

White Paper

# **Rockwell Automation Support For Process Analytical Technology in MES**

### *Objective*

The purpose of this document is to provide an overview on how Rockwell Automation's "Propack Data PMX", the production management solution for the Life Sciences industry, supports the Process Analytical Technology (PAT) that was initiated by US Federal Drug Administration (FDA) for the Life-Sciences industry. It identifies specific aspects of PAT that are related to Propack Data PMX features and shows how Propack Data PMX can be enabled to support them.

### *Scope*

This document focuses on PAT aspects that can be associated with requirements for and functionality of Propack Data® MES, CTM or RDM solutions. This white paper considers the current consensus on the related matter in the regulated industry and FDA and is based upon FDA's final guidance document for industry "PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" (September 2004). A comprehensive view on PAT that also includes also the discussion of the impact of PAT onto services technology, regulatory aspects and setting up a PAT program is given in Rockwell Automation's white paper "PAT Initiative Expected to Invigorate Pharmaceutical Industry with Improved Quality, Better Efficiency and Improved Profits".

### *Background of the Process Analytical Technology (PAT)*

Process Analytical Technology (PAT) has become a key role in FDA's initiative entitled "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach" announced in August 2002. The PAT initiative is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance.

In order to support the evolution of PAT, FDA set up a PAT subcommittee composed of senior pharmaceutical and generic manufacturers, government officials, and private and academic consultants to the pharmaceutical industry. This subcommittee provides recommendations on issues to be addressed in the proposed FDA guidance for adoption of PAT by regulated industry.

By definition, Process Analytical Technology refers to systems for analysis and control of manufacturing processes based on timely measurements of critical quality parameters and performance attributes of raw and in-process materials processes to assure acceptable end product quality at the completion of the process. PAT involves optimal applications of process analytical chemistry tools, feedback process control strategies, and information management tools and/or product/process optimization strategies to the manufacture of pharmaceuticals. Such systems will improve the efficiency of pharmaceutical manufacturing processes, thereby

significantly benefiting the public health, as well as the pharmaceutical industry and the FDA.

*Benefits of PAT for regulated industry*

PAT enables more flexible production processes, improved quality and significant cost reductions through better capacity utilization and increased outputs. This is achieved by better understanding of the manufacturing process, identification of root causes for product quality and process variance. The following benefits for regulated industry can be achieved:

- Reduction of cycle times
- Less batch failure
- Faster batch release times by introduction of real time release and electronic batch recording
- Better management of change control
- Reduced compliance and validation effort, time and cost
- Improved project schedule and speed of deployment
- Reduced start-up time

## Key Elements of FDA's PAT Framework

The following section gives a short overview on principles and tools of PAT [5].

### *Quality by Design*

The PAT framework is characterized by the recognition that product quality cannot be tested into the product, but rather must be built into the product from the beginning.

### *Process Understanding*

Better process understanding is key to assuring final product quality . Structured product and process development on a small scale, using experimental design and on- or in-line process analyzer to collect data in real time, can provide increased insight and understanding for process development, optimization, scale-up, technology transfer and control.

### *Continuous Improvement*

The goals for continuous improvement are:

- Systematic process development and optimization
- Improved process control
- Reaction on events in timely manner
- Minimize parameter variance

### *Real Time Release*

The goal of "real time release" in addition to the fast product clearance is to increase the confidence in the quality of each batch produced and delivered. One of the major goals is basically to reduce time consuming sampling and QC reviewing. Instead, for certain applications, sensor-based measurements can provide a useful process signature that may be related to the underlying process steps or transformations. Based on the level of process understanding, these signatures may also be useful for process monitoring, control, and end point determination when these patterns or signatures relate to product and process quality.

# Rockwell Automation MES Solutions on PAT requirements

## *Risk Management Principles*

Comprehensive statistical and risk analyses of the process are generally necessary to assess the reliability of predictive mathematical relationships. Based on the estimated risk, a simple correlation function may need further support or justification, such as a mechanistic explanation of causal links among the process, material measurements, and target quality specifications. Design and construction of the process equipment, the analyzer, and their interfaces are critical to ensure that collected data are relevant and representative of process and product attributes.

## *PAT Tools*

Tools for implementing or supporting the PAT principles are categorized into:

- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

Propack Data PMX solutions typically manage the master batch record specification, execution and documentation of the production of pharmaceutical or biotechnological products. They cover the whole production process from goods receipt, dispensing to packaging and goods issue.

