Process Automation Challenges in Generic API Plant

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Rockwell Automation
Process Solutions User Group (PSUG)
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**Introduction - Dr. Reddy’s**

- **Dr. Reddy’s** is a global, vertically integrated pharmaceutical company.
- Producing and delivering safe, innovative, and high quality finished dosage forms, active pharmaceutical ingredients and biological products.

**Pharmaceutical Services and Active Ingredients**
- **Active Pharmaceutical Ingredients**
- Custom Pharmaceutical Services

**Global Generics**
- North America
- EU (UK, Germany, Romania)
- India, Russia, Ukraine/CIS & Venezuela

**Proprietary Products**
- Biologics
- Specialty Pharmaceuticals

- Providing affordable and innovative medicines for healthier lives
Active Pharmaceutical Ingredients (API)

- Dr. Reddy’s began API operations in 1984 and started with a single drug
- Our Global API business offers over 100 molecules
- Sales in over 85 countries
- 8 USFDA approved facilities; serving 300+ SKUs across the globe
- Unmatched scale-up facilities
- Strong product lifecycle management
- Cost and technology leadership
Introduction - Pandian

- Part of Central Engineering at Dr. Reddy’s API business
- Mechanical Engineer, Six Sigma Black Belt, Certified Energy Auditor
- 25 years of association with companies like,
  - Pfizer
  - Hoechst India (now Sanofi Aventis)
  - Gharda Chemicals
- Instrumental and involved in couple of Automation Projects in GMP environment
Agenda

- Continuous Improvement and Conclusion
- FAT and Qualifications
- Rockwell and our SEZ
- Automation Rollout plan
- URS and the complications
- CPP AND CQA
- API (Active Pharmaceutical Ingredients) background
Pharma Background

- Global market is around US $ 800 billion and growing at 7%
- Plants are completely manual by tradition
- Focused on quality products
- Only capable processes are allowed to produce products
- Regulatory sword Hanging and fear of failure
- Huge amount of Sampling and record keeping
- Competition and price erosion challenges needs changes within the framework
- Legacy issues & Human errors
- Recording problems and Assignable causes in CAPA
- Labor intensive Review mechanism
Control approach

- Safety and environmental requirement
- Quality requirement
- Operational requirement
- Risk to the patient
Monitor and Control

CPP

- Temperature
- Pressure
- Volume addition
  - Level
  - Weight
  - Flow

CQA
CQA ???

- Density of batch
- Color
- Particle size distribution
- Bulk density
- Form
- pH, Conductivity
- Yield
### API CPP

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Crystallization</th>
<th>Distillation</th>
<th>Filtration</th>
<th>Drying</th>
<th>Milling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactants Quantity</td>
<td>Slurry Thickness</td>
<td>Distillation volume</td>
<td>Slurry feed rate</td>
<td>Drying time</td>
<td>Mill speed</td>
</tr>
<tr>
<td>Catalyst Quantity</td>
<td>Addition rate of solvent</td>
<td>Agitation Speed</td>
<td>Speed of centrifuging</td>
<td>Bed Temperature</td>
<td>feed rate</td>
</tr>
<tr>
<td>Carbon Quantity</td>
<td>Granulation Temperature</td>
<td>Pressure</td>
<td>Wash Solvent Quantity</td>
<td>Heating rate</td>
<td>Mill temperature</td>
</tr>
<tr>
<td>Water Quantity</td>
<td>Cooling Ramps</td>
<td>Distillation Temperature</td>
<td>Filtration time</td>
<td>Cooling rate</td>
<td>Screen size</td>
</tr>
<tr>
<td>Addition Rates</td>
<td>Speed of Agitation</td>
<td>Aging Time</td>
<td>Cycles of Filtration</td>
<td>Dryer Speed</td>
<td>Air pressure</td>
</tr>
<tr>
<td>Addition Temperature</td>
<td>Residential time</td>
<td>Final Concentration</td>
<td>Assay</td>
<td>Drying Pressure</td>
<td>Air temperature</td>
</tr>
<tr>
<td>Batch Temperature</td>
<td></td>
<td>Cooling Media Temperature</td>
<td>pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td></td>
<td>Cooling Media Flow</td>
<td>Particle Size Distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactor Pressure</td>
<td></td>
<td></td>
<td>Impurity Profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation Speed</td>
<td></td>
<td></td>
<td>Bulk Density</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Color</td>
<td></td>
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</tbody>
</table>

Independent or Interaction??
Complexity

Many stages

Many unit Procedures

Many critical procedures

Many phases
Problems

• Man is not a good copying machine

• Can not reproduce same results on repeating the same job
  – Controlling temperature – Maintain
  – flow rate - Additions
  – heating cooling rate - Ramps
  – Time management – Multiple activity

• What is observed not recorded at the same time

• Identifying Root cause of Failure

• Deviation Management

• Productivity and Profitability
The process is considered stable if the variations are less and the data spread is centered.
Sources of Variability

Inputs to the process control variability of the output

\[ y = f(x) \]

Variability - source of the big risks to the product
Process Capability

- How to get there???

