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Monitoring and Control Tools for Implementing PAT

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AUTHORS

Innovations in process analysis and control offer significant opportunities for improving pharmaceutical manufacturing operations

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The goal of the US Food and Drug Administration's process analytical technology (PAT) initiative is to encourage pharmaceutical manufacturers to improve their operations to reduce the cost of pharmaceuticals. Before the PAT initiative, there was not much emphasis on changing ongoing pharmaceutical operations—repeatability, not innovation, was the order of the day.

Now that the regulatory climate has changed, how can pharmaceutical manufacturers look to achieve results? Today's automation systems can be an excellent place to begin. Technology is now available to automatically evaluate measurement and control performance and point directly to those areas where improvements are possible. Reduction in process variability is one of the key areas that can be influenced by this effort. Imagine the impact on costs if production cycle times can be reduced or a few rejected, out-of-specification lots of material can be avoided by improving operations to ensure that all manufactured goods are made right the first time.

PAT initiative brings changes

The pharmaceutical industry has often been reluctant to introduce change into their manufacturing processes because of perceived regulatory complications. From a manufacturer's perspective, the regulatory process has been rigid and unfavorable to the introduction of innovation. Process changes are managed by time-consuming regulatory submission. Thus, many manufacturing procedures traditionally were treated as being unchangeable.

Realizing the impact this has on manufacturing efficiency and innovation, FDA established the PAT initiative to encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance. As part of this framework, an innovative approach has been developed for helping the pharmaceutical industry address regulatory issues and questions. This new approach is discussed in *A Guidance for Industry, PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance.* The agency's usual regulatory scrutiny has been tailored to meet the needs of PAT-based innovations that promote continuous improvement and improve manufacturing while maintaining or improving the current level of product quality.

The primary goal of PAT is to enhance understanding and control the manufacturing process to ensure final product quality. The concepts addressed by PAT are applicable to all manufacturing situations. Nonetheless, the gains in quality, safety, and efficiency will vary depending on the process. In general, these gains are anticipated to come from:

- reducing production cycle times by using measurements and control;
- preventing rejects, scrap, and reprocessing;
- improving operator safety and reducing human error;
- improving efficiency and managing variability.

There are many current and new automation tools that can effectively facilitate process understanding and achieve continuous improvement. The PAT framework defines the following tool categories:

- multivariate data acquisition and analysis tools;
- modern process analyzers and process analytical chemistry tools;
- process and endpoint monitoring and control tools;
- continuous improvement and knowledge management tools.

As defined in the PAT framework, an appropriate combination of some or all of these tools may be applicable to a single unit operation or to an entire manufacturing process and its quality assurance. The challenge for many manufacturers is to identify how best to

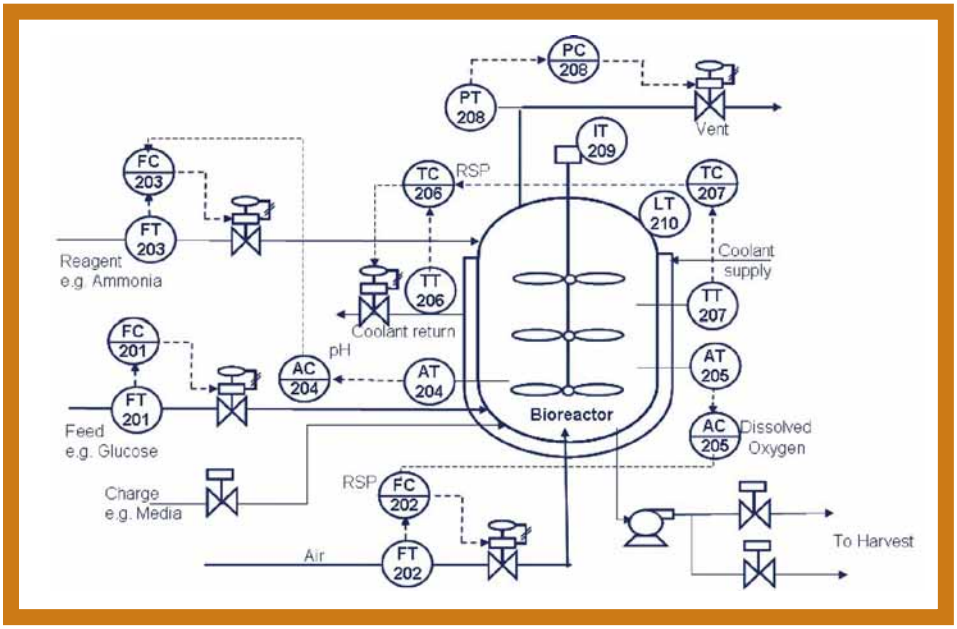

Figure 1: Batch process example: bioreactor.