Propack Data PMX solutions support PAT goals through

- Maintaining and improvement of the production process knowledge
- Collecting and evaluation of data during execution
- Timely decision making
- Lead-Time reduction and performance improvement
- Managing and Controlling the variability of the process
- Faster Scale-up
- Continuous "real time" assurance of quality

The following table gives an overview on typical PAT topics and how Rockwell Automation's MES offering support these activities.

*Quality by Design*

Activities and relevant PAT topics	Solution
<ul style="list-style-type: none"><li>• Identify parameters that are critical to product quality</li><li>• Identify quality measurements and analyze these parameters</li><li>• Identify appropriate instrumentation</li><li>• Identify how to control parameters throughout the process</li></ul>	<ul style="list-style-type: none"><li>• Consulting for simulation and modelling of manufacturing process MBR simulation / validation</li><li>• Integration of Formulation Development and Clinical Manufacturing data</li><li>• Specification of critical parameters in MBR of Propack Data PMX Recipe CTM/MES management</li><li>• Specification of deviation- and exception handling in MBR of Propack Data PMX Recipe CTM/MES management</li></ul>

*Process Understanding*

Activities and relevant PAT topics	Solution
<ul style="list-style-type: none"><li>• Define rules and process information on scientific base</li><li>• Define minimal number of parameters to evaluate (CCP, critical quality attributes)</li><li>• Risk assessment</li><li>• Predict product quality attributes</li><li>• Implement control of variability by the process</li><li>• Identify and explain all critical sources of variability</li></ul>	<ul style="list-style-type: none"><li>• Consulting for modelling of master batch records</li><li>• Propack Data PMX Recipe CTM/MES management</li><li>• Dynamic MBR, Process characteristics, CCPs</li><li>• Interface to data and process presentation and evaluation solutions</li></ul>

*Continuous Improvement*

Activities and relevant PAT topics	Solution
<ul style="list-style-type: none"><li>• Continuous monitoring &amp; data analysis</li><li>• Correlate data (Input/outputs)</li><li>• Long term evaluation</li><li>• Early detection &amp; reaction on variances in process or quality</li><li>• Action tracking</li><li>• Root cause analysis</li><li>• Risk monitoring</li></ul>	<ul style="list-style-type: none"><li>• Interface to<ul style="list-style-type: none"><li>○ Historian System</li><li>○ Batch Execution System</li><li>○ Control Logix</li></ul></li><li>• Propack Data PMX Recipe CTM/MES</li><li>• Propack Data PMX EBR MES</li><li>• Interface to workflow management systems for action tracking</li></ul>

*Real Time Release*

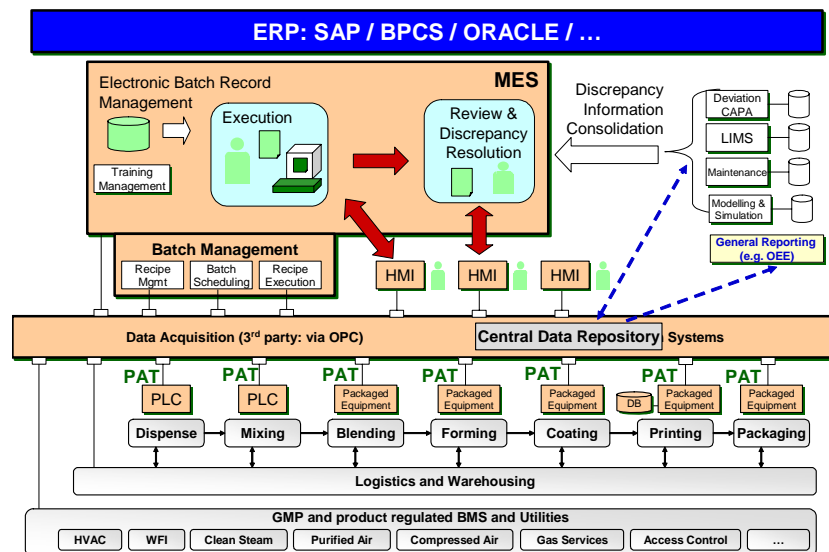
Activities and relevant PAT topics	Solution
<ul style="list-style-type: none"><li>• Presentation and recording of critical parameters</li><li>• Data support for decision making (trends, statistics)</li><li>• Electronic batch recording</li><li>• Control of specification limits</li><li>• Electronic records + signature</li></ul>	<ul style="list-style-type: none"><li>• Propack Data interface to<ul style="list-style-type: none"><li>○ Historian System</li><li>○ Batch Execution System</li><li>○ Control Logix</li></ul></li><li>• Propack Data PMX Recipe CTM/MES</li><li>• Propack Data PMX EBR MES including checklist management and limit control</li><li>• Interface to statistical process control system</li></ul>

