



Big Data Management Strategy for Continuous Pharmaceutical Manufacturing

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Outline

- Rutgers, C-SOPS, Continuous Manufacturing
- What is Continuous Pharmaceutical Manufacturing?
- Big Data Management Strategy for Continuous Pharmaceutical Manufacturing
 - Lab
 - Plant

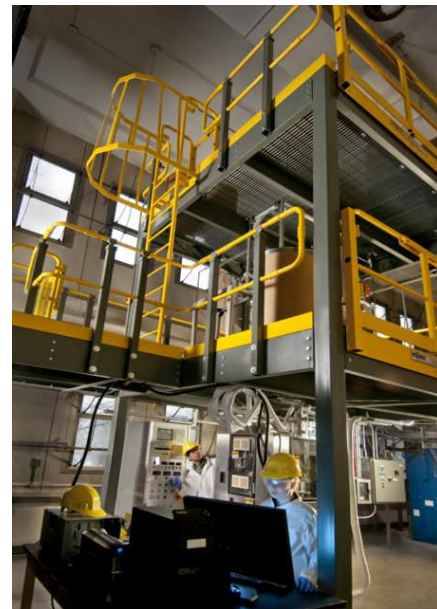
C-SOPS



C-SOPS is the sandbox where academia, industry, and regulators meet (virtually) to develop and refine the next generation of advanced pharmaceutical manufacturing

Highlights:

- Founded in 2006 as NSF ERC-SOPS – Rutgers, Purdue, NJIT, U of PR
- Aided in the development of the continuous version of Janssen's Prezista, first batch to CM conversion
- Funded by FDA to explore CM process/materials; I4.0, Bio modeling
- Working with numerous equipment vendors on characterization, integration, and development.

