Leveraging automation in Pharmaceutical operations for continuous improvement

GANADHISH KAMAT
Global head of Quality, Dr. Reddy’s Limited
Challenges faced by Pharma industry

- Pricing pressure due to government initiatives & consolidation of buyers in US
- Large number of approvals on day 1
- High cost of development, high investments & long gestation period for complex generics
- Increased regulatory expectations & scrutiny
- Increasing operating cost (including manpower cost)
How do we overcome the challenges

Continuous improvement
- First time right (Development / manufacturing)
  - Reducing failures / defect rates
  - Reducing COPQ / COPE
- Cost competitiveness
  - Doing more with less resources

One of the important enabler
- Adoption of new age technologies
Digital transformation around us

Success stories
- Google
- Amazon
- Uber
- Oyo

Missed opportunities
- Kodak
- Swiss watches
- Blockbuster
- Xerox

Akili Interactive has filed for FDA approval of their video game for the treatment of ADHD and have many more treatments in the pipeline.
Automation and digitization in Pharmaceutical operations
Automation / Digitization landscape in Pharmaceuticals

**ERP** – Operational Transactions

**DMS** – Document Controlled Distribution

**MES** – Weigh & Dispense AND eBPR

**WMS** – Bin Management & Container Management

**LIMS & CDS** Quality Control

**LMS** – Learning Management

**L2/ DAS**

Engineering Systems – Recipe Based Equipment/ Control Syst.

**QMS**

**Mobility/ Digital**

**ANALYTICS**

**WMS** – Bin Management & Container Management

**LIMS & CDS** Quality Control

**LMS** – Learning Management

**ERPA** – Operational Transactions
Benefits - Eliminate muscle work, Fully automated and integrated systems, Improved safety, efficiency and compliance
Process Automation & digitization

Digitization of Maintenance

- **Preventive Maintenance App**
  - Overall Efficiency - No paper based work
  - Almost real-time updating leads to increased compliance
  - Authenticity - better equipment handover through mobile sign-off
  - Ease of order management
  - Online record management for decisions

- **Mobile Label - Printing**
  - Mobile label printing directly from the app makes the activity robust and clean

- **Calibration Maintenance App**
  - Eliminate duplication, inefficiencies and errors that come with paper management.

- **QR Code Enablement**
  - QR code enablement on equipment will allow for evidence of an engineer actually performing the maintenance activity.

- **Breakdown & Facility Maintenance**
IT Enabled Functionalities in Utilities:
SCADA & DAS

Benefits
Digitization of Log Books
Improved Data Integrity & compliance
Effective tracking on Utilities Consumption
Uninterrupted Power cycles,
Electrical Loads - Control & Distribution
Enhanced Visibility on energy consumption
Product Traceability through Serialization

**Functionalities**
- Serialization - Data Generation & online Printing
- Online inspection – OCR & OCV
- 360 Inspection, Bulk Scanning
- 1D & 2D codes Handling
- Aggregation - Data marriage – bottle to shipper to pallet
- Parent Child Relationship
- Data commissioning & Batch Reporting
- Finished Goods online Report
- Data Posting - Cloud Data

**Benefits**: Supply chain traceability, elimination of counterfeiting
Laboratory Operations and Quality management
LIMS, CDS & Others

- **Chromatographic Data**
  - Empower
    - Collects data from HPLC / UPLC / GC.
    - Data processing and results calculation through software.

- **Specification**
  - Master Data Creation for each product & specification

- **Execution**
  - Sampling (Auto algorithm)
  - Sample Allotment
  - Sample Execution
  - Instrument Interface
  - Resources usage
  - Usage of calibrated instruments
  - Electronic review & Approval

- **Compliance**
  - Usage Decision & Stock posting
  - Stability
  - Process Validation

- **SAP**
  - Inspection Lot creation

- **LIMS**
  - E Raw Data
  - Standalone Instrument reports
  - CDS Reports

- **CDS – Empower**
  - Methods (for acquisition & processing)
  - Test results calculation electronically in CDS
  - Electronic Review & Sign-off