## Rockwell Automation PAT Architecture in MES

*An example of a PAT system/component architecture diagram*

The PAT environment can be a combination of the following:

1. Consulting services for system design, data mining, analysis, regulatory compliance, quality systems, documentation, chemo metric methods, implementation, and validation.
2. MES incorporate all compliant master data management as well as method development capabilities necessary to specify and maintain PAT environments and methods.
3. Process Control Systems for batch, discrete and continuous manufacturing process using advance process control (APC) strategies
4. Data collection, process data, typically online data collection and process historian, with some offline presentation and analysis capability
5. Online data collection of process data with offline/online presentation and analysis capability
6. Modeling and simulation tools
7. Instrumentation, both classic measurement and intelligent instruments, typically on-line
8. Multivariate Analysis tools

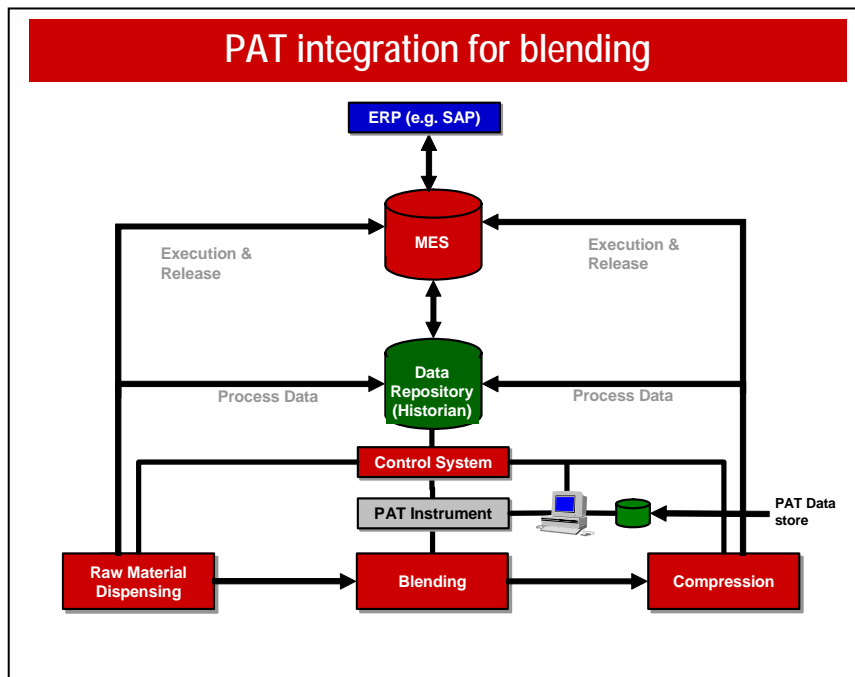


*Example PAT Integration for Blending*

The PAT integration for a blending process is shown below. Starting with the goods receipt of raw material, critical control parameters are directly measured using the appropriate instrumentation. The business process of raw material dispensing is controlled by the MES system using electronic batch recording:

- Based on the critical process parameter “particle size” the processing details for the next process step mixing are determined.
- Again proceeding to next process step is controlled by the MES system.
- Real-time data collected from the process control system is compared to the PAT prediction model to determine the subsequent process activities.

The business process flow is controlled by the MES and final results are sent to the ERP system.



