GE
Intelligent Platforms

Achieving Operational Excellence in Pharmaceutical Manufacturing

Using Manufacturing Intelligence to Drive Strategic Operational Results

Introduction

It is no secret that the pharmaceutical industry is feeling intense pressure to transform their operations and the way that they do business around the world. Institutions that have manufactured products the same way for decades are now being forced to reduce costs, add value and turn production into a competitive advantage. To survive, drug companies (big pharma in particular) have had to look at innovative ways to become more efficient and agile at manufacturing, and to embrace the change that is permeating the industry.

Patent expiration, generic competition, counterfeiting, and supply chain challenges are all having an enormous impact on manufacturing, and companies are looking at ways to improve. The 2006 Pharmaceutical Research Manufacturing Project estimated that manufacturing waste in the industry exceeds $50 billion. Many pharmaceutical plants today operate with efficiencies around 30%. A world-class pharmaceutical operation might operate close to 70%, but they are few. When compared with world-class manufacturing operations in other industries that have efficiencies over 90%, the need for improvement is apparent. In response, organizations are starting to gather more data and establish enterprise-level metrics to evaluate performance of manufacturing sites.

Globalization and the rapid emergence of developing economies are acting on pharmaceutical companies as well, forcing them to develop strategies to become more competitive. Tax benefits offered by places like Ireland, Singapore and Puerto Rico are no longer a significant competitive advantage, and organizations are evaluating where they will continue to manufacture products. The way companies have assessed risk is changing as well, requiring organizations to rethink their strategies. Focusing on the BRIC countries of Brazil, Russia, India and China (as well as Eastern Europe), pharmaceutical companies are appraising what opportunities exist there for marketing and manufacturing their products. They are also assessing the risks that those emerging economies present. Indian, Chinese, Brazilian and Eastern European pharmaceutical companies are beginning to make an impact on a global scale by manufacturing generic copies of name brand drugs, introducing products of their own and acquiring Western companies to strengthen their global footprint. No longer are countries like China and India simply the low-cost labor markets for the multi-billion dollar Western global drug corporations.

Initiatives such as Process Analytical Technology (PAT), Quality by Design (QbD) and Lean Manufacturing are aimed at goals like lead time reduction and flexible manufacturing. Those initiatives are slowly taking hold in the industry and starting to produce some results, but in the short term, organizations need to apply science and intelligence to their manufacturing to make production a competitive advantage. Moreover, the deployed technology solution must be aligned with the larger business strategy of improved quality, lower cost and greater manufacturing agility.

Fortunately, there are scalable solutions available today that allow organizations to start small at sites with little or no automation and deliver quick results. **Figure 1** illustrates the journey to operational excellence. Starting with a basic plant historian and web portal, organizations can begin collecting data from diverse automation sources to begin analyzing their operations. Moving to more advanced solutions, context can be given to the data to analyze downtime events by shift or crew, and a full OEE solution can be deployed. Adding an additional module now allows more complex quality analysis, like Cpk to be performed, and process capability can be analyzed with downtime data. Adding the component of batch analysis achieves deep, local OpEx within the four walls of the plant. Finally, integration with systems like LIMS, MES, ERP and CAPA provides context to data from across the enterprise and allows production to be analyzed and optimized.

Acquiring the Data

Over the last several decades, one of the key inhibitors to change and overall process improvement in the life sciences industry has been the stringent regulatory environment. For years, the relationship between drug companies and the FDA has been borderline adversarial. That relationship led to a situation where drug companies did not want to gather data about their processes for fear of what it might reveal to an FDA inspector. They obtained only the data that was absolutely necessary. However, the financial pressure on organizations combined with the FDA's PAT Guidance and Risk-Based enforcement position have provided an environment where companies are encouraged to collect more data so they can start to better understand their processes. A few innovative organizations have taken advantage of that situation and chosen to automate their equipment in order to start to get at the data that tells the story of their processes.

