Application note

Raman spectroscopy

Ramina Process Analyzer

Introduction

Manufacturing processes can be extremely complex, especially biopharmaceutical manufacturing. With processes that rely heavily on living organisms to generate products of interest, such as those within the Biopharma industry, complete understanding of the process is essential to success, because the more you know about the process, the more control you can exercise. The primary problem process analytical instruments and technologies have sought to alleviate has always been a lack of visibility into the underlying reactions. What you see, and also understand, you can control and optimize.

Subtle variations in the environment can have a huge impact on yield and quality. The consequences can range from failed batches and inefficient use of resources to products that don't meet quality specifications, and limited data to help make improvements over time. Ultimately, patient safety and stakeholder interests are at risk.

We are dedicated to making instruments that help our customers gain greater control of their processes that involve chemistry. One of the most powerful and advantageous analytical technologies that we use is Raman spectroscopy. It's extremely accurate and versatile, generates very rapid results, covers a multitude of functions, and is non-destructive to whatever sample or substance is being analyzed.

Until recently, Raman Spectroscopy required a well-trained technician to operate, and demanded complex, bulky, and expensive equipment that also made it at times unsuitable for in-line or field use.

We have introduced the Thermo Scientific™ Ramina™ Process Analyzer, a compact, easy-to-use, reliable, and affordable system that leverages the power of Raman spectroscopy to measure key variables in a process so that they may be controlled. The Ramina Process Analyzer also makes Raman technology more accessible to nonexperts through its simplified user interface. Since it is also small, it is uniquely qualified to solve a common problem faced by those who use chemistry to make things, i.e., portability and ease of use whether in the field or in the process development space.

What is RAMAN spectroscopy?

The underlying technology, Raman spectroscopy, is not new; it has been around since the 1950s. What Raman instruments have lacked until now is the size, reliability, ease of use, and affordability that enables manufacturers to integrate Raman spectroscopy into their production processes where it can be instrumental in improving efficiency and quality. Before Ramina, integrating Raman technology into a manufacturing process was problematic. There were challenges with the hardware; it was difficult to use and required a scientist on staff to operate and maintain it. Reliability and cost were also issues. Better hardware was needed, as well as a simplified, more user-friendly interface. These features and advantages are now realized in Ramina, but what exactly is Raman spectroscopy all about?

Non-destructive analysis and process monitoring

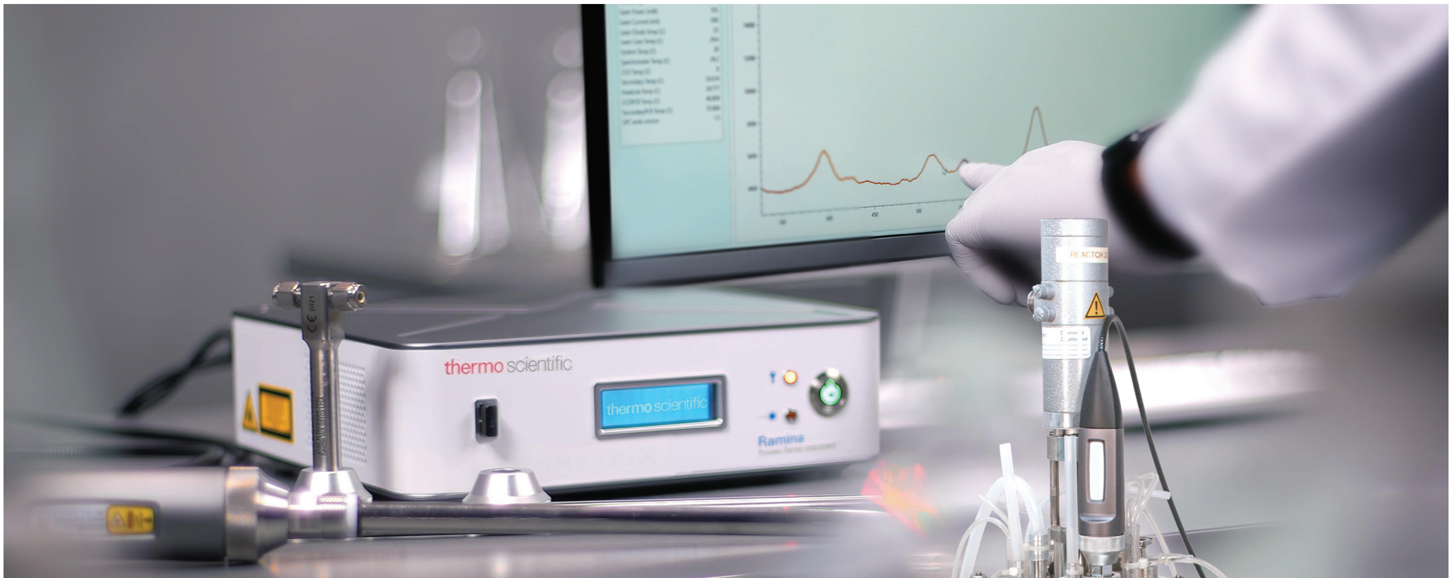
The technology begins with a laser that is directed at a substance or sample through a fiberoptic cable with a probe at the end. The energy from the laser light causes covalently bonded molecules in the substance to vibrate and the light from the laser may scatter elastically (the same laser energy is released as what caused the molecule to vibrate) or inelastically (some of the laser energy is absorbed by the molecule and a lesser amount of energy is released than what caused the molecule to vibrate). Some of this inelastically scattered light makes its way back into a detector within the Ramina Instrument. The detector collects and interprets the light scattered from the sample to generate a "picture" called a Raman spectrum. What makes this technology powerful is that the Raman spectrum of a molecule is unique, and for that reason it's sometimes referred to as its molecular fingerprint. Just as fingerprints may be used to identify people, we use the Raman spectrum to identify a given substance because the fingerprint can tell us not only qualitatively what something is, but also quantitatively how much there is of it- one may determine both the identity and concentration of a given analyte of interest. The non-destructive nature of Raman spectroscopy provides a tremendous value-add. This is very important because it can be integrated directly into a production line to measure and analyze on a continuous basis, serving as a process monitor. This is what is called in-line or online measurement. Raman technology is also fast, and most substances can be measured in a matter of seconds or less.

