Manufacturing

The requirement for process validation is one of the reasons for the relatively conservative manufacturing strategies traditionally adopted by the pharmaceutical industry. Validation involves developing a specific set of procedures with the aim of maximising the probability of reproducible operation. The approach is empirical. The same materials are fed into the process at each stage, the same operations are carried out and the same checks are made at each point with the aim of ensuring consistent product. The focus is repetitive action rather than true process understanding and control.

Process validation is a significant part of any submission to the FDA for approval of a new drug. Changes to the process require this documentation to be revisited and therefore tend to be avoided. Because of this, pharmaceutical manufacturers often stick with well-established processes, and the industry lags behind other manufacturing sectors when it comes to embracing new technologies.

The FDA’s process analytical technologies (PAT) initiative is designed to change this situation by encouraging the use of new analytical tools that facilitate a control-based rather than recipe-based approach. Its two main aims are the identification of techniques for real-time analysis of physical properties and chemical composition, and the removal of real and perceived regulatory barriers to the introduction of new methods. To promote change, the administration is offering ‘safe harbour’ incentives that facilitate the use of new instrumentation, in parallel, in existing processes. In the future, it is likely that the focus of FDA scrutiny will be processes with less well-developed control strategies. This obviously provides additional impetus for change.

In this article, one of the issues associated with the PAT initiative – the adoption of real-time analysis – is explored in some detail with reference to the potential benefits of on-line or in-line particle size measurement. In contrast to an off-line regime, on-line measurement produces a continuous stream of real-time data. The range of ways in which these data can be used to optimise process operation is highlighted using examples involving key pharmaceutical unit operations.

CHANGING CONVENTIONAL PRACTICE

A conventional pharmaceutical process is shown in Figure 1. Each stage is carried out batch-wise. The chemical composition of the product is fixed at an early stage by reaction and subsequent crystallisation. Final particle size and dose-to-dose uniformity are controlled...
in a series of downstream mechanical operations – milling, blending, compacting, granulation and tabletting. Each part of the process is separately validated. A range of off-line analyses is carried out after each operation prior to subsequent processing.

This approach works. It delivers drugs of the required quality, allowing manufacturers to meet customer expectations. It is not, however, particularly efficient, being capital- and labour-intensive. The manual input required for both operation and analysis is high, while the equipment involved tends to be large and under-utilised. Product yields are often low and, because the process is not always well understood, there is frequently a high degree of product non-conformance. If the final product does not meet the required specification, the reasons are often unknown.

Reliance on a significant degree of off-line analysis can be particularly problematic. The throughput of the analytical lab may limit production rates, and product containment may also be an issue. Off-line analysis increases the likelihood of human exposure to the product. In some cases, a drug’s ultimate potency may be limited by a combination of human exposure and product containment parameters.

A more attractive process layout is shown in Figure 2. Now the individual steps are more closely integrated, with much of the operation being carried out in small continuous units. Embedded real-time analysers deliver the required degree of control, and human exposure to the product is largely eliminated. When developing its enhanced GMPs for the 21st century, it is this type of processing that the FDA envisages. Such a change would bring the pharmaceutical sector more in line with other chemical manufacturers, who typically achieve product yields in excess of 98% and produce – relatively speaking – much less waste.

Development of this type of process requires reliable on-line or in-line analysers for a range of variables, most critically composition and particle size. Laser diffraction is a well-established technology for particle size measurement. Off-line instruments are already widely used within the sector, and on-line systems are becoming increasingly common in the pharmaceutical industry and elsewhere. As a result, the technical risk associated with this type of installation is relatively low.

**SWITCHING TO ON-LINE ANALYSIS**

With on- or in-line analysis many of the constraints and concerns associated with an off-line regime are removed. Analytical manpower requirement becomes negligible. More data, of higher quality, is produced much more rapidly. Concerns surrounding the representative nature of samples, repeatability in terms of both sample preparation and analytical procedure, changes in the sample during transport to the lab, and frequency of analysis relative to process changes, are all eliminated.