Manual operations still dominate pharmaceutical manufacturing. The process of weighing, dispensing, blending, drying, milling, compacting, coating and even some packaging is still manual in nature. It still requires a human to weigh out a given amount of Active Pharmaceutical Ingredient (API); people still wheel Intermediate Bulk Containers (IBCs) from suite to suite; and some sites still have operators who ladle sugar coating into a coating pan. However, with the wave of improvement projects and initiatives ongoing in the industry, automation has

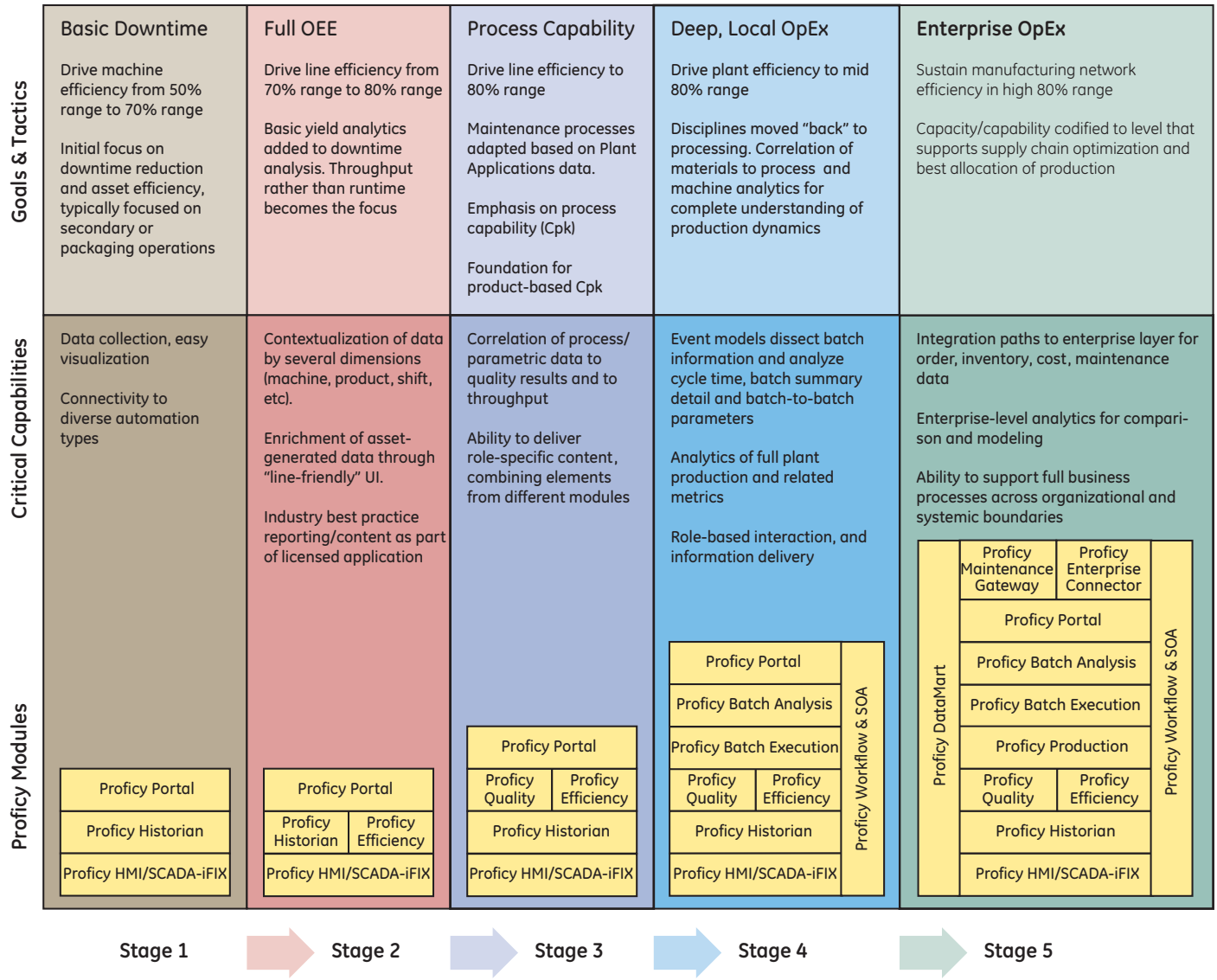


Figure 1 The Operational Excellence Journey

started to make more of an impact, if for no other reason than to acquire data for further analysis.