- **Lab**
  - Laboratory Instruments (Port Based)
  - Laboratory Instruments (Standalone)

- **Data output**
  - Data output
  - Reports

- **HPLC**
  - GC

- **Balance**
  - pH meter

- **Certificate of Analysis**
Benefits realization
LIMS (Reduction of incidents)

LIMS Eliminated
- Calculation errors
- Use of non-calibrated instrument
- Stock entry missing
- User not qualified
- Transcription errors
Electronic Lab Note Book

Authorized team which has access to the project

Subset of team which has access to notebook

Notebook_1 (Stage-A)

Notebook_2 (Stage-B)

Notebook_n (Stage-xyz)

Set of R&D experiments

Set of AR&D experiments

Electronic sample submission workflow for analysis followed by result posting in ELNB

Analyze, review and post results

Physical sample

Statistical Analysis tools

Auto compilation of results for all experiments

Visual exploratory data analysis

Benefits: Automated calculations, Enhanced data security, Storage space reduction, Interface with other systems, Ease of data retrieval, Improved compliance
Quality Management System

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Discontinuation

GMP

Management Reviews

- KPIs and Targets – Review through Dashboards
- Investigations (Incident, OOS, OOT, Market Complaint)

Quality System Elements

- Vendor Management
- Product Quality Monitoring
- Corrective Action / Preventive Action (CAPA)
- Change Management
- Quality Risk Management & Self Inspection

Enablers

- Knowledge / Training Management
- Documentation (Procedures, Master Documents, Reports)

- Process Digitized
- Process Digitized, Digital Lean
- Initiated / In Progress
Document Management System

**Creation**
- Author logs into DMS, selects document type & creates document
  
**Review**
- Concurrent collaborative review
  
**Approval**
- Author, reviewer approves, electronic signature
  
**Distribution Control, Storage & Archival (fully automated)**

**Training**
- LMS
  
- Easy search and retrieve – keywords and full content
- Controlled access and distribution – Watermarking
- Latest copies of SOPs
- Read and understood

**Features**
- + Automated workflow – Any bottlenecks visible
- + Notification to remind on related document changes
- + Right template made available
- + All comments visible and easy to collate
- + E signatures for approvers
- + E sign signatures for approvers
- + Controlled access and distribution – Watermarking
- + Auto retraction of older version
- + Right version available for training
- + Easy search and retrieve – keywords and full content
- + All comments visible and easy to collate
- + E signatures for approvers
- + Controlled access and distribution – Watermarking
- + Auto retraction of older version
- + Right version available for training

**Additional Benefits**
- + Automatic version control and audit trail
- + Revisions and periodic updates
- + Automation of doc collection and distribution saves 1000s of man months/yr
- + Easy search and retrieve – keywords and full content
- + All comments visible and easy to collate
- + E signatures for approvers
- + Controlled access and distribution – Watermarking
- + Auto retraction of older version
- + Right version available for training
- + Easy search and retrieve – keywords and full content
- + All comments visible and easy to collate
- + E signatures for approvers
- + Controlled access and distribution – Watermarking
- + Auto retraction of older version
- + Right version available for training

**Additional Features**
- + Automatic version control and audit trail
- + Revisions and periodic updates
- + Automation of doc collection and distribution saves 1000s of man months/yr

**Watermarking**
- + Auto retraction of older version
- + Right version available for training

**Automation of Doc Collection and Distribution**
- + Automation of doc collection and distribution saves 1000s of man months/yr
DMS Key Benefits

**Audit Readiness & Data Integrity**
- > 25 process interlocks for compliance
- Audit preparation time reduced by >60% to 1-2 days
- No more document movement or misplacement
- Change control mandatory for all doc changes
- Templates, numbering, work flows, signatures auto enforced
- Traceability of prints; recall; reconciliation
- Easy search and retrieval of documents
- Easy identification of all related documents
- Availability of soft copies ensures Audit prep does not deprive information for other activities