- Current issues
  - Addition of solvents
  - Cooling rate
  - Heating rate
  - Maintaining temperature of batch
  - Distillation
  - Phase separation
  - Drying
  - Micronizing
What makes a process stable?

- Less variations in raw Material
- Less variations in reaction Methods
- Less variations in Environments / Utility supplies
- Less variations in Measurements
- Less variations in Testing at Laboratories

OR

- Process is flexible to take care of these variations
- A stable process can not be disturbed by small variations from
  - Raw materials
  - Process
  - Equipment
  - Personnel
Automation Why??

1. Real time recording
2. Effortless trending
3. No subjectivity
4. Reproducibility
5. Easy deviation management
6. Online correction without HI
7. Easy to validate
8. Continuity of service
9. Scalability
10. Special cause identification
Automation - How?

• Moving from Manual plant to High level of Process Automation
• To have Equipment control and Process control as well
• 21 CFR Part 11 compliance
• To track the material movement as it enters the warehouse
• Track and Trace the material usage and status
• To keep a tap of Cycle time
Dr. Reddy's Laboratories

Process Automation with eBPR

Concept Note

Manish Kumar Singh
8/26/2010
Automation Roll Out Plan

Level 4 (ERP)
Resource Planning
- IT ERP system
- Documentum
- Quality System

Level 3 (MES)
Work Flow Management
- Enterprise Historian
- Alarm & Event Mgmt.
- Configuration Management
- Work Flow Management

Level 2 (DCS)
Supervisory Control
- Batch Management
- Application Interface
- Operator Interface
- Simulation / Training
- Backup Utility

Level 1
Process Control
- Controllers
- Controllers
- Controllers
- Controllers

Level 0
Process Equipments
- Phase-1
- Phase-2
- Phase-3

Devices – Foundation FieldBus, Profibus-DP & Direct wire & related protocols

Plant Network
Control Network
Device Network
OPC
Level 1 & 2

- Stand alone equipment
  - Water systems
  - Centrifuges
  - ANFDs
  - Refrigeration

- Systems
  - BMS
  - Solvent Transfer
  - Equipment controls
  - Process Automation
  - WWTP

Allen Bradley
Siemens
Mitsubishi
Emerson
E+H
Metler Toledo

Rockwell Automation
Emerson
Siemens
Level 3

• The Process Control and eBPR system must include the capability for ISA95 level 3 capabilities including:
  – Material Management (RSDTC)
  – Workflow (W,QA,QC,MFG, AUDITS)
  – Equipment Management (Status, Occupancy, History, Validation)
  – Personnel qualification, Resource management
  – Quality Management (RS Limits, Test Results, Decision Taking, BPR reviews, Deviation Management, Quality Assured)
Level 4

- SAP
  - Master recipe
  - BOM and approvals
  - Manufacturing Orders
  - Milestone controlling
  - Costing
  - Financial controlling
What we learned

• POC
  – Work flow management
  – Integration Issues in Level 2 & 3
  – eBPR writing and validating
  – Life cycle management of Project
  – What not to do
    • Choosing incorrect system and technology
    • Partnering with new vendors for implementation
    • Assume the capabilities and priorities
    • Assume the requirements
Rockwell for our SEZ

- Survey of Market on DCS, MES and SAP integration
- FTPharmaSuite was really good and have all the features required for Pharma Dispensing and QA
- Above important features were demonstrated through an integrated PlantPAx - FTPharmaSuite demo.
- Less customization required
- Implementation Experience in India – Rockwell scored less but we had considered the Rockwell promise on that
- Rockwell suggested FF technology
E+H Instrumentation, PlantPAx, FTPharmasuite with SAP integration
End to end integration from field to top - Integrated Architecture
Highlights on SEZ Architecture

