

Manufacturing Execution Systems

Moving to the Next Level

Ronelle Russell

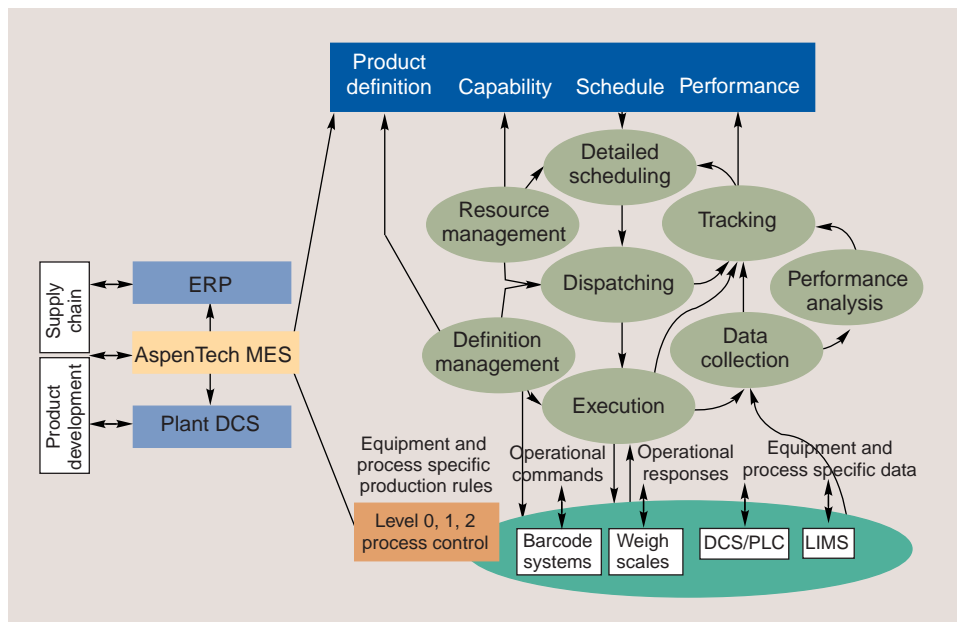
BACKGROUND: NOVARTIS; CAPTURE: PILGRIM SOFTWARE

The use of manufacturing execution systems (MESs) can provide important information to all parts of the pharma manufacturing business, helping **reduce compliance costs, improve overall product quality, and ensure that the correct processes are being followed.** Although MESs offer such benefits, companies must be aware of the time and costs associated with MES integration and maintenance.

Today, many companies find it difficult to keep current with the latest wave of technology upgrades and software aimed at enhancing productivity while still balancing costs with revenue. Pharmaceutical manufacturing companies are definitely no exception as they try to maintain the software systems used to monitor their plant-floor operations and assess and forecast their business. To balance these concerns, many pharmaceutical companies are using or are currently implementing manufacturing execution systems (MESs). Although these systems can provide many benefits in terms of greater automated functionality and better communication between business areas, a company should be aware of the time and costs associated with the integration and maintenance of MESs.

MESs have been used by pharmaceutical companies for several years and have provided an important interface between

enterprise resource planning (ERP) systems and plant-floor control or distributed control systems (DCSs). ERP systems manage the business supply chain (i.e., demand forecasting and planning and strategic supply organizational planning) as well as the informational supply chain, which includes facility management, control, and operational and materials planning. ERP also has the job of matching the company's projected manufacturing-floor demand and its actual orders. Consequently, it must be updated weekly, biweekly, or monthly. ERP offers the broad, forward-looking view for a company, while the DCS provides the actual minute-by-minute, second-by-second real-time operation of a plant floor. The DCS is a combination of hardware and software that controls all the equipment in a plant down to the closing and opening of valves and taking readings from and setting values for actuators and sensors.



The MES solution from Aspen Technology addresses the key operations defined by S95, including performance analysis and production scheduling, dispatching, data collection, and execution.