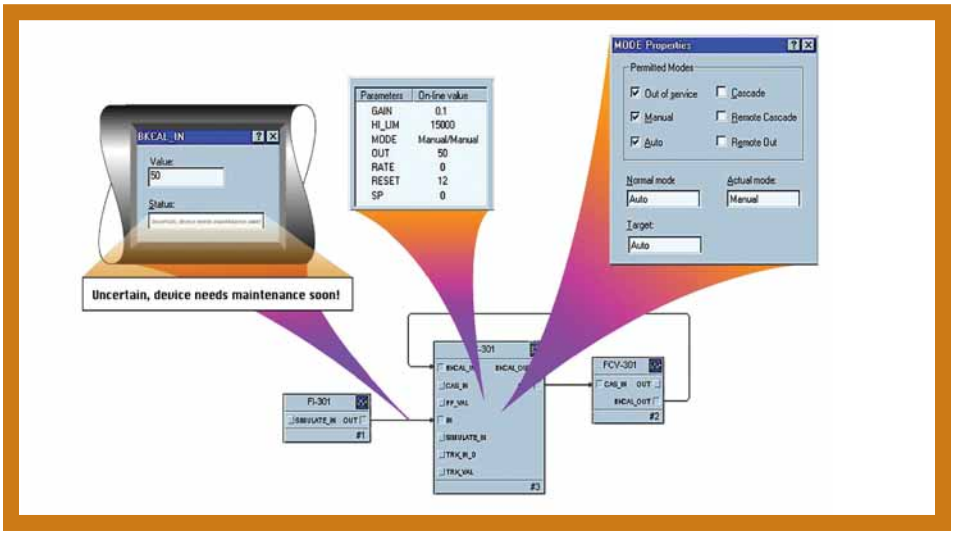

Figure 2: Typical diagnostic signal from a Foundation fieldbus device.

address the opportunities that PAT offers. This article focuses on the first steps that may be taken to improve operation through process monitoring and control tools. Often these tools are available in your existing automation system or may be easily added to the system.

The control challenge

Conventional pharmaceutical manufacturing is generally accomplished using batch processes with laboratory testing conducted on collected samples to evaluate quality. Also, most pharmaceutical processes are based on time-defined end points. The role of the automation control system is to control all critical quality attributes to insure consistent quality of the end product. Thus, as outlined in the PAT framework, process controls play an important part in the design of the manufacturing process and in the validation process. In such batch applications, however, the control system itself may face many challenges that affect how closely the control parameters may be maintained

> The performance-monitoring application must take into account the operating state of the process.

and how quickly the control system can respond to process changes throughout the batch cycle.

One of the greatest challenges in the design and commissioning of a batch-control system is the wide range of operating conditions the control system must undergo during the batch cycle.

For example, consider the control issues associated with a typical bioreactor shown in Figure 1. During the batch cycle, the feed flow, reagent, and oxygen demand may vary by as much as two orders of magnitude, making it difficult or impossible for typical control devices to continuously maintain desired operating conditions. Also, operation over such a wide range may exceed sensor measurement limits for key operating parameters. When analytical measurements are used in the process, there also is an opportunity for drift in the measurement due to coating or faults in the sensor elements. Poor performance of these measurement and control devices usually contribute to variability in the process operation and deviation in key product quality parameters. Thus, often one of the first basic steps that should be taken in addressing PAT is to implement ongoing performance monitoring of measurement and control.

Performance monitoring of measurement and control is not necessarily a difficult undertaking and can deliver immediate results. The process understanding that monitoring provides may lead to early detection of problems. This can permit action to head off these issues before they impact key operational parameters that could lead to a failure of the products to meet specification. Moreover, the information provided by such a performance monitoring system lays the foundation for identifying areas for improvement in measurement and control.