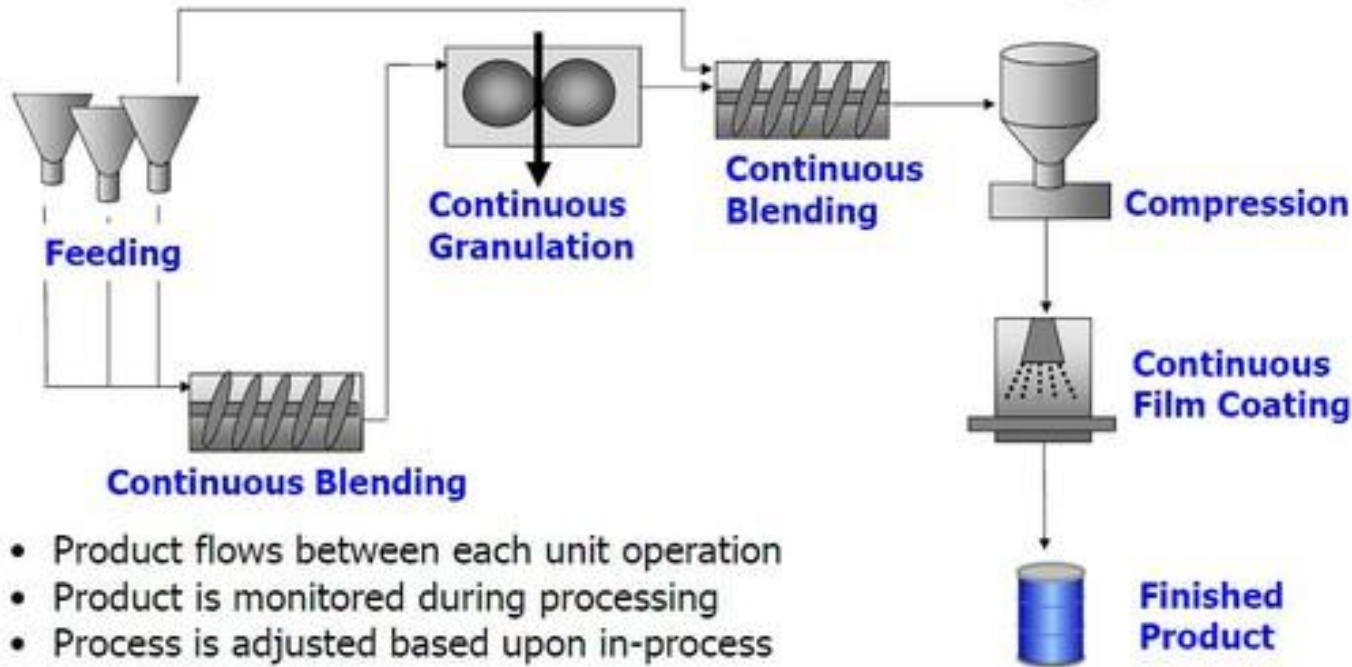


Current MFG in Pharma (Batch)



Figure courtesy of the FDA

New MFG in Pharma (Continuous)



- Product flows between each unit operation
- Product is monitored during processing
- Process is adjusted based upon in-process measurements
- Actual processing time = minutes to hours

Figure courtesy of the FDA

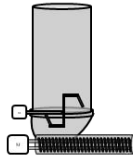
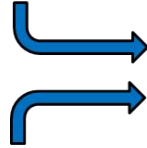
C-SOPS Approach

Solid Dose Advanced Pharmaceutical Manufacturing



Material Properties

e.g., Flow, Bulk Density,
Angle of Repose



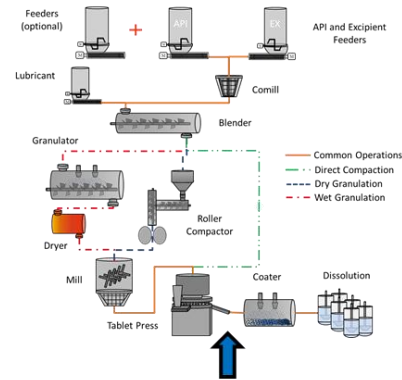
$$y = f(x, a, t, m, n)$$

$$\frac{dy}{dt} = g(x, a, t, m, n)$$

Unit Ops Models

e.g., Feeders

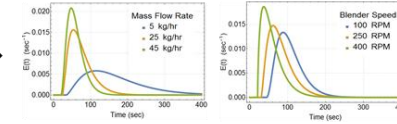
Integrated Process Model "Flowsheets"



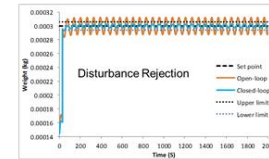
Experimental & Design Parameters



Predictive Modeling



Control Design



Demonstration/Tech Transfer



CM Solid Dose Adoption Landscape

Regulatory

- FDA actively promoting it (advanced controls and enhanced process understanding required), strong proponent, draft guidance document
- EMA voice has changed from *open to CM* to *encouraging CM*; ETT mindset “big pharma isn’t coming early enough to talk”
- PMDA is starting to provide recommendations (nearly verbatim of C-SOPS Best Practices Document); EMA similar too
- A growing list of regulatory bodies have been exposed to CM and approved processes, including in key markets like Brazil
- ***ICH has decided to take up CM as a 2019 topic!***

CM Solid Dose Adoption Landscape

Branded Pharma

- 2 Vertex, 2 J&J/Janssen, 1 Eli Lilly and 1 Pfizer product(s) already approved in U.S. and other markets
- Above 4 companies have additional products in CM development
- GSK, MSD, Shire/Takeda will all file their first submissions (various markets) within the next few months
- Celgene, Merck KGaA, transitioning from R&D to commercial; working on trials/development with CMOs
- AZ has purchased a commercial GEA system
- BMS revisiting CM using inhouse DC line for development while partnering with a CMO