Although ERP and DCS are both integral parts of a company's automated operation, the two systems must be linked so the plant floor will know what's happening at the business level and vice versa. This is where MES fits in, taking a seat right in the middle. Before MES, this communication took place via paper documents with substantial human involvement—a process that required a great deal of time and was prone to errors. MES applications respond to this problem by automating and recording the data, thereby reducing errors and the time required to transfer information.

MES software systems send the manufacturing plan (what products to make, how many batches, and how to make them) from the ERP down to the plant floor. It then sends the data from the plant-floor operations back up to the ERP to ensure that the proper amounts of materials have been obtained and the time-to-market or customer ship deadlines are being met. The MES does this by providing recipe management and electronic batch record keeping. Therefore, MES provides important information to all parts of the pharma manufacturing business, helping reduce compliance costs, improve overall product quality, and ensure that the correct processes are being followed.

Though the potential benefits of implementing an MES are substantial, they're also not without their challenges. The time required to implement and configure an MES, the cost of initially validating the system and revalidating each time there is a change, and the combined time and cost of staying current with FDA regulations all weigh heavily on the minds of company owners when considering MES as a production automation option. Though the benefits of an MES can be great and lead a company to higher profitability, manage-

ment should also assess and evaluate the difficulties they could face as a result of integrating such a system.

Implementation

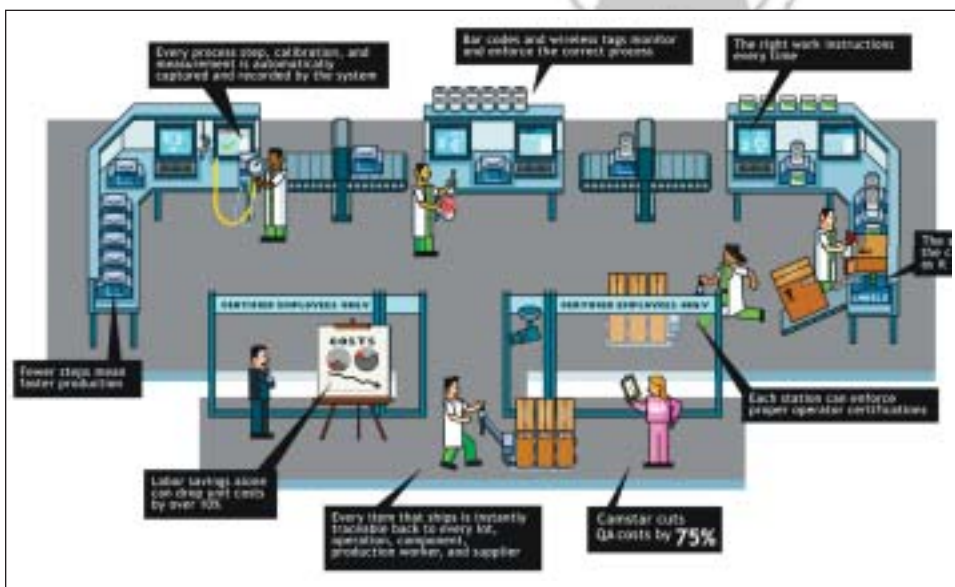
One of the main challenges of MES implementation is the time it takes to integrate it into a company's existing automated systems. Because each company's processes and plants are different, a successful implementation requires a certain amount of unique configuration or customization. There are typically two approaches to implementing an MES: one is to implement an entire MES at once, which is a longer and more costly process but provides complete MES functionality; and a phased approach in which a

company incrementally implements parts of an MES, achieving a subset of functionality, in less time and at lower cost, but without all the benefits of a full implementation.

Many large pharma companies adopt the first approach because they typically have the expertise, employee numbers, and money to invest in the technology. Small pharma companies, on the other hand, usually opt for the second approach. However, according to Mark Roache, associate director of IT Consulting Services at KMI, a division of Parexel International LLC (Waltham, MA), which is a consulting company that helps companies use MES, not fully implementing an MES can mean missing out on its essential functions. "I've worked with some small companies that have tried to implement MES and then found it to be cost-prohibitive. MES is one of those things in which if you complete 80% of what you said you were going to do, the remaining 20% is where all the value was," says Roache. "The value of an MES lies in the integration and the interfaces. The kind of cohesiveness you get from a well-implemented MES is nirvana, but often not found."

