

## Value of MES

# A 'PAT' for the process

FDA rules and regulations are so stringent that even the slightest change in an existing manufacturing process requires its approval once again. Being a long and tedious procedure, most pharma manufacturers do not change their process methods and instead prefer to continue taking a hit on operational efficiencies. Due to this, the FDA has come up with an innovative concept - process analytical technology (PAT) - that helps in processing. This article not only explores the benefits of a PAT-enabled process, but also how it can work well in tandem with manufacturing execution systems (MES). Read on to get the best of both...



**Shripad Lale**

**F**or the past many years, the pharmaceuticals industry has been one of the most constrained industries from a regulatory compliance perspective - and with good reason too. In most manufacturing industries, a faulty product can result in a totally furious customer, but in the pharma industry, the consequences can be fatal. Hence, all moves made by the industry are subject to the approval and scrutiny for compliance of the FDA. By and large, this has had the necessary effect on the quality of pharmaceutical products. In spite of

the billions of individual products that are made and sold every day, one finds an infinitesimal proportion of customers claiming that a product does not work as advertised, compared to the automotive or consumer electronics industry.

However, this system of controls, checks and balances, has had an adverse effect on a completely different area of the pharmaceutical industry - its production efficiency. While a large part of the pharma industry is quite similar to the chemicals industry, manufacturing efficiencies are significantly lower in the pharma industry compared to the chemicals industry. The reason is the nature in which the FDA

used to implement its controls in the industry.

**FDA compliance**

The FDA has a very simple way of ensuring that pharmaceutical drugs do not harm people. First, the pharma company is required to document and publish the recipe and process by which a particular drug is going to be manufactured. Then, it is required to publish production data that provides proof of its compliance

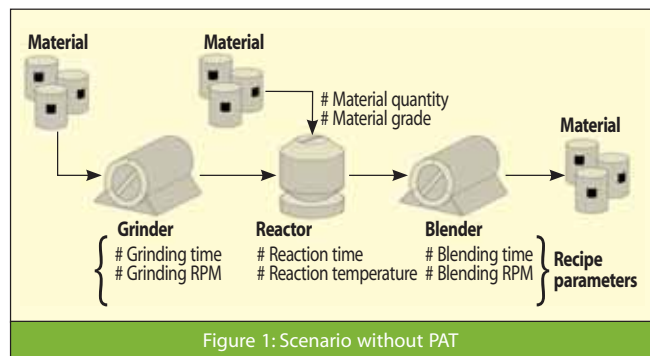


Figure 1: Scenario without PAT

with the published recipe during the manufacturing process. The next step is to provide double blind and randomised clinical trials data proving that the drug indeed does not have any adverse effect on humans.

The above three elements, among others when taken together form an approval package for the FDA. Subsequent to this approval, pharma companies are required to follow the approved process to the last dot. No modifications to the process are permitted, and in case there is a modification, a completely new approval package would need to be created and approved by the FDA, before these modifications could be brought into manufacturing operations.

**The root problem**

Process improvement is usually incremental in nature. Once a process is pressed into service, the operators and supervisors of a manufacturing plant usually discover areas of improving the process through

experience. These improvements could be towards making a process faster and/or cheaper (for example by reducing waste, consuming lesser energy), or improving the product quality. However, making any change in the process will need to go through an FDA approval process all over again. This is a time-consuming and expensive procedure, and at times, the incremental benefits derived by doing these process improvements did not justify the

cost of going through a re-validation and approval process. Hence, pharma companies continue to operate their plants as per the approved process, and thus, taking a hit on operational efficiencies. The end result of all this is drugs with high-manufacturing costs. This extra cost is invariably passed on to the consumer, who ends up paying a lot more than what he would need to if the manufacturer had solved the operational efficiency problem.

**Process analytical technology**

In one of the most significant amendments to its stipulations, the FDA has come up with the process analytical technology (PAT) initiative to encourage drug manufacturers to optimise their manufacturing processes. The optimisation should be in a manner that not only ensures quality of the final product as per FDA stipulations, but also gives the manufacturer the

required control over the process to achieve operational efficiency.

To quote from the FDA website link (<http://www.fda.gov/Cder/OPS/PAT.htm>): "A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency. Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from: Reducing production cycle times by using on-, in-, and/or at-line measurements & controls; preventing rejects, scrap, & re-processing; considering the possibility of real-time release; increasing automation to improve operator safety & reduce human errors and facilitating continuous processing to improve efficiency and manage variability."