- FF enabled Field Instrumentation from E+H for premier integration.
- Five sets of Redundant PlantPAx controllers.
- Redundant 3 Nos. HMI Servers, FTHistorian server, FTVantagepoint server, 24 Operator Workstation in safe and hazardous area.
- FT batch for batch management
- MES Factorytalk Pharmasuite and its components.
- Remote IOs suitable for hazardous area (Zone 1, Group IIA IIB) are installed and connected to controllers on Profibus-DP.
- Hence Digital signals are on Profibus and all Analog signals are on Foundation Field bus.
- All Third party stand alone PLCs are connected to Controllers on serial Modbus.
- Also have provision of OPC connectivity for connecting the Lab instruments on OPC. (this is for future integration)
- Also the System is capable of having a wireless node for connecting transmitter on wireless Hart protocol.
- MES is integrated to SAP on IDOC, as DRL SAP integration team had experience on this, and challenges' were known.
SAP Interface

<table>
<thead>
<tr>
<th>Inbound Object</th>
<th>MDI Map</th>
<th>Java Transfer Object</th>
<th>IDOC XML</th>
</tr>
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<tbody>
<tr>
<td>Inbound JMS Queue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outbound JMS Queue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP Response JMS Queue</td>
<td></td>
<td></td>
<td></td>
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<td>ActiveMQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factory Talk PharmaSuite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inbound Activity</td>
<td>Shop Operations Server</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outbound Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production Database</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Implementation Methodology

Detailed process flow /auto execution of process steps as defined in BPR

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Activity</th>
<th>Physical Location in the plant</th>
<th>Department</th>
<th>Software (MES/DCS/SAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recipe preparation/modification for a particular batch using predefined operations (As per manual approved BPR)</td>
<td>CONTROL ROOM</td>
<td>IPDO/ MFG</td>
<td>MES-DCS</td>
</tr>
<tr>
<td>2</td>
<td>Recipe approval and release for a particular batch. Modification and re-approval /Version control. And handling recipes for multiple batches</td>
<td>CONTROL ROOM /QA</td>
<td>QA</td>
<td>MES</td>
</tr>
<tr>
<td>3</td>
<td>BOM Generation and release, approval, update in SAP</td>
<td>CONTROL ROOM /QA</td>
<td>auto generation of BOM, QA to Approve</td>
<td>MES-SAP</td>
</tr>
<tr>
<td>4</td>
<td>Receipt of Process orders and release, Batch number allocation from SAP</td>
<td>MFG &amp; W / H</td>
<td>MFG &amp; W / H</td>
<td>SAP-MES</td>
</tr>
<tr>
<td>5</td>
<td>Dispensing of Solvents, bulk tanks to Day tanks and drum solvents, Updation in SAP</td>
<td>W/ H &amp; TANKFARM</td>
<td>W / H</td>
<td>MES-SAP-DCS</td>
</tr>
<tr>
<td>6</td>
<td>Dispensing of Solids and other consumables</td>
<td>W / H</td>
<td>W / H</td>
<td>MES-SAP</td>
</tr>
<tr>
<td>7</td>
<td>Label/Barcode printing only afterDispensing</td>
<td>W / H</td>
<td>W / H</td>
<td>MES</td>
</tr>
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<tr>
<td>8</td>
<td><strong>Automatic-Execution of Master recipe/BPR</strong></td>
<td>PRODUCTION</td>
<td>MFG</td>
<td>MES-DCS</td>
</tr>
<tr>
<td>8.1</td>
<td>Execute Respective Unit procedure as specified in the recipe for all the equipments</td>
<td>MFG / UTILITIES /TANKFARM</td>
<td>AUTO EXECUTION</td>
<td>DCS</td>
</tr>
<tr>
<td>8.2</td>
<td>Auto execution of each Operation/Phase (As per S88 standards). And acknowledging operator prompts with proper E-signatures, wherever applicable</td>
<td>PRODUCTION</td>
<td>MFG</td>
<td>DCS</td>
</tr>
<tr>
<td>8.3</td>
<td>Inprocess sampling, barcoding and testing</td>
<td>PRODUCTION / QC</td>
<td>MFG / QC</td>
<td>MES-DCS</td>
</tr>
<tr>
<td>8.4</td>
<td>Auto Holding &amp; restarting and aborting</td>
<td>PRODUCTION</td>
<td>AUTO EXECUTION</td>
<td>DCS</td>
</tr>
<tr>
<td>8.6</td>
<td>feasibility to start a operation that is not specified in the recipe using manual hold and record unplanned deviation</td>
<td>PRODUCTION /QA</td>
<td>OPERATOR</td>
<td>DCS-MES</td>
</tr>
<tr>
<td>A</td>
<td>Activity</td>
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<tr>
<td>----</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>8.9</td>
<td>Alarms and handling of alarms and deviation recording</td>
<td>MFG</td>
<td>AUTO EXECUTION</td>
<td>DCS</td>
</tr>
<tr>
<td>8.10</td>
<td>Barcode printing and reading during sampling and charging</td>
<td>MFG / QC</td>
<td>MFG / QC</td>
<td>DCS-MES</td>
</tr>
<tr>
<td>8.11</td>
<td>Feasibility of running the entire batch using only Equipment modules</td>
<td>MFG</td>
<td>MFG</td>
<td>DCS</td>
</tr>
<tr>
<td></td>
<td>(semi-auto, worst case scenario)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>trends/control charts etc for critical process parameters during/after</td>
<td>MFG / QA</td>
<td>AUTO EXECUTION /QA</td>
<td>DCS</td>
</tr>
<tr>
<td></td>
<td>the execution of Recipe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Executed eBPR review and approval</td>
<td>MFG / QA</td>
<td>MFG / QA</td>
<td>MES</td>
</tr>
<tr>
<td>11</td>
<td>Printing of final/executed eBPR, trends etc</td>
<td>MFG / QA</td>
<td>MFG / QA</td>
<td>MES</td>
</tr>
</tbody>
</table>
URS and FRS

