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**Feature Article**

# FDA Pushes PAT and Companies Shove Back

## Even with Perks, PAT Implementation Remains Stalled

**Eric S. Langer**

Back in 2002 the FDA announced an initiative to shift regulation of drug manufacturing to a more process-centric validation approach, as opposed to the current product-centric one. Process analytical technology (PAT) was set up to optimize manufacturing and reduce resistance to the use of new production technologies.

PAT requires real-time measuring of process variables using sensors, computer analysis, control technology, and continuous improvement data analysis. While PAT is voluntary, the FDA appears committed to encouraging its adoption by offering reduced regulatory oversight burden, which might result in faster approvals.

To determine how and where within the implementation process the industry currently stands on PAT, we surveyed companies about their PAT implementation plans. We found that nearly 58% of the 434 industry respondents are considering PAT for new processes vs. 42.6% for existing processes. Although, only about 3% have already implemented PAT initiatives. About 3% indicate they will not implement PAT for new processes. The study shows that PAT implementation appears to be considered more often for new rather than existing processes. This may be the result of perceived regulatory difficulties in adding or changing monitoring procedures.

“It is somewhat surprising that the difference in what is being implemented for new vs. existing processes is relatively small (2.8%),” explained Beth Junker, senior director, bioprocess R&D, Merck. “The gap is large (15%) for processes being considered for PAT implementation, reflecting a potential industry perception that it may become harder in the future to implement PAT for existing licensed processes.”

With all the potential good from PAT, many have asked why relatively few facilities have implemented it. As John Walker, vp of engineering at Merck, noted, quality-by-design and PAT require an integrated approach to product and process development. The drastically reduced tolerance for variation that PAT brings means that much of the current equipment is not appropriate for use with PAT.

That leaves three options, Walker said, live with the existing equipment, do not pursue PAT and endure the closer attention of the FDA, reduced yields, and higher costs of production; upgrade the existing integrated equipment with PAT front ends; or introduce capable integrated equipment with PAT-based controls.

### Industry Objections to PAT

According to the survey, the industry’s biggest objections regarding the implementation of PAT initiatives are the time involved, the lack of staff, and uncertainty regarding how regulators will use PAT information.

“It is natural to try to avoid change, especially if it is perceived that the FDA doesn’t want or allow change,” Lou Bellafiore, president and CSO at TechniKrom, said. “Of course, the opposite is true today, and the FDA wants to end the technology stagnation created by the industry’s incorrect assumption that old technologies are already approved and innovation is frowned upon.”

Bellafiore speculated that the reason why few companies are implementing PAT is because “companies are implementing product analytical technology rather than process analytical technology, and no cost or quality benefits are being realized.”

In fact, only about 20% of the industry, according to the survey, indicated it is currently in the process of implementing PAT initiatives. At issue is whether this will change anytime soon. Bellafiore feels it will, “when industry executives recognize the need to reduce cost and generate innate product quality as a result of the process not post-process corrections.”

Simply installing sensors to trend product status is costly and does not yield an economic benefit because it does not improve the

process in real time. The safety net of post-process QC focuses on product attributes as the key requirement of manufacturing, and this is one of the reasons for the slow uptake of PAT. Further, the promise of cost savings and quality offered by PAT are only now being seen.

**Hurdles to Implementation**

According to the survey, the most significant hurdles in implementing PAT were time required to implement (71.6%) and insufficient people in-house to manage implementation (64.5%). In addition, over half (50.8%) of the respondents were concerned about how regulators will deal with the information generated by PAT.

Other hurdles that respondents felt may be hindering PAT included—unproven technology, no real driver to adopt in face of risks involved; justification of validation; development data supporting PAT is required; methods to be used for more detailed in-process monitoring need to be developed; cultural acceptance of PAT controls in-process needs to be increased; and, U.S. regulatory guidance and global regulatory concurrence are inadequate.

“The combined uncertainty regarding how regulators will deal with PAT information (50.8%), and perceptions that implementing PAT increases regulatory risk (34.7%), together form the greatest hurdle,” Junker said.

Another perceived hurdle is the time required to implement PAT (71.6%), which is related to resource limitations (65.4%) and cost (48.8%).

This data suggests that the perceived risks associated with PAT implementation, which include both regulatory and cost/resource risks, are substantial and may still be perceived to outweigh the potential benefits.

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