and quality. Today, process monitoring usually requires manual sampling and offline analysis, which can take up valuable personnel resources and cause delays in implementing corrective actions.

- To overcome this challenge, SCHOTT developed the ViewPort® spectrometer interface, which enables advanced in-situ monitoring of bioprocesses through a hermetically sealed optical window without compromising the sterile boundary. Combining this novel process analytical technology (PAT) component with time-gated Raman spectroscopy enables continuous monitoring of multiple analytes.

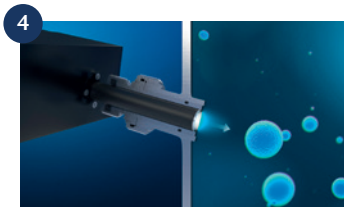
2. | Principal Setup and Assembly



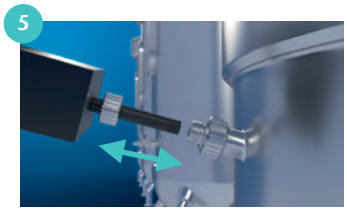
ViewPort® connected to standardized ports

Sterilizable with bioreactor

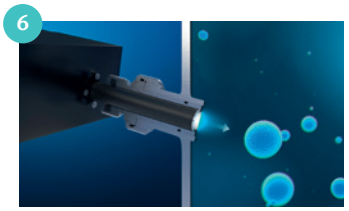
Interface for sensors or spectrometers



Real-time monitoring through optical window



Sensor exchangeable **any time** while **running** cultivation, while ViewPort® provides sterile integrity



Continue real-time monitoring

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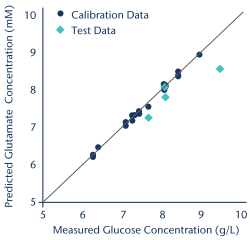
glass made of ideas

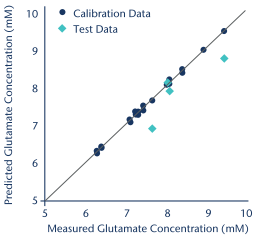
3. | Use case: Production of monoclonal antibodies by CHO cell line

In-situ real-time prediction: Regression model

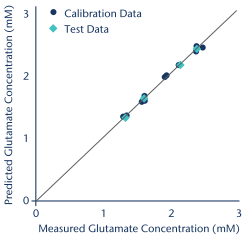
1. | Glucose



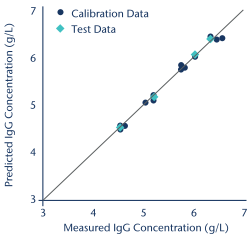
2. | Glutamate



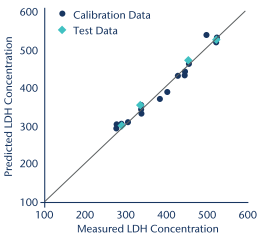
3. | Glutamine



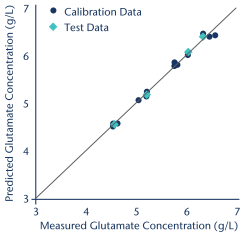
4. | IgG



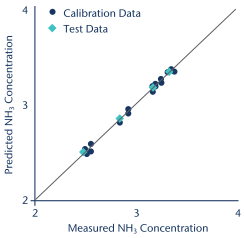
5. | LDH



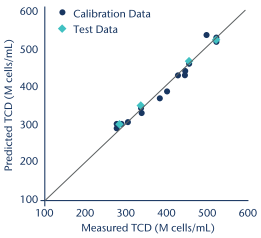
6. | Lactate



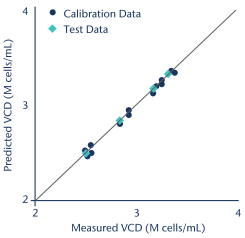
7. | Ammonia (NH_3)



8. | TCD



9. | VCD



- **Test set-up:** ViewPort® spectrometer interface (SCHOTT, Germany) and time-gated Raman spectrometer with 532nm pulsed laser (Timegate, Finland); the spectrometer interface was attached to and sterilized together with a 50-liter bioreactor
- Offline methods for comparison with in-situ process control: nutrients and metabolites concentration; cell concentration and viability
- Thirty-one raw spectra were processed to build a PLS model with in-house MATLAB scripts. Correlation with offline HPLC was performed for the analytes glucose, glutamate, glutamine, IgG, LDH, lactate, and ammonia as well as for TCD and VCD.
- Samples were distributed over the bioprocess runtime to calculate root mean square errors (RSME) and correlations (R-squared values) between offline and in-situ measurements.

CHO = Chinese Hamster Ovary; PLS = Partial Least Squares; HPLC = High Performance Liquid Chromatography; IgG = Immunoglobulin G; LDH = Lactate Dehydrogenase; TCD = Total Cell Density; VCD = Viable Cell Density

4. | Results

- The predicted R-squared values for **glucose, glutamate, glutamine, IgG, LDH, lactate, ammonia, TCD, and VCD** were 0.78, 0.79, >0.99, >0.99, >0.99, >0.99, >0.99, 0.97, and 0.98. These results demonstrate that the time-gated Raman spectrometer combined with the ViewPort® spectrometer interface enabled **real-time process control for multiple key analytes.**
- This approach allows **deviations** from target values to be **identified and adjustments made immediately**, which is a prerequisite for optimized yield. The ViewPort® spectrometer interface maintained **sterile integrity at all times during cultivation**, even when the probe head was unmounted.

5. | Summary

- Perform high-quality measurements without penetrating the **sterile** boundary of the bioreactor
- Enhance **automation** by comprehensive system solution design (sensor + reactor interface)
- Flexibly exchange measurement system – ViewPort® is the only **wetted part**
- Reduce effort and costs with **in-situ** process control

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