Performance monitoring

Continuous learning through data collection and analysis of measurement and control performance over the life cycle of a product is important. This analysis process can provide insights that contribute to justifying proposals for post-approval changes. As recognized in the PAT framework, information technology systems that support knowledge acquisition are valuable for the manufacturer and can also facilitate scientific communication with the Agency. During the past 10 years, a variety of manufacturers have developed process monitoring applications that may be layered onto an existing control system. Also, in some modern control systems this capa-

bility is actually embedded within the control system. When this capability is embedded in the control system, then usually you will find that the initial setup and on-going maintenance of the monitoring system can be made much easier. Embedding monitoring within the automation system facilitates configuration and implementation; eliminating the difficult integration normally needed by layered systems.

There are many differences in the ways measurement and control performance monitoring can be implemented. Many of today's commercially available products were designed primarily to monitor continuous process. For typical pharmaceutical batch processes it is critical that the performance monitoring application take into account the operating state of the process. Without this capability, the monitoring system will provide many false indications of failed measurement when the process is off-line or is an alternate phase of operation such as a sterilization or cleaning cycle.

Measurement quality

There are key differences in the ability to judge the health of the devices monitoring and controlling a process based on the technology embedded within those devices. When using a traditional analog transmitter for a process measurement, the determination of the health of the measurement must be made on the basis of a transmitter signal value; that is, whether the value is outside the normal measurement range. When digital transmitters are used, then the device performs self diagnostics and can provide a clear indication of the health of the measurement. For example, the health of the measurement made with a Foundation fieldbus device is communicated as a status that accompanies the measurement value, as illustrated in Figure 2. The status indications of measurement quality are categorized as follows:

- Good: The measurement value may be used for control calculations and actions.
- Uncertain: The quality of the value is less than normal, but the value may still be useful.
- Bad: The value is not useful.

The measurement status also contains information indicating whether the measurement is limited and the reason for the quality being "Uncertain" or "Bad."

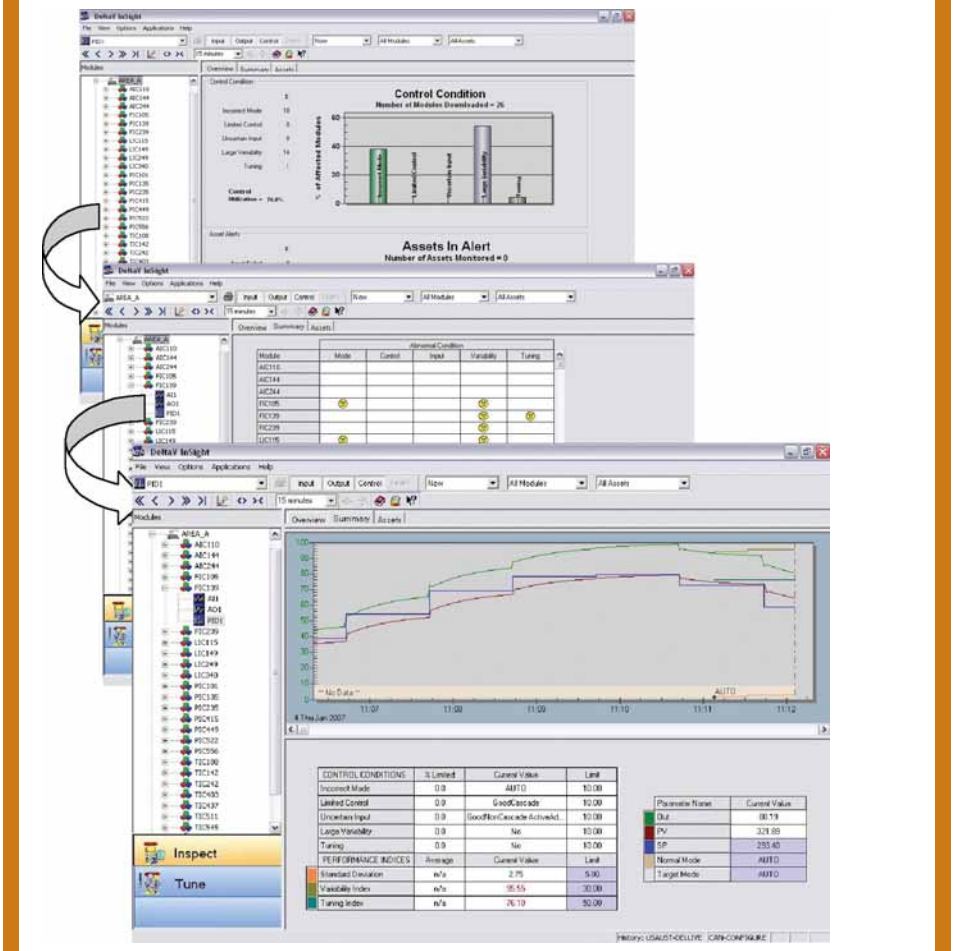

Figure 3: A simple three-step process allows users to find the origin of process problems using modern data analysis tools such as DeltaV InSight.