- Multi product complication
- Perception of users about their own requirement
- Perception of Process Engineers about their Process – design space
- Perception of control Engineers about their System
- URS and FRS made with perceptions

It’s a living document, hence lot many changes as we go on
Vendor and his understanding

- P&IDs are given for I/O counts and positioning of Field Instruments
- Layouts are given for cable scheduling
- Work flow, Recipes and Ranges are given for Programming
- GMP requirements are given
- Safety requirements are given
- Operational requirements and sequence are given
- What is not given is
  - What is done when things go wrong – nothing like this in BPR
  - What the operator does apart from SOP
Perception Vs Reality

- Gap in understanding the process requirement by a control Engineer
- Gap in understanding instrumentation capabilities by a manufacturing personnel
- Gap in understanding the Automation structures by manufacturing personnel
- There is no successful mediator who makes it “Right the First Time”
• Team is new
• First time understanding the process flow on the screen
• Imaginations and visualizations are at work
• Office and site conditions are different
• The team is not completely satisfied
• Every one assumes that they know better
• Generally concludes with a huge punch list
Installation

- Easy and no issues
- Qualification of Installation goes the protocol way
• Impact on Process from Control action is not always understood!!
• They simulate and test
• Water trial is not clear to them
• Feed back from instruments is missed in some cases
• Instruments behave differently with water and differently with batch
• Handling software bugs during OQ is major challenge
• OQ of system along with mechanical completion is a challenge
• Disturbance from other agencies
• Speed to market put lot of pressure
GAPs

- The gap widen if the product comes from design space to manufacturing space
- There is manageable gap if the product is already being manufactured
- There are still rooms for process improvement within the framework
- This is why yield variations
- All processes are capable but not necessarily stable
- One trial batch and the traditional 3 validation batches not sufficient for stabilizing
Actual Issues

• Field
  – Difference in the measurement of Flow and level
  – Calibrated Instruments
  – Controlled addition
  – Consistency in the cooling
  – Feedback not known
  – Design issues are not understood

• System
  – It capture every thing ( more deviations and documentation )
  – OQ tests
  – Water trials, delays, tuning issues
  – PQ wants the ( trials / validation ) overall system to produce the API
  – Trials and validation poses lot many challenges and deviations
Controls

• Process control
  – Device control
  – Equipment module control
  – Phase control
  – Recipe control

• Combination of manual and automation in API Plants
  – Charging of solids
  – Transfer to next equipment
  – Sampling
  – End point detection

• Combination of Recipe driven phases and human work instructions
Continuous Improvement

• Brings changes in the development

• Recipes are added / modified (CCF)

• Project to Project moving ahead on technology
  – Intelligent Field instruments
  – Better diagnostic capabilities
  – Flexibilities
CONCLUSION

• Focus on what I do not know about the other side
  – Process behavior, Regulatory, Automation capabilities

• Once we know what we do not know about the other side
  – The difficulties start decreasing
  – Gaps start shrinking
  – OQ becomes easy
  – PQ with less deviations
  – Customer satisfaction and moving ahead