Using PAT to improve manufacturing is great – but only if you've got enough entry points to your reactor to fit all the instruments. **May Ling Yeow** and colleagues overcame the problem

Access all areas

FOLLOWING the publication of *Guidance for Industrial PAT – A framework for innovative pharmaceutical development, manufacturing, and quality assurance* by the FDA in 2004, there has been a significant increase in commitment and investment by the pharmaceutical industry to develop the use of PAT to streamline and improve manufacturing processes.

Staff at Pfizer R&D have introduced online mid-infrared (IR) spectroscopy in the research laboratories as an important tool for understanding and optimising processes on a small scale. Understanding the data from PAT measurements at that scale can provide valuable insight into the up-scaling of processes from the laboratory to the pilot plant and ultimately into commercial manufacturing processes.

There are significant challenges facing the transition of this technology from the laboratory to larger-scale manufacturing. These can include difficulties in customising the measurement instrumentation to allow use in classified hazardous areas, and the complexities of modifying the existing processing infrastructure to allow use of complex analytical instrumentation. However, the most significant challenges arise because of the general lack of suitable entry points for the measurement technology into the reactor vessels and the prohibitively high cost of modifying or replacing the reactors in a facility to enable PAT to be used throughout.

> *"significant challenges arise because of the general lack of suitable entry points for measuring technology"*

bespoke PAT

To overcome this problem, we designed and implemented a bespoke base valve configuration with built-in online IR monitoring capability.

Figure 1 shows the schematic of the basevalve with integrated IR probe. In this design, an oversized actuator and valve bellows were used to accommodate the extra diameter required for an IR probe. In use, the IR probe protrudes through the valve plug, adjacent to a temperature probe, and performs measurements in the body of the liquid held in a reactor. A specialised two-seal design enables the IR probe to be retracted for replacement or repair if required. This overall design also provides another layer of flexibility because the probe is a standalone unit and can be connected to an online mid-IR instrument or transferred to the laboratory and used with a lab-based instrument. These Hastelloy valves have been designed with two types of bespoke reactor seal so that they can be used on both

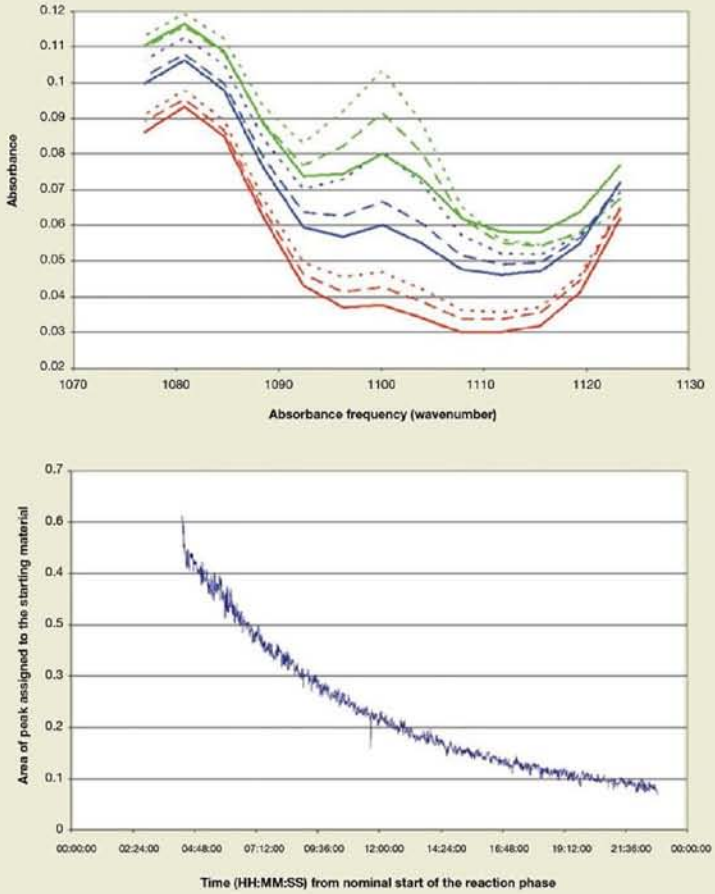
(Left) Figures 4 and (inset) 5: Basevalve with integrated IR probe installed in a reactor, connected to an online reaction monitoring instrument