The FDA's PAT and cGMPs for the 21st Century guidance have allowed more flexibility for organizations to collect data and to interface disparate systems like supervisory control and data acquisition (SCADA), laboratory information management systems (LIMS), corrective action and preventative action (CAPA) systems, manufacturing execution systems (MES) and enterprise resource planning (ERP) systems to make more efficient use of information to improve manufacturing. While automation has been around in pharmaceutical manufacturing since the early 1990's, most of those systems were installed to simplify and automate the operation of a blender or a dryer for instance. The intent of the FDA's guidance is to encourage innovation and better process understanding. Supporting this move toward data collection and interfacing of systems has led to a greater use of automation to collect data about processes, report on downtime events and report alarm and event information into enterprise systems.

Automation solutions like SCADA and Programmable Logic Controllers (PLCs) provide a simple and cost-effective means of automating equipment to begin the process of acquiring

data. Beyond simple SCADA and PLC solutions, the use of a process historian is an excellent tool for capturing critical process parameters. The reliability, power and security of plant-wide data historians have been well established. When combined with a cluster environment or fault tolerant hardware, process historians offer 24/7/365 data availability, and "store and forward" functionality removes concerns about network reliability. Historians today offer sustained storage and retrieval rates of more than 20,000 events per second. Compression algorithms ensure that data storage is managed efficiently, and precise time stamps comply with 21 CFR Part 11 guidelines—providing accountability and security.

To make effective use of the data that exists in manufacturing-processes, a few recommendations should be followed:

- First, data should be collected electronically and automatically when possible. Manual, paper-based data collection is an inefficient means of collecting data such as downtime and reason codes. In addition, if the data is stored electronically, it is available for further analysis.
- Second, the data collection should be fast. Ideally, the system will reflect efficiency and quality data in real time, so a rapid means of collecting the data is necessary for the information to have the greatest impact.
- Third, the data must be accurate. This can sometimes be difficult to accomplish, so an effective process should be applied to the practice of collecting data.
- Fourth, the data collection should be flexible to allow for different types of analysis as priorities change and also extensible so the system can grow.
- Fifth, the data collection should be consistent and aligned with the goals of the business. Different departments may measure things like OEE differently so it's imperative to have a consistent measurement across the business.

Applying Intelligence to the Data

Once the data has been gathered and stored, an effective process of analyzing the data needs to be followed. A potential pitfall to avoid is the problem of "silos of information." This refers to data that is viewed stand-alone and without context. A perfect example of this is a measurement viewed over time. This time-series data shows a value like temperature or level or pressure changing over time, but it shows little more than that. It provides no context to the data. An innovative approach to this problem is to collect all production and process-related data associated with a particular event when it happens, and then correlate all of that data together to provide context-rich information to disparate plant data residing in the process historian. This is accomplished by utilizing an integrated, S95 data reference model. This approach uses a product model to define products and recipes, a plant model to define equipment and capabilities, an event model for the definition of critical manufacturing events, an execution model that provides business rules for product flow, and a calculation engine for analytical calculations and KPIs.

Once the data has been correlated, it can provide critical plant KPI visibility instantaneously. Users of this information-rich data set can now calculate downtime, efficiency, process capability, utilization, waste, and yield. Correlation of the data provides the ability to drill down for root cause analysis and production optimization and to summarize and analyze data in the context of production events by equipment, by product or by personnel. Personnel driving process improvement initiatives can analyze and trend quality and manufacturing data in context of production events such as batch, lot, item and time period.