Versatile, precise, providing a wealth of information

Additionally, the Raman spectrum provides us with a great deal of information about the substance being tested; every one of the peaks in the Raman spectrum tells us something unique about what we're testing, providing us with many opportunities to identify what we're looking for. This is extremely important when measuring in a bioreactor, for example, containing many molecules of different types. The next advantage is that there's a direct and linear relationship between the concentration of a given substance and the intensity of the peaks in the spectrum. This means that building quantitative models is easier. With a relatively small number of samples, we can build a model that accurately predicts concentration across our range of detection. We can also measure substances in all forms, whether they're solid, liquid, gas, powder, or slurry. A final advantage is that unlike other forms of spectroscopy, water does not distort Raman measurements; therefore, we can see clearly what's happening in the aqueous solution like that found inside of a bioreactor. Competitively, Ramina is better suited for inline and online measurements in aqueous-based solutions than competing technologies, but perhaps its greatest advantage is that it is non-destructive.

Process control

There are Raman applications that span the entire biopharma manufacturing process. Verifying the integrity of raw materials is the first step where Ramina can help ensure that the process gets off to a good start. In practice, we've observed notable variations in the chemical composition of growth media, variations significant enough to have an impact on yields and cycle times. It's important to be able to detect changes in the material in real time. For example, customers want to know what's happening in the bioreactor so that they can make adjustments if necessary. This is true regardless of whether or not manufacturing is done via batch or continuous flow, and Ramina works in either scenario. Do the cells have the right amount of glucose? Are too many secondary metabolites building up? Are the cells beginning to produce the product of interest? How much product has been produced, and does it have the right characteristics? Ramina enables answers to all of these questions, and because the unit can interface with third-party control systems, adjustments can be made in near real-time to optimize conditions. Finally, when capturing finished product downstream, manufacturers need to know exactly when and how much protein is coming out of a purification column, for example. These are just a few examples of how Ramina helps achieve higher efficiency and quality in chemistry-dependent manufacturing.



Robust yet simple operation

Ramina is easy to use. A technician with no prior Raman experience can typically begin taking measurements within 15 minutes of removing the instrument from the box. Facilities across the country can use Ramina to take hundreds of measurements daily without the need for any scientific staff to maintain and calibrate the instrument.