**Understanding PAT**

PAT is a concept and not a specific technology. There are several technologies that enable PAT within a manufacturing process. These technologies span a wide range, right from an intelligent process analysis instrument, to sophisticated decision support systems (DSS) that utilise the capabilities of these intelligent instruments. But the ultimate purpose of PAT as a concept is quite simple

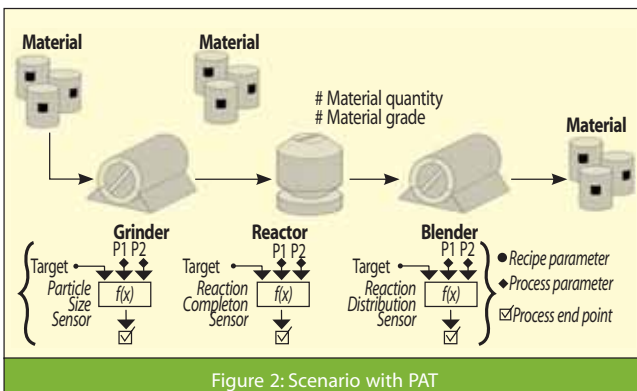


Figure 2: Scenario with PAT

- 'end-point detection'. This can be better understood with a case study. Consider the following process:

- ❖ Material comes in from the warehouse in the form of drums
- ❖ The material is ground to a certain particle size using a grinder
- ❖ The material is mixed with other materials into a reactor and allowed to react
- ❖ It is then blended into a consistent mixture in a blender
- ❖ The finished product is discharged into drums and taken to warehouse

This process however, can be considered in two scenarios: one without PAT (the classical way of doing things in the pharma industry) and one with PAT (an innovative technology).

### Scenario 1 : Without PAT

In a scenario without PAT (refer to Figure 1), the process is controlled on the basis of recipe parameters. These recipe parameters may include:

- ❖ **For grinding:** Grinding time and rpm of the grinding drum
- ❖ **For reactor:** Reaction temperature and time
- ❖ **For blender:** Blending time and blender drum rpm

These recipe parameters are part of an approved recipe and hence, it is not easy to change their values without creating a deviation from the approved recipe. The new recipe would need to be explained during an FDA audit.

In case there is a variation in the quality of the input material, the reaction time for such material may vary slightly. Using standard recipe parameters for materials at the extreme ends of the input quality, variance typically leads to reduction in yield. In situations where the recipe is rigid, it is not possible to change the recipe parameters to suit the current situation. The manufacturing plant needs to execute the recipe as per the approved parameters, and either suffer rework or take a hit on the yield, if it comes to that.

### Scenario 2 : With PAT

A PAT-enabled process dispels this absolute dependence on operational recipe parameters. Instead of specifying operational recipe parameters like grinding time, a PAT-enabled recipe specifies result parameters (like particle size) that are given as target inputs to sophisticated 'end-point detection' systems or 'end-point detection sensors'.

Thus, the process (Figure 2), with a PAT-enabled recipe would be as follows:

- ❖ **For grinding:** The recipe parameter would now be target particle size. Rpm may also be specified, but not grinding time. A sophisticated particle size sensor would detect when the size of the particles has reached the target particle size and automatically stop the grinding process. Thus, any over-grinding or under-grinding that may have occurred in a static recipe, due to harder or softer input material, or newer or older grinding medium, is avoided.
- ❖ **For reactor:** The recipe parameter would now be 'reaction completion characteristic'. For reactors, this could get quite complex since at the end of a reaction, the target state may be characterised by a specific

composition of elements in the material. This may require high-end equipment like X-Ray spectrometers, Raman effect spectrometers, near infrared, far infrared spectrometers, among others. The implementation of PAT in any case involves installing a device that can detect the 'reaction end point', and the recipe parameters would be the element composition of the substance that is being produced, such that an end-point sensor can detect when that composition is reached.

- ❖ **For blender:** The end point in this case would be the material blended uniformly, which may be detected by a particle distribution measurement for solids, or viscosity for liquids. The recipe parameter in this case would be the desired distribution or viscosity that needs to be achieved. Once this distribution is reached, blending stops, avoiding the energy cost of unnecessary blending.