Eduardo Handoko, a senior analyst at KMI, agrees with Roache's assessment and adds that incorporating only part of an MES can cause other problems as well. "I've seen MES projects where, even when you reach 95% of implementation, and you think that there's only 5% left, the scope has changed, so there's an additional functionality that requires more modification," Handoko says.

Bill Swanton, vice-president of research at AMR Research (Boston, MA), an independent research analyst firm, agrees this has been true in the past, but says newer MES products are overcoming this hurdle. "More often, vendors have established a



Above: The state of a manufacturing floor before the integration of an MES. Below: Camstar's MES solution can improve overall manufacturing performance and efficiency and supports good manufacturing practices.

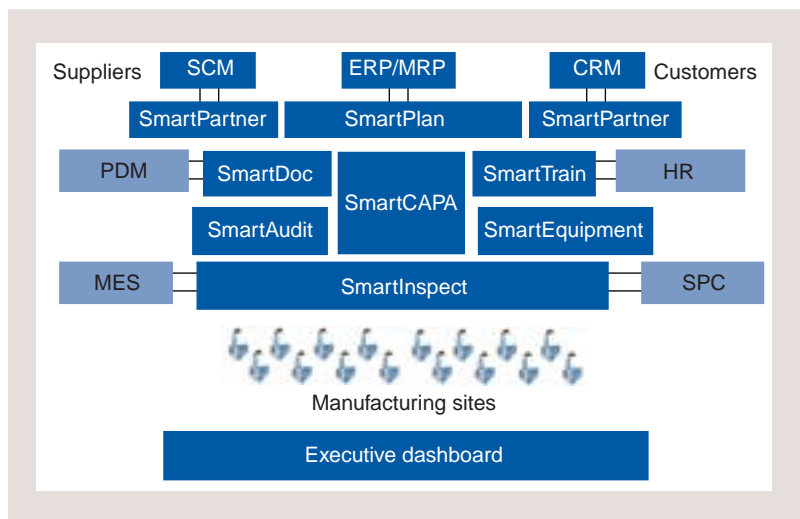
more diverse delivery of products so that companies can receive benefits faster. In the secondary pharmaceutical market, it's very common for vendors to package a separable form of product in modules," he says. Swanton points to weigh and dispense as one functional module that vendors have separated from the entire MES where it can provide companies a near-immediate benefit.

Several MES vendors find the modular approach to MES implementation a better way to serve their customers. Jim Huff, director of MES product management at Aspen Technology (Cambridge, MA), says companies will typically choose to implement an MES one module at a time to affect the area where they see their greatest need, especially in response to FDA regulations. "Companies that implement two or three pieces of the overall solution to comply with FDA will actually start to reap benefits they didn't expect because

they also receive built-in functions such as the ability to perform production performance analysis," says Huff. He also agrees that customers that fully implement an MES do, in fact, receive the most benefit, but notes that the modular approach to MES implementation allows companies to achieve benefits much faster as each module is implemented. Aspen provides an MES of this type called "Plantelligence," which requires anywhere from 8 to 24 months to implement. Huff adds that Aspen provides an analysis of each customer's systems to identify the areas where they need the most improvement. "We try to see where the gaps are and where they want to go, then we build a road map of our solutions to help them get there quickly," Huff states.

Roache concedes that the phased or modular approach can be beneficial to some companies, but maintains that the full MES solution is really the best approach. "It's certainly true that MES modules help speed the process of implementation, but it's a double-edged sword. You get it in early, but the benefit is in the last little bit," Roache says. "I don't think the modular MES vendors can claim advantage, only flexibility and all that comes with that. You still have to have 90% or more of an MES to get what you want out of it."