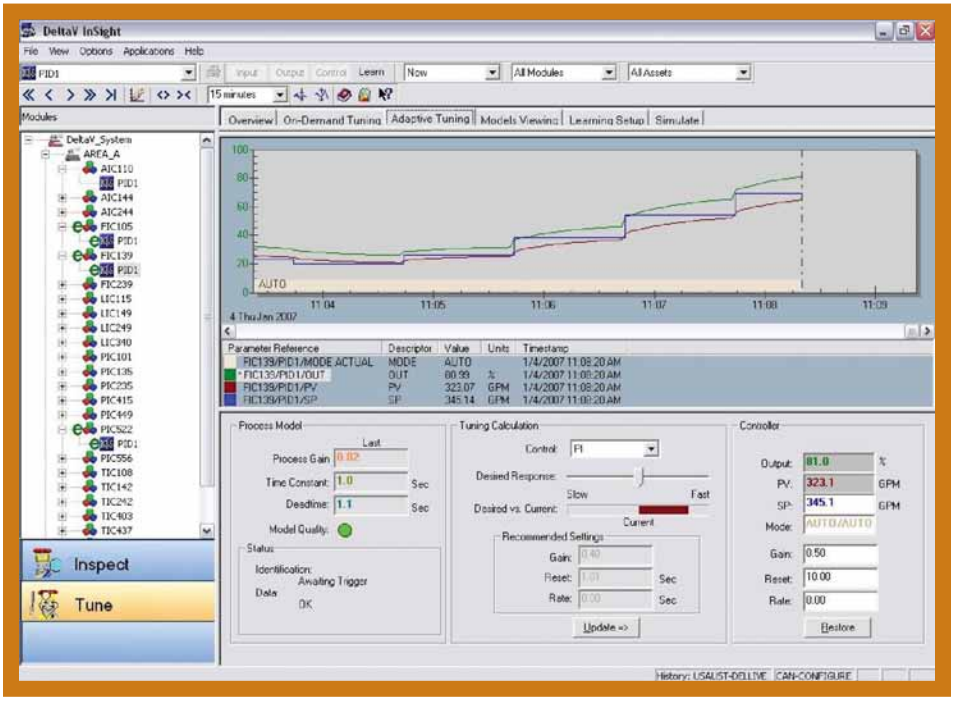

Figure 4: Automation-system tuning parameters can be automatically determined based on process conditions, permitting optimal control system performance to be achieved.

In addition to monitoring quality, some measure of variability is usually provided. Typically, variability may be expressed in statistical terms such as the measured standard deviation.

The proper design of the control system's user interface is key to being able to quickly identify problem areas. When the monitoring application is embedded in the control system, it is possible to make this information available at all operator and engineering stations. Typically, an overview of the process measurement and control performance will provide insights to the measurements and control loops that have incorrect mode, high variability, limited operation, or a value with bad or uncertain quality. It is also possible to look at how these problems have been occurring over time. Using options in the analysis, tools users may evaluate performance for the current operation within a selected period of time that may span multiple batches. For example, by selecting a single measurement or control loop of interest, it is possible to easily "drill down" into more detail to obtain information about the identified problem. An example of this type of navigation is shown in Figure 3.