### The role of MES

The end goal of any PAT implementation is to achieve higher production efficiencies, quality consistencies and waste reduction. All the methods and technologies

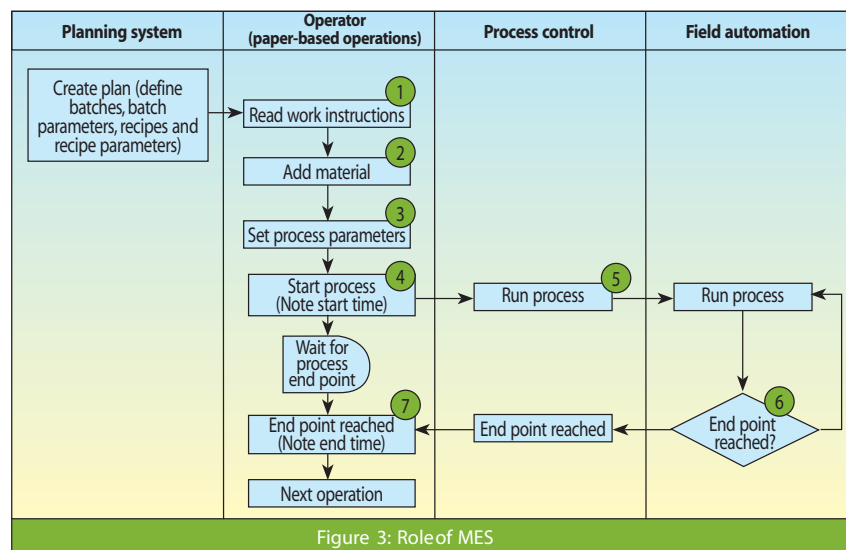


Figure 3: Role of MES

Table 1: PAT, with and without an MES

Task	Without MES	With MES
1. Read work instructions	Operator reads work instructions from a paper work instruction sheet or batch ticket. No bearing on PAT	No difference, except that the operator reads electronic works instructions, that are in sync with the recipe being executed
2. Add material	Operator adds material to the equipment (mixer, grinder, reactor)	No difference
3. Set process parameters	<p>The operator sets process parameters. This is straightforward in a system 'without PAT', but with PAT, the process parameters themselves are dynamic and depend on the recipe being executed (what product, what quantity). If the recipe changes frequently, or the quantity is dynamic (which is often the case),</p> <ul style="list-style-type: none"> <li>❖ It become difficult for the operator to keep the parameters in sync with the latest recipe or quantity</li> <li>❖ Since the operator is potentially entering different parameters every time, there is opportunity for error</li> <li>❖ The operator entering parameters in a system every time wastes time, which may take away some of the time gained by the PAT implementation</li> </ul>	<p>There is no problem with a dynamic recipe</p> <ul style="list-style-type: none"> <li>❖ The MES system ensures that the latest recipe gets converted into the latest electronic work instructions (EWI), which are presented to the operator for execution</li> <li>❖ The process parameters are computed by the MES system each time. Hence, there is no opportunity for error in calculations</li> <li>❖ The process parameters are downloaded by the MES system directly to the process. No operator intervention is required. This eliminates the delay and the opportunity for error</li> </ul>
4. Start process	Operator starts process and notes start time. Most of the time, the metrics derived for the benefits of a PAT system have a crucial dependency on this start time. If this time is noted wrong, all the metrics would be wrong, potentially negating the purpose of the PAT system	No opportunity for error. The MES system notes all start and end times, and communicates them accurately and instantly to the planning system. This enables maximum leverage of the PAT system
5. Run process	The process is run by the process control system	No difference


discussed so far, deal with the 'process control' layer of a manufacturing plant. These technologies are designed to work at the micro layer, but have no knowledge about the macro-level view of 'production'. For instance, a highly sophisticated end-point detection sensor for a reactor, detects the point at which the reaction is complete, but has no knowledge of the difference it has made to the overall production efficiency. This is the realm of a manufacturing execution system (MES). Figure 3 represents the role of MES in a typical PAT system.

The behaviour of a PAT-based system in an environment without and with an MES system differs (Table 1).

### Conclusion

In a pharma/biotech company, productivity and efficiency can be thought of at three levels: Planning efficiency (how much time it takes for creating a plan, and its accuracy); operations efficiency (compliance to planned cost/quality/schedule); and process efficiency (optimal operation of the chemical/biological process producing the material).

Various advanced planning products like the SAP APO, or I2 address Part 1, while PAT systems address Part 3 of this problem. The operations efficiency piece (Part 2) remains a challenge, since it is the only piece that requires humans, computer systems, and machines to work together by exchanging information and passing control to

each other in a well-orchestrated manner. An MES system, helps bridge the gap between planning improvement (advanced planning) and PAT initiatives, leading to the maximum leverage of investments in these systems. 



Shripad Lale is the vice president of Product Engineering for Performix Inc, responsible for Product Strategy

and Engineering of the xMES™ suite of products. Over the past 20 years, he has been involved in providing manufacturing IT solutions to Fortune 100 customers across the world. Lale's core capabilities are in the areas of software engineering, manufacturing automation, and manufacturing IT. He can be contacted on email: [shripad@performixinc.com](mailto:shripad@performixinc.com)