In addition to automation and data collection systems, major capital investment has been made in recent years in MES solutions. Some of those investments have been made with process improvement or operational excellence initiatives in mind. However, MES applications in life sciences are typically EBR-centric. That is, focus is on the creation of an electronic batch record and regulatory compliance and not on operational excellence. The benefits of EBR projects are obvious, in that they allow for review by exception, dramatically decreasing the time needed to review and approve the batch record, normally kept on paper.

MES solutions also interface with ERP systems and manage equipment, personnel, materials and the download of recipe parameters to the machine. MES solutions manage the execution very well. However, there are some areas where MES falls short. One of the key areas where MES systems do not do well is that most MES solutions do not connect manufacturing with the supply chain. The system is managed very well within the four walls but not beyond. The goal of MES should be true demand pull. MES should coordinate manufacturing with the broader supply chain. Another area where MES solutions fall short is the lack of tight integration with process information. While they have the ability to connect to SCADA systems via OPC, few have a true historian and don't offer a complete view of the production environment. An effective production management system like Proficy Plant Applications will augment the MES solution and aggregate and analyze plant floor process, alarm and event, batch and EBR data and provide a level of manufacturing intelligence aimed at achieving operational excellence. The data is used to drive operational metrics that are reported in near-real-time as production capability information.

Operational Excellence Solution #1: OEE

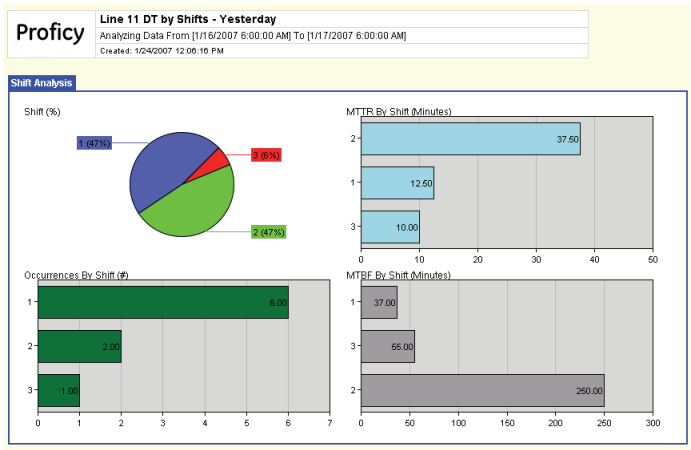
A popular method for driving rapid operational improvement is to measure Overall Equipment Efficiency (OEE). OEE projects

rely on obtaining information about availability of equipment, throughput of the equipment and the quality of what is actually produced. There are a variety of ways to perform these calculations but the most efficient and reliable way of performing the calculations is to base them on automatically collected data as opposed to manually entered information, which is more prone to operator error. Automated systems and plant historians provide an excellent foundation for automatically collected data and a secure storage mechanism to ensure accuracy.

OEE is calculated by measuring three things: Equipment Availability, Performance, and Product Quality. Effectively, this calculation is asking, "Is my machine up or down (as a function of scheduled uptime), how much am I producing (as a function of expected throughput), and how much "good" product am I making (as opposed to waste or scrapped product)?" Availability first attempts to calculate Total Operating Time by subtracting Downtime (OEE will also capture the reasons for downtime) from Operating Time or Uptime. Performance then looks at the Total Output of the machine versus the Potential Output. Finally, Quality measures the Good Output as compared with the Total Output. OEE, expressed as a percentage, is then calculated by multiplying those three factors together to come up with a number. This number provides the foundation for improvement by allowing the Efficiency to be measured against other plant metrics as well as against other industries for benchmarking.

The beginning of this paper mentioned that many pharmaceutical plants today operate with efficiencies around 30%. However, there are many organizations out there operating at 30-40% doing manual OEE that believe they are operating at 70% or even 80%. Manual attempts at OEE have a much higher propensity for error than those based on automatically collected data. OEE done correctly allows managers to make effective, accurate and objective decisions in real time.

