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On The Path To PAT

6/29/2005

At a recent workshop on controlling tablet lubricants, attendees learned how PAT (process analytical technology) devices can identify processing inconsistencies long before those flaws have a chance to derail product quality.

By Tom von Gunden

Like many of you, I have been watching for the industry's response to the FDA guidance (issued in September 2004) for implementing PAT (process analytical technology). As you know, the major thrust of the guidance is process improvement. FDA wants to encourage pharmaceutical manufacturers to bring in methods, equipment, and instruments that enable more frequent process monitoring and tweaking. The goal is to identify potential threats to final quality before products have marched down irreversible paths toward completion. If potentially troublesome variations from product targets and standards can be identified earlier in the manufacturing process, they can be addressed with process alterations to ensure that downstream steps are not undermined by upstream problems.

Although the PAT supplier field is fairly green and user adoption even greener, process analytical technology, whether embedded in process equipment or attached to it (e.g. a monitoring device mounted on a blender), is already available from some vendors. One notable supplier is Mathis Instruments of New Brunswick, Canada. The company's core offerings are sensors based on founder Nancy Mathis' patented technology for measuring thermal effusivity, or the capability of a material or substance to transfer heat. As PAT devices, Mathis' thermal effusivity sensors are designed to alert equipment operators, lab specialists, and the like when process deviations threaten to derail product consistency and quality.

I witnessed thermal effusivity sensors in action at a recent two-day workshop Mathis Instruments organized and presented. Billed as "The Magnesium Stearate Solution," the event focused on a particular application of PAT principles and technologies: controlling the addition of magnesium stearate, a commonly used lubricant, during the process of blending and compressing powders for tablet making. As any experienced tablet press operator can attest, a blend containing an optimal amount of lubricant — mag stearate, in particular — has a much better chance of producing a tablet batch that consistently demonstrates correspondingly optimal levels of hardness, friability, surface appearance, required ejection force, and so on. A less-than-optimal blend is much more likely to lead to problems at the press (e.g. picking, sticking, capping, softness) or later (e.g. poor disintegration, slowed or blocked dissolution, uneven distribution of the API). Because adding lubricant to a blend affects thermal effusivity, the folks from Mathis reason that measuring effusivity at various points in the blending process can uncover inconsistencies. Those problems can then be corrected before the blend makes its way to the tablet press and beyond.

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Mathis Instruments is not alone in acknowledging a correlation between thermal effusivity and the identification of optimal conditions resulting in blend uniformity (or deviations from same). The cornerstone of the two-day workshop — a demonstration of effusivity monitoring done during an actual blending process — was led by Stephen Closs, manager of process development engineering for contract manufacturer Patheon. Mathis' Patrick Okoye, field application specialist, joined Closs for the demonstration. Replicating in miniature a recent full-scale research project he steered, Closs led participants in a hands-on session on PAT-driven testing of powder blends. The results revealed effusivity readings that showed significant differences depending on varying processing factors such as amount of lubricant, length of blending time, tablet weight, tablet hardness, and so on.

Those differences seemed to support the general rationale for PAT implementations: that process components, such as blending, can and should be tweaked if in-process measurements identify early indicators of potentially diminished returns in product quality. Undertaking in-process changes, so the argument goes, enables the current batch to be "saved," as opposed to being eventually declared unusable in response to post-run QC testing. It also significantly cuts into the lengthy delays commonly occurring between the act of sending blend samples off for lab testing and the moment when results point to problematic batches — often large ones. The demonstration echoed a suggestion Nancy Mathis made in an earlier presentation regarding a key mental shift manufacturers will have to undergo in order to leverage the benefits of PAT. Rather than follow predefined process requirements to the letter and move from one process step to the next only at preset endpoints (e.g. "blend for 20 minutes; add lubricant; blend for 10 more minutes"), manufacturers will be able to use PAT-driven results to alter procedures as necessary. "Stop the blender when the product is blended," Mathis advised. "Stop lubricating when the product is lubed."

Suppliers Respond To The PAT Push

I also found particular significance in the setting for the two-day session, the Technical Training Center on Natoli Engineering's corporate campus in suburban St. Louis. While event organizer Mathis Instruments set the agenda and lined up the guest presenters, Natoli Engineering, a supplier of tooling, tablet presses, and tablet press refurbishment services, served as the meeting's host. The Technical Training Center is a non-commercial facility that Natoli has dedicated for educational use by other vendors and stakeholders in the tablet compression industry.

On the surface, it might seem odd that a company primarily known for making tablet press tooling would emerge as an early supporter of PAT instrumentation. After all, although they are often highly sophisticated in terms of conceptual design, as well as in the skills and technologies required to produce them, punches are still punches, dies are still dies, i.e. they are among the most functionally basic, mechanical components of the tablet-making process. In fact, Natoli Technical Service Manager Doug Kirsch admitted as much at the outset of his presentation on the effective use of tablet press equipment and tooling. But, as Kirsch also reminded the audience, the success of any tablet-making operation stems, in large part, from the quality and consistency of upstream process stages, including blending and lubricating — stages which, as the

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Mathis/Patheon PAT demonstration suggested, can be improved by in-process changes. Moreover, the very offering of Natoli's tablet press refurbishment service underscores the point that final product quality is in jeopardy whenever process components break down. That breakdown could occur, of course, because of a bad powder blend, the kind that could be detected with the help of a PAT instrument. Or, it could be the result of machine wear or misuse, a condition that would be evident on a to-be-refurbished press.

Joining Natoli and Patheon in helping Mathis paint the bigger picture of PAT-driven, multi-stage process improvement were representatives from blender supplier Patterson-Kelley; training provider and equipment reseller DI Pharma Tech; and process automation, control, and validation company Brock Solutions. The cynics among us might suspect a bandwagon mentality making its way across the vendor community. But, I don't see it that way. What I see are vendor companies willing to stick their reputations and, hence, their competitive necks out there very early on. Remember, it's been less than a year since the official FDA guidance on PAT was issued. And, despite their appearance at events like the one described above, equipment and services providers are admitting that they don't have PAT completely figured out, certainly not at the level of knowing exactly what will be required to implement it in your shop. Nor, do they profess to know exactly how PAT will affect additions and enhancements to their product lines and service offerings. As the Mathis-led, Natoli-hosted workshop demonstrated, what vendors are currently offering the pharmaceutical manufacturing community is very much a "let's learn together as we go" proposition. Some product releases here, some implementations there, and a lot of consultation in the meantime. Attendees at this helpful, feet-wetting workshop should be off to a solid, knowledgeable start as they return to their in-house discussions about next steps and best practices for PAT in their organizations.

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