**Productivity/ Cost Improvement**
- QA - 400 man months (40% of DCQA resources)
- RA -250 man months;
- End users – 1150 man months
- “INR 9 Cr/year in manpower savings
- 60 lakh sheets of paper/year reduced => ~ INR 2 Cr
- 1800 man months (150 FTE) saved/year
- No more printing, stamping, filing of documents
- Eliminate manual movement of a paper doc for review and approval
- Reduce constraints on prints and reprints; manage w/ better governance
- Recall and reconciliation made easy
- Easily find docs with full content search

**User Experience**
- Over 2.5 lakh Emails eliminated
- Single dashboard for all pending document tasks
- Compliance built in. Fewer decisions to make
- Harmonised processes across all units. Easy to follow and assure

**Visibility for decision support**
- Bottlenecks in workflows visible and actionable
- Interconnectedness of documents – simplification made possible
- Insights into cycle time and quality of work
Analytics for simplification and continuous improvement
How to put the data to use

• KPI Dashboards
  • Turn Around Time Analysis
  • Pending Samples Analysis
  • OOS Analysis
  • Incident Analysis
  • Change Control Analysis
  • Product scorecard & CQA analytics
  • Stability alerts

• Support in investigation (Root cause predictor)

• PAT

• Process improvements

• Continuous Process Verification

• APQRs
Problem statement

Low dissolution in one batch of ER product.

Multivariate analysis (using partial least square regression) showed two lots were different compared to good lots.

The individual plots were within the control limits.

The contribution plot of the difference between bad and good lots in terms of standard deviation indicated bad lots were run at low AH and RH in comparison to good lots.
PAT for process improvement & parametric release

Unique peak identification – S. Golay + 2nd derivative

Outcome: Reduction of process time & Deletion of blend analysis
Golden Tunnel based process monitoring

**Building PLS Model**
- Identify Batches with desired CQA
- Build “Golden tunnel” of process parameters based on these “good” batches data.
- Build Machine learning models to arrive at principal components that explain the behavior of process

**Online Monitoring**
- Create Score Plot - 1 Principal component that combines effects & interactions on all Process Parameters.
- Alerts when current production parameters deviate from “golden batch” conditions.

**Contribution Plots**
- Highlight contribution of individual process parameters
- Identify corrective actions in real time.
Use of Machine Learning based approach

**Understand Process Flow**
- Understand Process Flow and identify Process parameters to be analysed
- Random Forest and Lasso Regression etc. models are used to identify the important parameters.

**Decision Trees**
- Create Decision Trees to identify the set of “golden batch” parameters needed for target yield.

**Deploy Model**
- Deploy model in commercial manufacturing and categorize effects based on obtained actual yield.
Prescriptive model to Optimize machine setup

Faster Setup & Reduced Scrap to improve Op. Efficiency

**Identify Correlations**
- Through data models, study the data and detect Inputs that have a strong correlation with outputs.

**Run Simulations**
- Operator to run simulations by keying in Batch to be compressed.
- System retrieves necessary specifications, compares with operator selected Inputs.

**Throw Predictions**
- Help the operator with prediction of CQA values that the machine will produce if the selected batch is run with simulated CPPs.
Focus on Core Operating Process

**Integrated Planner & Scheduler**

- **Integrated Planning**
  - Digital Value Stream Map
  - Flow Optimization (Ageing)
  - Capacity Planning Optimizer, Planner for Equipment & Manpower including QC Lab Scheduling.

- **Proactive Decision Making**
  - Scheduling model automatically generates optimized schedule
  - Web app for manual adjustments and building scenarios

- **Digital Performance Management**
  - Leverage big data to create real-time transparency of performance.
  - Live tracking of test completion on performance board
Challenges of Automation

• Cost
  • License cost, Hardware, Implementation, Computer system validation, AMC,
  • Escalations
  • Upgrades

• Data migration

• Increased Regulatory scrutiny
  • Design (security, integrity, access controls, privileges)
  • Computer system validation
  • Data storage (backups, retrieval, control, audit trails)

• Change management

• Training of people
  • Operators & Supervisors
Thank you