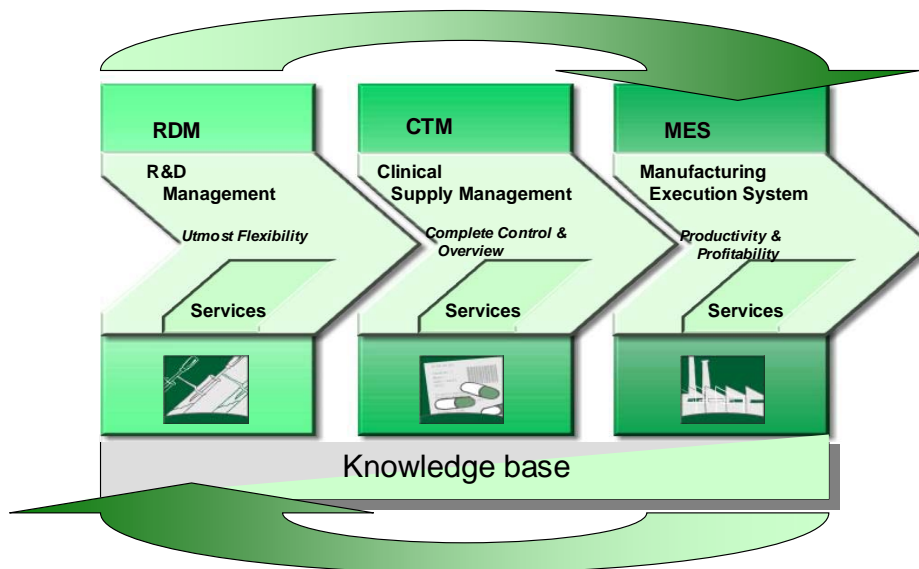
*Integrate knowledge data  
from Research and Clinical  
Trials*

Product quality information and process know-how is typically developed during research and development and clinical trial manufacturing. Several scale-up steps may influence the production process. Therefore, integrating and evaluating all existing data for a product throughout the complete life cycle improves the manufacturing process.

The manufacturing process can be controlled and improved considering following information from previous product lifecycle stages like Research and Development and manufacturing for Clinical Trials by re-using and learning from:

- Bill of material (BOM)
- Recipes
- Methods
- Specifications
- PAT model and data

BOM, Recipe, Methods, Specs, PAT model, PAT data



Good practices, Incidents/Issues, PAT process measures

In addition new research activities can participate from the gathered process know-how of the upscale production by applying good practices, strategies to handle and resolve incidents and by a potential re-use of concrete process measures.

## How will PAT impact MES systems in the future?

Based on the current thinking and status of discussion on PAT it can be expected that the following aspects will gain further relevance:

- The further integration of systems that provide real-time data of the production process into MES for electronic batch recording.
- The further integration of systems that support decision making based on predefined and approved rules into MES for real-time release during electronic batch recording and batch review. This will include additional interfaces to 3rd party tools as well as additional reports and statistics on variances and trends of critical batch data.
- The need to implement more complex control loops and procedures into master batch records in order to implement and maintain process know-how relevant for manufacturing.
- The need to simulate and qualify master batch records before approval of the master batch record.
- The need to model risk based approaches in the master batch record and react on real time events based on their risk classification
- The need to integrate data from previous product development steps (Formulation development and manufacturing for Clinical trials) in order to evaluate and correlate quality data during scale-up, clinical trial and manufacturing.
- Manufacturing process development will be based on the interdisciplinary cross-functional teams of pharmacist /biologist, chemist, process engineers.

## Example - Integrated Electronic Batch Recording Control

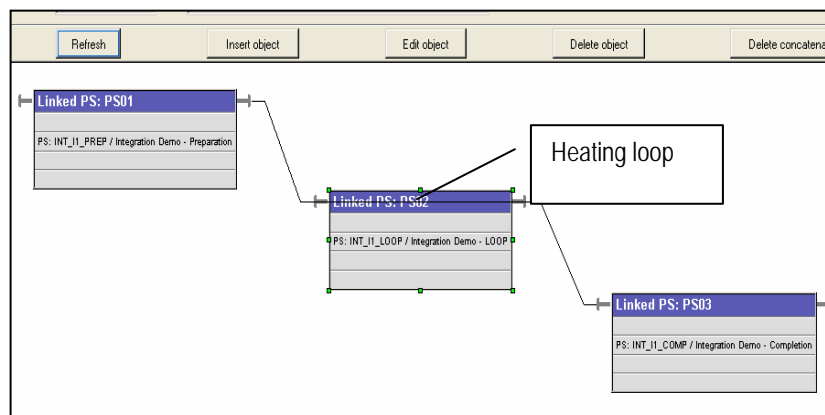
The following example illustrates the integration of Propack Data PMX MES™, RSBatch and RSView in order to support PAT. The example covers the integration of MES and a process control system and covers the following aspects:

1. Implementation of dynamic closed loop control in MBR (Propack Data PMX Recipe MES™). The specification of the control loop must be derived from knowledge gained from previous product development phases
2. Identification of critical parameters to be read in to master batch record (MBR) and execution with real-time data
3. Definition of control of limits and critical control parameters in MBR
4. Execute the master batch record using EBR™ and feed process control system with real time data
5. Execute the manufacturing steps and collect real-time data from process control system
6. Dynamically repeat the manufacturing steps until the control limits are met or end criteria are reached
7. Finally, perform batch record review and electronically approve the produced batch

For the example, it is assumed that the critical control parameters are known already.

The PAT example process is as follows:

1. Define a master batch record in Propack Data PMX Recipe MES™



## 2. Execute EBR™ for electronic batch recording

Activity	
Temperature	<input type="button" value="Get Parameters"/> 49.03 04/01/2005 11:58:57 AM <input type="button" value="Create log"/> <input type="button" value="Force"/>
Continue the process?	<p data-bbox="1312 516 1395 537">OPC-Tag: Heatloop</p> <div data-bbox="1052 562 1382 617" style="border: 1px solid blue; padding: 2px;"><input type="button" value="Read Tag"/> 0 04/01/2005 11:59:19 AM <input type="button" value="Create log"/> <input type="button" value="Force"/></div> <div data-bbox="1024 646 1377 680"><input type="button" value="Reset Loop Tag"/> 04/01/2005 11:59:17 AM <input type="button" value="Create log"/> <input type="button" value="Force"/></div>

3. Steering of RSBatch execution by using EBR™ and monitor batch execution. Real-time process and data presentation using RSVIEW and process control using RSBatch.

4. Verify critical control parameter "Heating Loop" and refine until it is within the allowed limits

**propack data**

**Material 1**      **Material 2**

**Tank 1**

Valve 1      Valve 2

Valve 4      Valve 5

Air      Water

Fill Level  
95 cm

Temperature  
99.85 °C  
50.00 °C

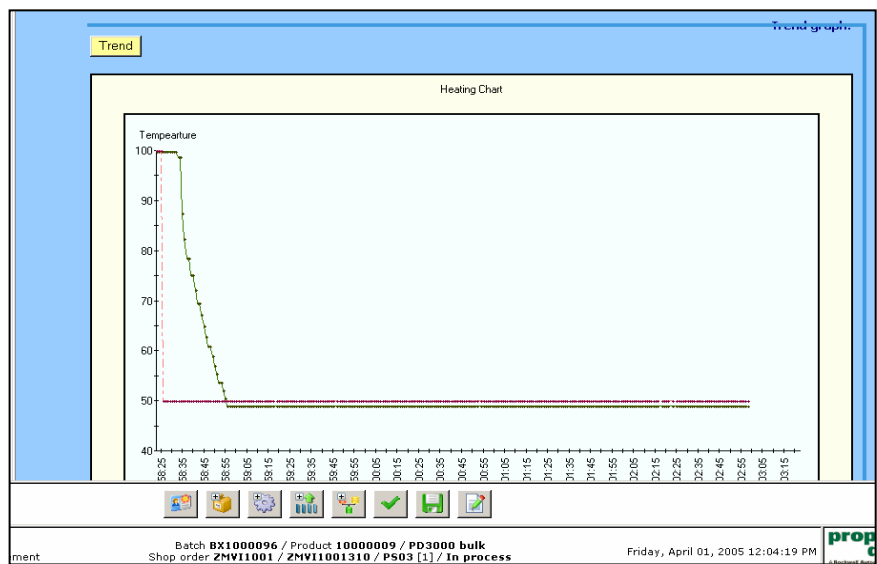
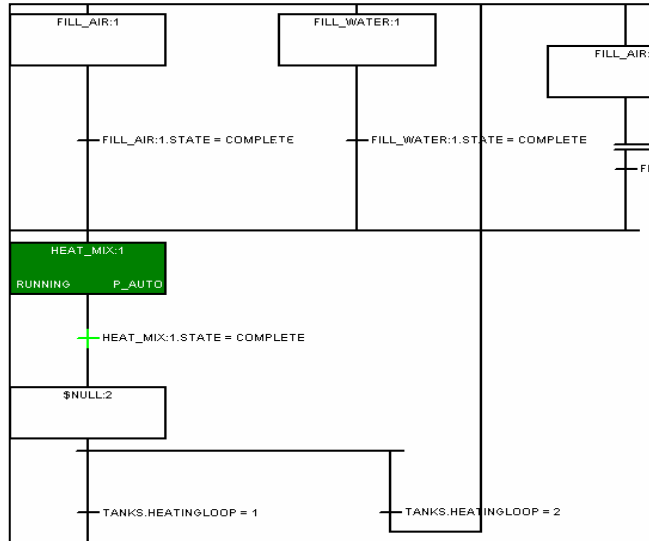
Valve 3      Final