On-line analysis allows the operator a real-time continuous view of the process that can be used to transform operational efficiency. More effective manual control strategies can be developed, and automated control becomes an option.

The beneficial ways in which on-line data are used can be grouped under the following four headings.

**Steady State Optimisation**

If a unit is operating continuously in a steady state, then ideally it is running as close as possible to the required specification. If this goal is achieved, then product quality will be optimal; waste will be reduced and variable costs minimised.

With off-line analysis, samples may be taken and measured every hour, and the analysis may take 30 minutes. This means that the plant is controlled using hourly data that describes what was happening 30 minutes ago. Any drift away from specification is therefore rectified fairly slowly. The consequences of actions will only be revealed some time after they were taken.

The net result is relatively poor plant control. It is also difficult to gain an understanding of how to control the process effectively, or to have real confidence that the material produced will be in-specification. In this environment, over-processing is quite common – the material may be over-milled, for example, just to ensure that nothing too large is passed through to the next stage.

In contrast, with on-line analysis, measurements can be made at a rate of four per second. The operator can quickly observe any drift away from the required specification, and can immediately see the result of any corrective action taken. Correlations between manipulated variables and product quality become clear, and confidence that the plant can be well controlled increases. Now the plant can be operated optimally, at
the required specification with minimal effort—particularly if automated control is installed. Plant throughput and process efficiency are maximised.

**Process Upset Detection**

There is an interruption in feed supply, a mechanical failure or loss of utilities—how quickly is it detected? With on-line analysis, a process upset that has a significant impact on product quality can be spotted almost instantaneously. A screenshot highlighting an interruption in feed supply to a roll compactor is shown in Figure 3.

These measurements were made using a Malvern Insitec—a laser diffraction-based particle size analyser. With laser diffraction, particle size is determined from the pattern produced as light is scattered by particles in a sample. Penetration of light through the sample is a prerequisite for analysis and is therefore monitored using the variable transmission. When transmission is high, more light passes through the sample. The spike in transmission in Figure 3 is therefore indicative of a lower concentration of material in the sample line—feed rate has reduced. This observation is confirmed by particle size measurements. Particle size has decreased. Flow through the compactor has been reduced and this has resulted in a reduction in compaction efficiency. More particles are passing through the system uncompacted.

The ability to detect this kind of problem allows rapid action to be taken to avoid ruining a batch or significant quantity of material.

**Transient Operation**

Even when units are run continuously, periods of transient operation occur, especially where more than one product is being made. During start-up, shut-down and product changeovers, the plant can be particularly difficult to operate well. The aim is to pass through these periods rapidly to minimise the length of time for which the plant is not producing useful material.

During transient operation, variables are manipulated to bring the plant to the operating point as quickly as possible. With real-time data, the effect of these actions is seen immediately and corrections are made much more rapidly. An example involving start-up of a pharmaceutical mill illustrates this. With off-line analysis, it took around 50 minutes to bring the mill to the point where it was producing on-spec material. The iterative procedure involved making a change to milling parameters, sampling and analysis, then making another change and so on. With on-line analysis, start-up takes seven minutes and is much less labour-intensive. The effect of any actions can be seen instantly, and so start-up time is limited only by the dynamics of the mill.

**Endpoint Detection**

Where batch processes are retained, real-time data can still be used to improve process efficiency by allowing accurate determination of a process endpoint. With batch granulation, for example, the aim is to increase particle size until the exact specification is reached, and then stop the process. Figure 4 shows particle size growth being tracked. With this data, it is easy to estimate the rate of growth and therefore the time at which the batch will be complete.

With an off-line regime, significant effort is expended in sampling and analysis to establish how the process is behaving, and endpoint determination is much less precise.

**CONCLUSION**

The aim of the PAT initiative is to encourage pharmaceutical manufacturers to use analytical tools to improve process efficiency. On-line analysis affords manufacturers a detailed view of the process that translates directly into improved understanding, greater knowledge and enhanced process control. Its use facilitates a change from experience-based to knowledge-based operation, and delivers significant economic gains. The technology for on-line particle size analysis is well-established, and the risk-reward balance is therefore heavily weighted towards the positive.

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