An effectively deployed OEE tracking and reporting solution allows the business to track and monitor production and business-driven key performance indicators (KPIs). Utilizing automatically collected data, managers can track downtime, waste, production counts, and user-defined events, and automatically or manually associate events with a specific cause on a real-time basis. By utilizing an integrated, S95 data reference model, organizations can analyze equipment effectiveness based on reasons and details to identify root causes, and summarize and analyze data in the context of production events such as by equipment, by product, or by personnel (hour, shift and day) for improvement. Events and reasons can be correlated to actual production operations. Based on these data reports, dashboards can be developed for real-time decision-making.



Standard Proficy Downtime by Shift Report

Operational Excellence Solution #2: Process Capability Analysis (Cpk)

This year's Operation Excellence survey conducted by Pharmaceutical Manufacturing magazine listed "Improve Internal Quality Management" as the number one goal of organizations for 2008. With a response of 59%, it beat out "Improve Manufacturing Agility" (48%) and "Improve Capacity Utilization" (47%). Interesting to note was that the tool cited as most frequently used for achieving that goal was Process Capability Analysis (Cpk). Cpk had traditionally been rated as less important in the past but its emergence signals a new trend in the industry toward controlling process variation. The website www.isixsigma.com defines Cpk as follows:

"Process Capability index ('equivalent') taking account of off-centeredness: effectively the Cp for a centered process producing a similar level of defects - the ratio between permissible deviation, measured from the mean value to the nearest specific limit of acceptability, and the actual one-sided 3 x sigma spread of the process. As a formula, Cpk = either (USL-Mean)/(3 x sigma) or (Mean-LSL)/(3 x sigma) whichever is the smaller (i.e. depending on whether the shift is up or down). Note this ignores the vanishingly small probability of defects at the opposite end of the tolerance range. Cpk of at least 1.33 is desired."

A more practical and effective definition of Cpk is the capability of the process to remain within the upper and lower specification limits. By applying the S95 data model to correlated process data, a solution like Proficy Plant Applications can determine statistical normality, verify that the process is in control thru SPC analysis, and then calculate process capability (Cpk). Product-based Cpk values for selected parameters can be displayed to an operator or supervisor via standard reporting. This approach allows the

operator to make real-time decisions about the process. In addition, it can generate alarms for quality, control or specification conditions. Finally, correlated data can help deliver critical manufacturing information in real time via the web and product-based Cpk analysis can be used for Annual Product Review.

Adding to the Cpk calculation is the ability to correlate values, reason codes, research notes, recipe, batch, lot, material and production information and evaluate quality conformance in real time. Quality data can also be correlated from across the process as well as integrating process and laboratory data. Cpk and quality data can also be trended and analyzed in the context of production events such as batch, lot, item, serial number, material, time period and can be reported on for real-time decision making.

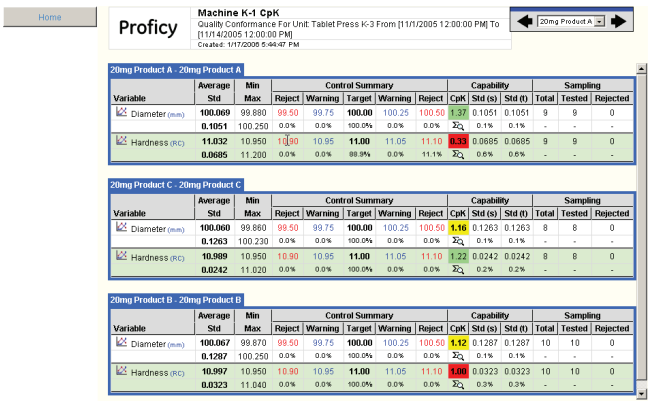
Operational Excellence Solution #3: Batch Analysis

Many batch systems today, often home grown systems, lack advanced analysis and reporting tools necessary to present a comprehensive picture of batch operations in the context of an entire life sciences manufacturing facility. Without these key tools, it is very difficult for manufacturers to drive improvement initiatives like Operational Excellence or Lean. Proficy Batch Analysis is an ideal fit in these types of applications as it facilitates the increase of overall quality and consistency of products and enables better understanding and controlling of variation and the ability to analyze and optimize production in both new and existing batching applications.