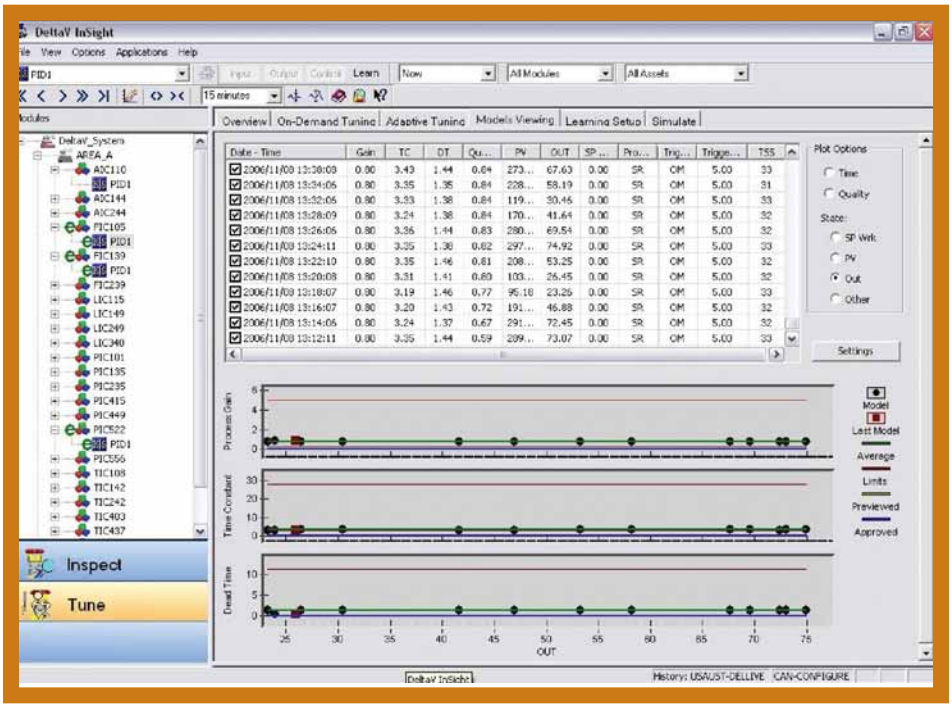

Figure 5: A representative database of derived process models typical of a process modeling tool.

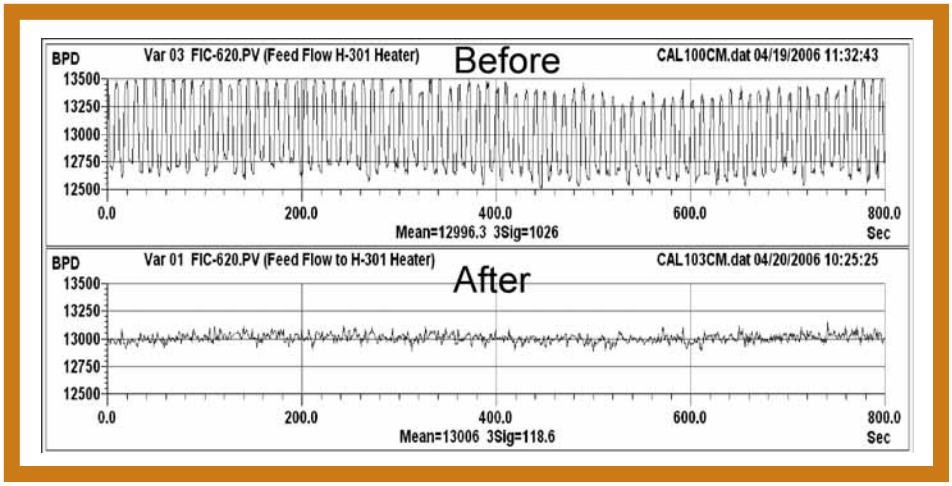

Figure 6: A high-performance digital positioner provides an 88% reduction in process variability.

Control performance

A basic measurement of control performance is the percent of time the feedback control loop actually runs its designed mode of operation without reaching limits on its range of control. In batch operations, the mode parameter associated with feedback control loops will typically switch between automatic and manual modes in various phases of a batch. The performance-monitoring system must compare the actual mode of operation to the design mode of operation to account for this switch. The performance-monitoring system also should identify when a control loop is not operating properly because its range of control has become limited.

Another common measurement of control performance is process variability and the ability of the control system to maintain a desired operating condition and compensate for unexpected disturbances. Statistics on control loop error, such as standard deviation, and a control-performance index that benchmarks actual *versus* ideal operation are typical measures of control performance. Unfortunately, these statistical methods often require some knowledge of the process and may only provide a relative measure of performance.

Process model identification

One of the most significant developments in process monitoring is the ability of some of these packages, such as DeltaV InSight, to automatically identify the process dynamic and gain during normal plant operation. Changes in the process are automatically reflected in the process model that is derived by this package. Thus, it is possible to accurately predict absolute control improvements without the need for the configuration and maintenance that is associated with a traditional control-performance index. The expected improvement in control is expressed as a "tuning index."