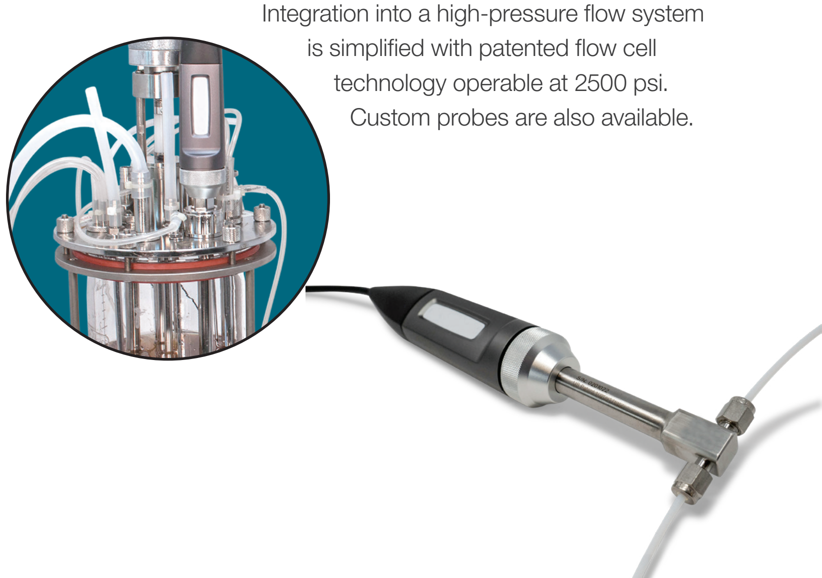
Ramina is compact. With a footprint less than one square foot and three inches tall, Ramina is sized to be placed at or near the point of measurement and with no moving parts other than its cooling fan, Ramina is designed to be reliable and stable. Up time exceeds 99% and calibrations performed in the factory remain accurate for years. By being easy to use and reliable, Ramina is also less costly to install and operate over time, with a very low cost of ownership.

A wide range of easily-swappable probes are available

The Ramina Process Analyzer can be adapted to almost any R&D production or process system. It features a fiber head and ball probe system that fits any need due to a wide array of easily interchangeable probes. Swapping the probe is easy; simply unscrew the fastener, remove the probe, swap in another, and tighten it down again. Our tapered fitting allows for easy indexing, requires no alignment, and there's no need to recalibrate the system.

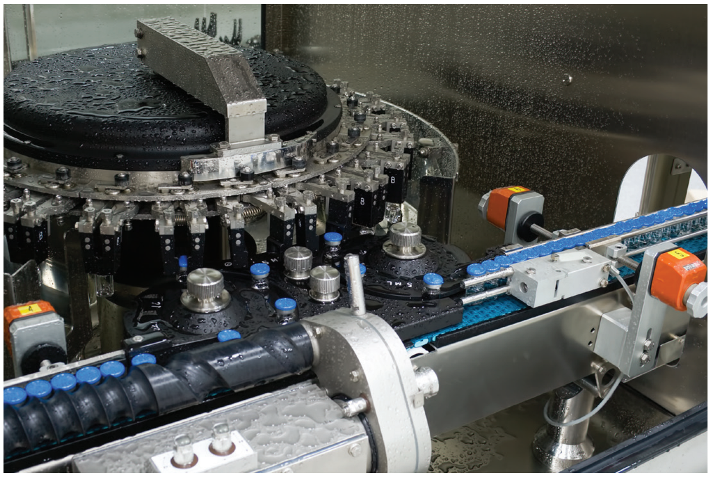
Ramina's lineup of standard fiber probes allows measurement of compounds in any form, e.g., solids, liquids, gas, slurries, pastes, and gels. It can measure by contact or immersion with its performance half inch ball probe and/or standard ball probes which range in size from 1/2" down to 1/8". For higher temperatures and harsh chemicals, there are process ball probes that are gold sealed and temperature safe to 350 degrees Celsius. Ball probes are also available in bioreactor-specific versions with a seal and nut to allow for immersion in a reaction vessel, be it a dedicated stainless-steel bioreactor or a single-use bioreactor. These bioreactor probes are autoclavable, either while attached to the bioreactor, or on their own when cleaning and sterilizing the ball probe separately.