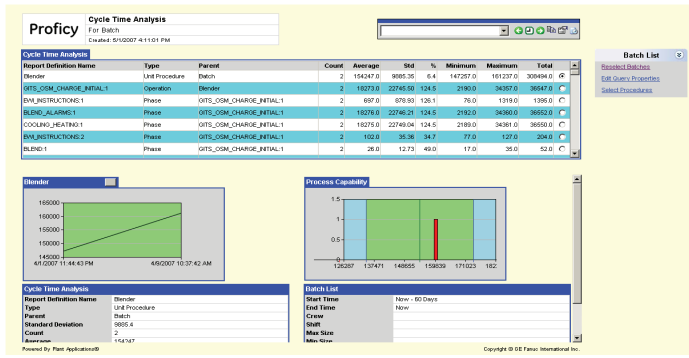
Driving more efficient batch operations starts by tapping into the batch records or "journal" information that is produced by the batching system. Most commercially available batch systems today log the journal or batch activity to tables in a relational database. Once the information is stored in the relational database tables, the Plant Applications Batch Interface extracts data from the journal tables, and the Event Models dissect the batch information and client applications can begin to immediately analyze context rich information.

In the context of an Operational Excellence campaign, Proficy Batch Analysis will help drive batch to batch consistency, minimized variance, maximized yields, reduced raw material loss, reduced rework and scrap, and increased uptime all in a compliant manner utilizing 21CFR Part 11 tools. Batch queries allow users to create a batch listing to include time frame, units, products, crew, shift or even size—enabling users to limit the scope of the batch runs they are interested in analyzing. The Batch Event Detail provides a detailed summary of a given batch, including start time, end time, initial and final weights, parameter summaries, and time trending across variables.

Cycle Time Analysis provides a detailed summary and comparative analysis over a selected set of batches. The Cycle Time Analysis provides a comprehensive statistical breakdown of each "step" of the process across the selected batches and provides information such as average, standard deviation, and minimum and maximum. By comparing operations, phases, and unit procedures across different batches, users can easily identify variation in the process. The Batch Summary provides a detailed report of batch genealogy, procedure details and parameter details for a selected batch. It provides procedural and parameter summaries in a "cross-tab" format, listing parameters for each unit (Unit Procedure) and variable.



Online Tablet Press Cpk Report



Batch Cycle Time Analysis Report

Batch Trending allows users to create and save comprehensive batch trends that provide context-based trending—plotting variables against one another at different stages of batch operations. Each batch trend can accommodate and overlay many different batches on a single display. Batch variables and even data points from historians can be dynamically added to each chart, providing a powerful set of analytical capabilities. Easy-to-use dialogs allow users to quickly and easily modify the trends. A number of contextual display elements are provided for highlighting and analyzing trends—including markers denoting where significant events occurred (start and end of an operation, for example) and confidence bands placing a plot "silhouette" around each line.

Conclusion

The challenging environment in the life sciences industry today is forcing companies to adapt and innovate. Organizations need to find new ways to manufacture drugs and to turn their production into a competitive advantage. An effectively deployed solution like Proficy Plant Applications tailored to the unique needs of the pharmaceutical industry can deliver rapid results aligned with the business goals of the organization.

By applying intelligence to process data and introducing science into the analysis of process information, organizations can drive more competitive advantage into their manufacturing operations. Delivered results include elimination of basic errors, reduced inventory levels, reduced cycle time, reduction in WIP inventory, reduced finished goods inventory, improved operational predictability and improved accuracy of delivery schedule. With intelligence and visibility into the process, dramatic results can be achieved.

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