Lack of standardization. Another obstacle to MES implementation is the lack of standardization in the industry. "Integration is, by far, one of the more labor-intensive parts of implementation and also one of the most technically risky parts," says Roache. "Implementing the MES so that it matches the processes of a particular user, given that those processes change radically from user to user, means that the implementation is different every time." Roache explains that to achieve greater standardization, pharma companies must communicate with each other to identify the ways that their processes and technologies are similar. However, many companies are reluctant to do so because of fears over access to their intellectual property. Still, Roache points out, "There's only so many ways to make a tablet or a capsule. There are some unusual dosage forms such as aerosols and dry powder inhalers that tend to be techno-



Pilgrim Software's SmartSolve product is a multi-tiered system that can be integrated with existing business applications to provide additional quality and compliance functionality.

logically dependent, but 89% of what's produced at the manufacturing process level is not that different from each other. If MES vendors could help people understand the similarities, then I think there'd be more market for MES."

Configuration and customization. Because of the differences in companies' processes and software/hardware systems, a great deal of configuration and customization is typically required to implement MES, which can be tricky, costly, and time-consuming. "The hardest part of implementing a MES is getting the system to fit the customer's actual business processes," KMI's Handoko says. "Customization always takes longer than expected, and as a result, any activity related to testing ends up taking more time, which inevitably delays manufacturing projects." Handoko's observation is that, because vendors don't have enough documentation about specific functions, they tend to forget that a module is somehow related to another, and forget to check the effects when they configure a module differently. "It just takes time to isolate and map back to what you've changed."

Roache agrees. "When you customize something, that inevitably means changing it, and it's very difficult to work out where the effect of your change ends," he says. "It's like ripples in a pond. At some point, the effects of changes become so insignificant that you can forget about them, but it isn't easy to work out what that point is." To make the configuration process more efficient, Roache espouses the idea that MES vendors should simplify core MES technologies and adopt standard interface technologies such as extensible markup language (XML).

Validation

Once an MES has been implemented, it must be validated to ensure that it works according to the specifications of the system's designers. In such a

highly regulated industry, this validation process is costly and time-consuming. Jason Dietrich, vice-president of sales at MES vendor Cimnet (Robesonia, PA), which provides an MES called "Factelligence," has noticed a difference in the way that pharma companies purchase MESs versus companies in nonregulated industries. "Most of the pharma companies we deal with tell us they'd like to maintain one code base once their systems have been validated. If a company wants to upgrade or integrate a new software solution, in some cases, they'll have to redo their validation, so they usually want to limit any modifications or updates because of the time and the cost associated with revalidating," Dietrich says. He explains that most companies have a standard operating procedure or checklist to verify whether their modification, such as a new interface or piece of code, will require revalidation or only a simple addendum.

Alistair Gillanders, senior business consultant at Aspen Technology, agrees. "Once MES projects get validated, companies don't want to make changes too quickly." Gillanders says the vendor community is starting to pull together much more advanced capabilities than have been possible previously, but in spite of this, there's an inertia created by the regulatory environment that is slowing down the rate of innovation. Still, he adds, "That's to be expected. People expect the regulatory environment to do that."

Milan Bhalala, director of marketing at Camstar Systems (San Jose, CA), says that although validation is a difficult area for companies, it can also be an opportunity for MES vendors. "Validation is a long grueling process. No one likes doing it, so whatever vendors do to minimize the work that it takes will add to customer satisfaction." Bhalala notes that companies are liable for all their own validation, and although they can hire consultants to help them, the contracted firms won't take the responsibility for validating an entire operation. "Companies basically have to do it on their own," Bhalala explains. "So the key is how much your vendors, or your partners, can do to make validation as simple as possible." Camstar has developed an MES product called "InSite" that incorporates prevalidated core technologies and a configurable layer that companies can use to model (or customize) their processes. Camstar estimates that this added feature gives their product 80% finished validation when purchased. "We've done everything we possibly can to take everything up to the point of modeling out of the validation loop. Then, all you have to do is model the software and validate that little piece. For example, if you added a new business process to your MES, all you have to revalidate is the new process," says Bhalala.