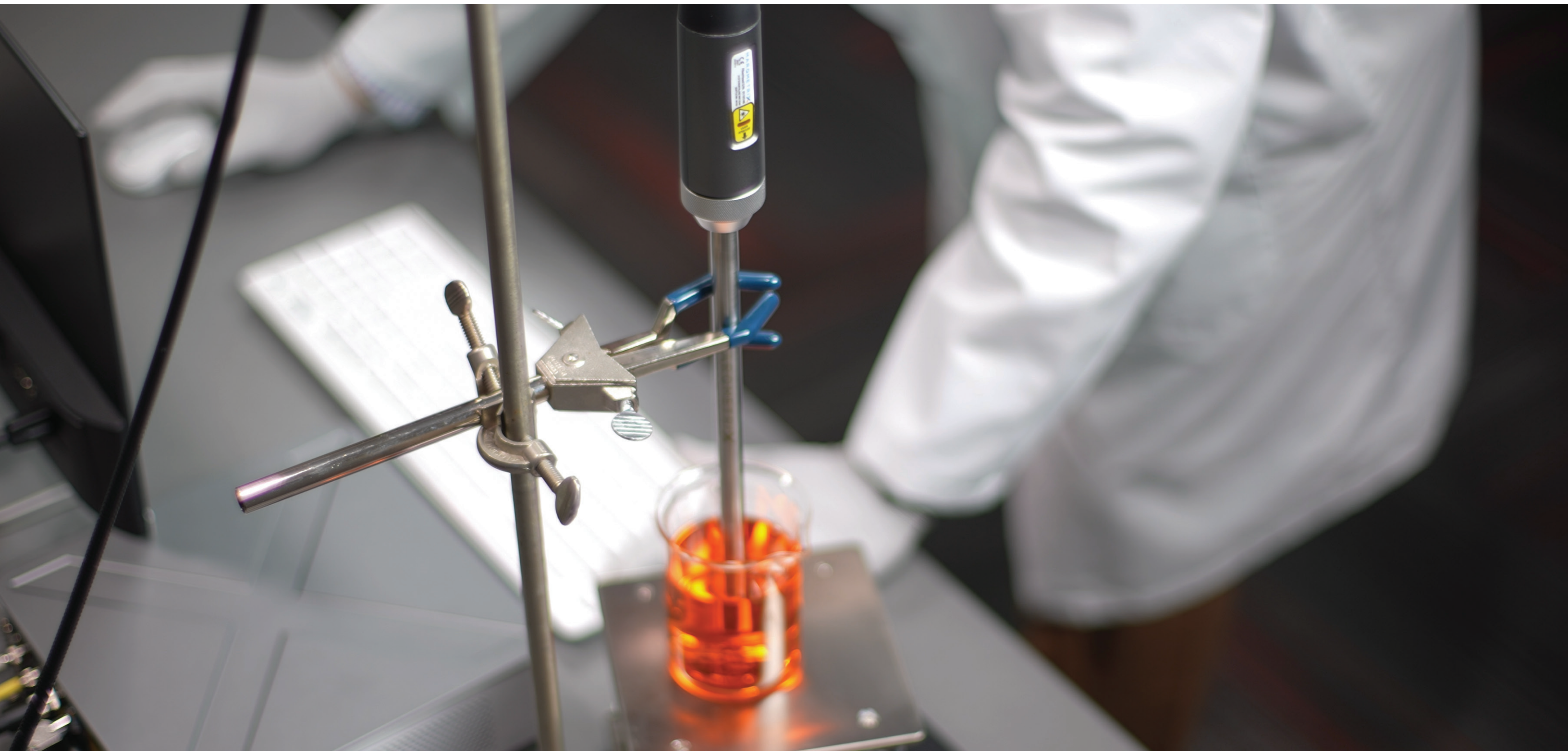
Integration into a high-pressure flow system is simplified with patented flow cell technology operable at 2500 psi. Custom probes are also available.



ThermoFisher
SCIENTIFIC

At Thermo Fisher, we're realizing the full potential of Raman technology by building better instruments, and we're all about making Raman spectroscopy more accessible to help our customers control chemistry. We're opening up new applications for Raman and increasing the returns on existing applications- returns that come in the form of faster cycle times, higher yields, and better quality.





thermo scientific

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

SENTINEL
PROCESS SYSTEMS, INC

3265 Sunset Lane Hatboro, PA 19040 | 215-675-5700 | sentinelprocess.com

 PR-RAMINA1-0322 v01