Manual Dump

Heating Loop / Dump

Control Recipe

Batch ID	Recipe	Description	Start Time	Elapsed Time	State	Mode	Failure	Proce
BX1000096	MIX_PRODUCT_LOOP	-PMX	4/1/2005 11:57:16	0:01:04	RUNNING	O_AUTO		TANK



## 5. Create Batch Report

Batch ID
Started on
Finished on
Report generated on

BX1000096
04/01/2005 11:57:12 AM
04/01/2005 12:04:33 PM

- 1. BES Recipe Information
- 2. BES Equipment Information
- 3. Batch Commands
- 4. Recipe Parameters and Prompts
- 5. Report Values
- 6. Mode Commands
- 7. Operator Comments
- 8. Owner Change
- 9. Deviations / Abnormal Handling

### 1. BES Recipe Information

Description	Value	Unit
Version	1.0	
Version Date	3/30/2005 16:27:14	
Author	Administrator	
Product Code	UNDEFINED	
Product Description	UNDEFINED	
Class or Instance	Class	
Recipe Type	UP	
Area Model File Name	\\OPTI-1\BATCHCTL\BATCHPROJECTS\INTERPACKDEMO\INTERPACK.CFG	
Area Model Validated Against	3/31/2005 18:07:48	
Validation Time	4/1/2005 10:09:50	
File Name	\\OPTI-1\BATCHCTL\BATCHPROJECTS\INTERPACKDEMO\RECIPES\MIX_PRODUCT_LOOP.UPC	
Scale	100	%

### 2. BES Equipment Information

0200004  
pddeka-  
w10-37/MES41

MV  
Central training management

Batch BX1000096 / Product 1000009 / PD3000 bulk  
Shop order ZMVI1001 / ZMVI1001310 / PS03 [1] / In pr

## 6. Analyze, review and approve batch report for real-time release.

Shop order ZMVI1001 / batch BX1000096 / PD3000 bulk
🔍 🏆

- ☑️ Signature data 🔍
- ☑️ Order-related bill of materials 🔍
- ☑️ Bill of equipment 🔍
- 📁 Order step(s) (1 found) 📁
  - 📁 ZMVI1001310 / Mixing / BX1000096 🔍 📁 🏆
    - 📁 Predecessor(s) (0 found)
    - 📁 Successor(s) (0 found)
    - ☑️ Signature data 🔍
    - 📁 Log(s) (0 found) 📁
    - 📁 MFC
    - 📁 EFC
    - 📁 Procedure step(s) (7 found) 📁
      - 📁 PS01 [1] / Integration Demo - Preparation 🔍 📁 🏆
      - 📁 PS02 [1] / Integration Demo - LOOP 🔍 📁 🏆
      - 📁 PS02 [2] / Integration Demo - LOOP 🔍 📁 🏆
      - 📁 PS02 [3] / Integration Demo - LOOP 🔍 📁 🏆
      - 📁 PS02 [4] / Integration Demo - LOOP 🔍 📁 🏆
      - 📁 PS03 [1] / Integration Demo - Completion 🔍 📁 🏆
      - 📁 P\_I1\_01 [1] / Mixing I1 🔍 📁
      - 📁 IPC

0200004  
pddeka-  
w10-37/MES41

MV  
Central training management

## Summary

In today's lean manufacturing environment, it's critical for companies of all sizes to focus on optimizing their production processes. By adopting the PAT framework and building-in quality on the front end, pharmaceutical manufacturers can more effectively maximize their production assets and will be better positioned to adapt quickly to market changes. Moreover, since the initiatives have the support of regulatory agencies, a successful PAT initiative can lead to regulatory incentives.