ISA 95—A new standard for MES

The Instrumentation, Systems, and Automation (ISA) society is developing a new standard for MES that will help manufacturers assess their current automated operations and determine the areas that need improvement. The ISA 95 standard, commonly called S95, has three parts—the first two of which have already been released to the public and focus on the interaction between ERP systems, the supply chain, and the shop floor.

Part 1 of S95 is already being applied as an international standard, and Part 2 is still out for the final international vote. The objective of Parts 1 and 2 of S95 was to develop a means to describe the information that flows between a supply chain and the manufacturing floor in a way that is vendor independent, allowing a company to use the standard regardless of what brand of automation systems they have. The World Batch Forum has helped accomplish this goal by augmenting Parts 1 and 2 with a set of XML schemas to define data so that they can be easily exchanged between different applications.

Part 3 is still being developed, incorporating four areas of MES application that manufacturers can use to identify places for improvement in their operations. These four areas consist of the manufacturing or production floor, laboratory and testing systems, maintenance systems, and inventory management or warehousing systems.

Dennis Brandl, the editor of S95 and president of BR&L Consulting, describes S95 as a way to apply an objective perspective to a manufacturer's entire operation. "Many times people will build their manufacturing facilities based on company tradition and the way they've done it before, so it's very difficult for someone to evaluate different manufacturing plants, operations, and operational philosophies," Brandl says. "S95 gives a common definition instead of everyone getting entrenched in their own way with their own terminology."

After a company has assessed its needs on the basis of S95, it can then purchase the appropriate software systems or augment an existing system. Brandl adds that S95 is already being implemented by several MES vendors, which are using the model in Part 3 to restructure how they describe their solutions so that end-user companies will find it easier to compare various MESs.

As it stands now, the new standard mentions electronic records and can be applied to 21 *CFR* Part 11 systems; however, ISA is working on integrating Part 11 requirements into S95 to more closely identify the areas in which electronic records are required.

a very big issue in the FDA-regulated market today because companies want to minimize their risk of receiving 483s, warning letters, citations, and consent decrees in FDA inspections and audits." Pilgrim and Camstar have a strategic partnership in which Camstar has embedded several of Pilgrim's quality and compliance solutions such as its corrective and preventive action (CAPA) solution in its InSite MES. Willett explains that the convergence of MES vendors and quality management providers is becoming more of a trend as quality compliance has become increasingly important to both FDA and pharma companies. "The data that are contained in an MES, which is not traditionally part of a quality system, are data that we're gathering within our own business environment to provide that additional business intelligence so companies can understand whether they're in compliance." Willett says.

"It's a very synergistic relationship," says Bhalala. "We don't just want to address companies' regulatory concerns, we also want to address their business issues while still keeping them in compliance."

Tamar June, director of marketing at AssurX Inc. (Morgan Hill, CA), another quality management provider, says that MES customers should have several options when it comes to the type of quality functionality they need, even though several MESs have that functionality built in. She explains that quality systems affect a company both globally and corporate-wide, while MESs are usually more plant-floor oriented. "What's on the factory floor doesn't necessarily fit with what works in the global arena," says June. "Each of the systems has a separate scope and is typically reviewed and decided upon using different criteria." AssurX's CATSWeb product has an open architecture that allows it to be integrated with any type of MES.

21 *CFR* Part 11. The reinterpretation of FDA's 21 *CFR* Part 11 guidance in August 2003 affects MES vendors and customers to different degrees and in various ways. "Part 11 hits at the heart of what MES was intended to do—to eliminate paper, create electronic batch records, and keep all the records of your manufacturing process on a database," explains KMI's Roache. "So when FDA issued the new guidance for Part 11, they were basically saying, 'We want you to be risk-focused and do the right thing based on risk such as testing systems and making sure they work.'"

This reinterpretation has allowed companies to start pursuing the benefits of new technology without having to worry about a negative impact on compliance. "Instead, they're worrying if they're doing the right things and if they've properly identified the risks in their systems," says Roache.