> The performance-monitoring system must compare the actual mode of operation to the design mode of operation.

Once a process model is identified, then it may be used within the monitoring system for other functions. For example, based on the process model it is possible to automatically provide the best tuning

needed to achieve the performance improvement, as shown in Figure 4.

Automation system tuning may be suboptimal as a result of simple changes in process dynamics. It is most often impractical to manually retune systems based on day-to-day conditions. This can lead to increased variability in process performance. Through the application of best tuning determined by process modeling software, however, it is possible in many cases to quickly address this source of high variability in a control loop.

Modeling tools facilitate the analysis of process models.

As process models are identified during a batch, great insight into the process can be obtained by observing changes in the model throughout the batch. By comparing identified process models and recommended tuning identified during batches where various products are made with the same equipment, then the effect of these products on control becomes apparent. Also, by comparing the models developed for the same product but using different equipment, one can determine the effect of vessel size and other equipment differences on the process response and gain.

Today's process modeling tools can facilitate the analysis of process models. For example, it is possible to store the hundreds of process models identified for each loop that have been automatically captured and saved in a database. Tools allow the user to easily analyze changes in a process model and to determine the cause of these changes (*e.g.*, product grade, feed concentration, time in batch). An example of the interface used for model analysis is shown in Figure 5.

Addressing areas of improvement

By implementing process monitoring, it is possible to quickly identify problem areas in the process that could influence final-product quality or production rate. Industry surveys have shown that without the capability of these new performance monitoring tools, many of these problems may go undetected until they influence production or product quality. On a recent PAT project to implement model predictive control on batch distillation at a major pharmaceutical facility, more than half of the control loops had problems that contributed to increased variability. The action that should be taken to correct such problems depends highly on the process instrumentation and the process design. Some common problems that may be detected through process monitoring are listed in the sidebar, "Common problems."

One of the more challenging areas to troubleshoot is to determine the source of high variability in a control loop. If the monitoring system supports model identification and provides recommended tuning, then this information may be used to determine whether the tuning is correct for the current operating conditions and whether this changes during the batch or with varying operating conditions. If the process conditions continuously change, it may be advantageous to continually adapt tuning parameters based on tuning calculations during various stages of the batch cycle. By providing best operation at all points, it is often possible to reduce process variation and provide quicker response to setpoint changes. Such improvements can often have a direct effect on final product quality.

Some monitoring systems also can identify problems with control devices such as control valve actuators. When the process variation is caused by poor actuator performance, then there may be an opportunity to achieve greater performance with the installation of a digital actuator. For example, a digital HART-based actuator system may be retrofitted on an existing valve and work directly with a controller providing a standard 4-20 mA output. On a new installation, a Foundation Fieldbus digital actuator may be used to achieve the best performance. An example of the control performance improvement provided by a high-performance digital actuator system is shown in Figure 6.

During various stages of the batch cycle, it may be advantageous to continually adapt tuning parameters.

Common problems

Control limited
- Valve actuator calibration;
- Valve size incorrect for the application;
- Supply pressure is insufficient.

Bad or uncertain quality
- transmitter or element failure;
- transmitter calibration is incorrect of the operating conditions.

Incorrect mode
- Control setup is incorrect, not allowing proper operation in Automatic;
- Actuator or measurement needed for control is not working or reliable.

High variability
- The loop tuning is not correct for the process conditions encountered during normal operation;
- The actuator has poor resolution or high deadband;
- The installed valve characteristic is highly nonlinear, resulting in varying process gain as a function of valve position;
- Upstream disturbances are unmeasured.

Conclusion

The PAT initiative offers the pharmaceutical industry an opportunity to improve the operation of existing installations. A good first step in identifying opportunities for improving batch operations is to use a process-monitoring system. Many products available on the market today are designed to meet batch-processing requirements. These systems may be layered on an existing control system or, in the case of a newer installation, a performance-monitoring capability may be embedded in the control system. Throughout the application of performance monitoring, problem areas may be identified in an on-going manner. Digital transmitters may be used to provide an indication of measurement quality that may be used by the monitoring system for early detection of measurement faults. The ability of some systems to automatically identify the process models associated with a control loop represents an advancement in process monitoring. The insight this provides into changes in the process dynamics and gain may be useful in expanding the understanding of the process. Also, this information may be used directly to provide best control for all operating conditions. PT

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