As PAT evolves, additional functions related to PAT principles and standardized interfaces to PAT tools like knowledge management systems and expert systems, and analytical systems will gain further significance for MES systems. More data will be collected online from PAT analytical systems, sensors and process control systems. The knowledge for evaluating this data needs to save in scientific methods, process control and master batch report.

By using the integrated architecture and the complete EPM solutions Rockwell Automation's products and solutions support PAT already today based on an exemplary vertical integration of MES systems and process control system that allows customers:

- Complete Electronic Batch Protocol with Propack Data PMX
- Close loop control in electronic batch recording and evaluation of online result from RSBizWare based process control systems
- Process data collection and process data presentation using RSBizWare
- Infinity QS for statistical process control in order to evaluate real-time data
- Simulation of processes to improve process know by using Arena

Rockwell Automation engineers and consultants help you taking advantage from PAT and improving your productivity and reaching your quality goals. This covers:

- PAT program plan development
- Using process simulation and optimization
- Risk Assessments Process
- Propack Data system implementation and
- PAT integration for electronic batch recording.

## Glossary

The following terminology is often used in this paper.

Term	Definition
CCP	Critical control point
CPMP	Committee for proprietary medicinal products
CPP	Critical process parameter
CTM	Clinical trial management
CVMP	Committee for veterinary medicinal products
EMA	European agency for the evaluation of medicinal products
EPM	Enterprise Production Management
FDA	Food and Drug Administration
MBR	Master batch record
MES	Manufacturing execution system
Multivariate analysis	A specific statistical method to analyse data.
NIR	Near Infrared Reflectance Spectroscopy
PAT	Process Analytical Technology
RDM	Research and Development
PAT Environment	<p>The real world combination of all the components associated with the equipment performing, controlling or monitoring the manufacturing operation:</p> <ul style="list-style-type: none"> <li>• Process Control System</li> <li>• Process Historian</li> <li>• PAT Instruments</li> <li>• PAT Data Analysis Tools</li> <li>• Other pertinent systems</li> </ul> <p>From a systems perspective, the definition includes the identification of the components, their association as a group and the provision of integration with respect to their roles and responsibilities.</p>
PAT Method	<p>The method with which the manufacturing process data is collected for the purposes of monitoring, modeling and ultimately prediction through multivariate models. Predictions can, where required, provide feedback to the appropriate process control system. The PAT method is based on:</p> <ul style="list-style-type: none"> <li>• PAT Instrument Status</li> <li>• PAT Instrument Configuration (i.e. scan rate)</li> <li>• Data Sources (PAT Instruments, Process Sensors, Process Parameters)</li> <li>• Data Format</li> </ul>

Term	Definition
	<ul style="list-style-type: none"> <li>• Analysis (PAT Process Model (see below))</li> <li>• Output Data and Prediction</li> </ul>
PAT Process Model	The model or algorithm used to provide statistical analysis of the data generated by the PAT Method. The model can then be used to provide feedback that is then used, according to the PAT Method, for process control.
Chemo metric Tool	The software applications that support multivariate statistical analysis.
Control Systems	Control of process and discrete manufacturing equipment, ranging from local machine stop/start through to PLC, SCADA and DCS control
Data Acquisition	Gathering of data, both from process measurements (temp, pressure, flow etc) and process analytical instruments (spectral data, key derived variables etc)

## Reference Documents

[1]	<i>Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach</i> (FDA 2002) ( <a href="http://www.fda.gov/oc/guidance/gmp.html">http://www.fda.gov/oc/guidance/gmp.html</a> )
[2]	21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies (FDA, 1987)
[3]	21 CFR Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals, (FDA, 1978)
[4]	21 CFR Part 820, Medical Devices; Current Good Manufacturing Practice, Final Rule; Quality System regulation (FDA, 1996)
[5]	<i>Guidance for Industry – PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance</i> (Pharmaceutical CGMPs, September 2004)
[6]	<i>A New Framework Concept from the FDA for Pharmaceutical Production – PAT will be the Key Concept for Production and Quality Assurance</i> (G.I.T. Laboratory Journal 5/2004)
[7]	<i>PAT Initiative Expected to Invigorate Pharmaceutical Industry with Improved Quality, Better Efficiency and Improved Profits.</i> White Paper – Rockwell Automation
[8]	EMEA home page ( <a href="http://www.emea.eu.int/">http://www.emea.eu.int/</a> )

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