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Regulation and compliance

FDA regulations are one of the main determinants in the type of MES a company chooses, but they're also a primary reason for having an MES to begin with. Companies usually want an MES for its functions of quality enforcement, quality requirements definition, and to avoid noncompliance. "A lot of what's driving MES functionality and implementation are regulatory issues, and you can actually solve a lot of your regulatory problems by leveraging MES quality systems while still improving your business operations," states Bhalala. "The MES has moved from a manufacturing-centric approach to kind of a quality-centric approach." Bhalala explains that companies can reduce the cost of compliance with an MES because an MES mirrors the processes that FDA finds important, but at the same time, an MES addresses business concerns by ensuring that processes are being followed correctly, which helps improve overall quality.

Nikki Willett, director of product management at Pilgrim Software (Tampa, FL), says "Quality is paramount for pharma companies because that's one of FDA's biggest concerns. Compliance is also

Gillanders at Aspen says the reinterpretation of the guidance has affected his customers as well. "One major biotech company told me that [the reinterpretation] will reduce the number of systems that must be compliant from 200 to 3. It's become a much more practical environment to work in and avoids much greater expense," he says. Gillanders reinforces his point by estimating that Part 11, in its original form, would have cost companies much more than their Y2K upgrades did. "Companies are now reevaluating their compliance efforts. Part 11 is still a big issue to the customer, but many MES vendors can integrate Part 11 compliance into their systems."

Not all MES vendors and their partners are noticing a huge impact from the reevaluation, however. "From our perspective, there really hasn't been any change," says Willett from Pilgrim. "Part 11 hasn't gone away with the recent reinterpretation, but there's nothing in it that would really change the way we do things. We're providing all the components that our customers need for Part 11."

Likewise, Cimnet's Dietrich doesn't see a major impact. "It hasn't affected our company too much. We have to do some reviews of our structure and verify that it's still compliant, but the modifications are minor."

KMI's Roache recognizes that the reevaluation may not have affected how MES vendors build their products, but it may affect their sales in the new year. He predicts an increase in spending on all types of system implementations affected by Part 11 in the first quarter of 2004, with not much spending until then because of the impending close of the budgeting period and project year. "If the reevaluation hasn't made a difference to MES vendors," Roache says, "then they're doing things wrong."

The future of MES

With the difficulties companies face in implementing, configuring, and validating MES, the future of this type of application is still being debated. Some believe that it will continue to provide the benefits that customers have come to rely on, but others say it will be overcome by burgeoning

technologies. "My prediction is that MES as an application will dwindle and die over the next decade, while MES functionality will move into plant-floor control and ERP systems," says Roache. "One will migrate upwards and one will migrate downwards, cutting out the middle man." Roache qualifies his prediction, however, by stating that the dwindling of MES applications will hit the large MES vendors the hardest. "Start-up pharma companies need interim solutions as they grow, so the small MES providers of interim solutions will be OK."

Swanton of AMR recognizes the expansion of functionality in ERP and DCS, but also wonders if it will be a worthwhile option. "Some ERP vendors are making a huge effort to expand functionality in their systems, but the real question is whether they can do it cost-effectively." Swanton believes there's room in the market for MES vendors for the next few years until ERP system providers can prove they can provide MES functionality inexpensively. "There'll be a lot of large company rollouts of MES solutions, and once companies make a commitment to MES, they'll implement it in the same way in each of their plants."

Aspen's Huff doesn't see ERP ever pushing down to the plant-control level. "It's just not meant to do that," says Huff. "MES is morphing or evolving to be more aligned with the needs of the business versus the needs of the plant flow-type activities."

Huff adds that he believes the future of MES will be driven by the technologies available and by staying current with the problems that manufacturers face and adapting to them. "The guidance we're getting from our customers is to pay more attention to business processes than the purely technical IT-type things, and I think we've got some fairly good direction from them in that area."

Bhalala of Camstar agrees. "MES can only expand, just because there's so much demand. A large percentage of the time, we're not replacing any kind of automated system. It's just not there." **PT**

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