Hastelloy and glass-lined reactors of various sizes, eliminating the risk of damaging the glass-lined reactor neck.

low-cost solution

This relatively low-cost solution has enabled PAT technology to be applied across 22 reactors in the facility without the need to modify any of the equipment – a significant improvement from the three reactors that previously had ports suitable for the IR probes. Although it was previously possible to install a IR probe via a recirculation loop incorporating an IR flow cell, this arrangement has a number of safety concerns. These include hazards associated with reactive chemistries in flexible hoses; difficulty in recirculation of heavy slurries and also this setup is not suitable for temperature-sensitive chemistry.

Figures 2 & 3: Mid-IR spectrum following a reaction progression and tracking area of interest through the course of a reaction



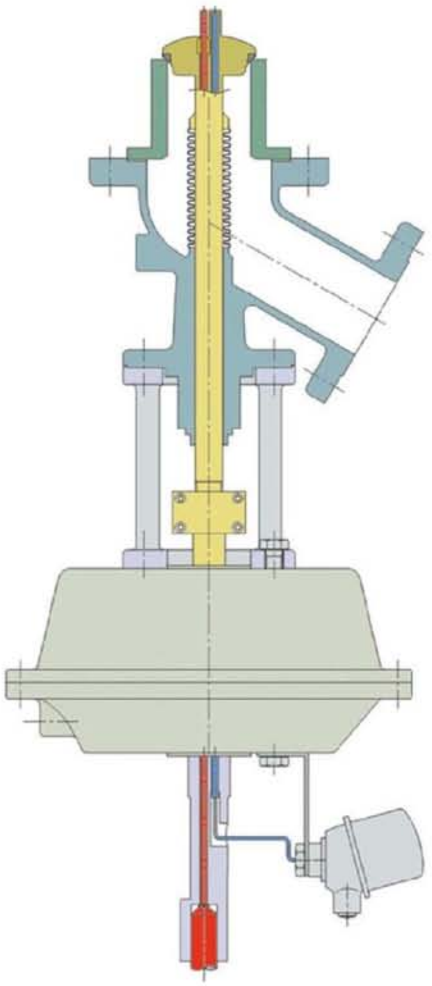


Figure 1: Schematic of a bespoke basevalve with two integrated probes – infra red probe (red) and temperature probe (blue); Figure included with permission from SchuF UK

Further advantages offered by this approach include the fact that we can generate PAT data even at the minimum working volume in a reactor, we are able to monitor cryogenic and high-temperature reactions, and if required, correct the spectral data for the effect of changing reactor content temperature.

quick-fix

We commissioned and validated the first valve in just three days after arriving on site, a significant achievement involving close partnership between various departments. Within a few days of the installation and commissioning, the valve was used to support a manufacturing campaign. Figure 2 shows a small portion of the mid-IR spectrum of the contents of the reactor, giving data at approximately two-hour intervals during the course of a reaction. The changes in the spectrum as the reaction proceeds are quite clear in this view and, when mathematically treated by simply integrating the peak area (and correcting for spectral offsets) over the course of the reaction phase of the batch, we could follow the reaction in real time over an extended period (shown Figure 3).

Figure 4 and 5 show the basevalve with integrated IR probe installed in a pilot plant reactor, connected to an online reaction monitoring instrument suitable for classified hazardous area.

Therefore this relatively simple but innovative valve installation has the potential to significantly impact the business through reduced batch cycle time, improved quality and increased process robustness. **tce**

May Ling Yeow (mayling.yeow@pfizer.com) is a project & technology engineer at Pfizer; Ruth Hardy, Paul Richards, Laura Aiken, Kyle Leeman, Ian Clegg are also based at Pfizer