CM Solid Dose Adoption Landscape

CMOs

- Patheon and Hovione are both now offering solid dose CM contract services

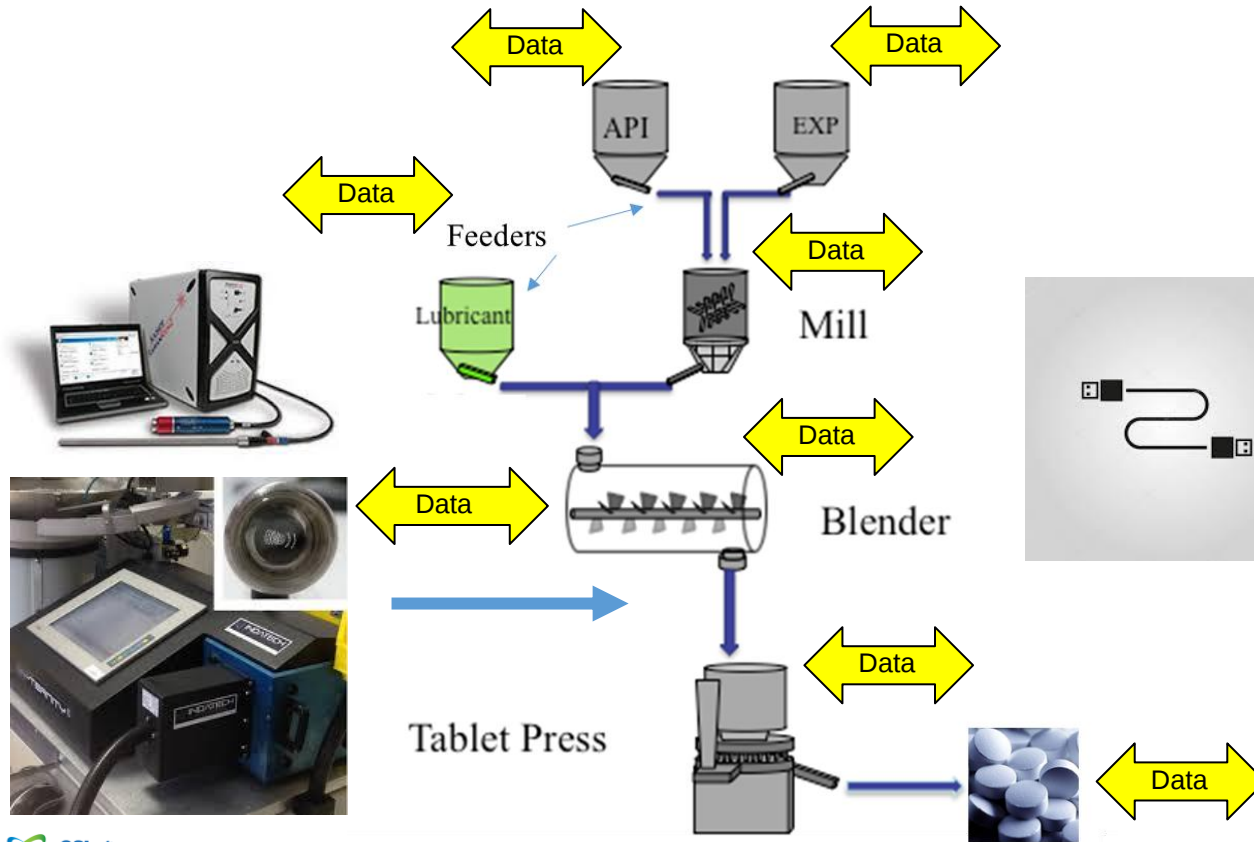
Generics

- Major generic players such as Dr. Reddy's beginning to purchase integrated lines
- In at least one instance pursuing end-to-end CM with integrated drugs substance manufacturing

Vendors

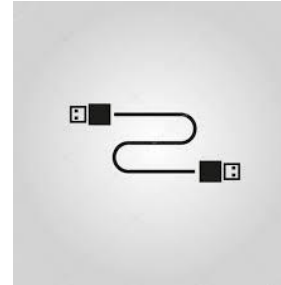
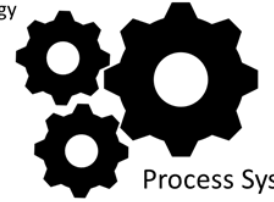
- 5 vendors now offer an integrated solution: GEA, Glatt, Bohle, Powrex, Bosch

Rutgers Direct Compression (DC) CM Line

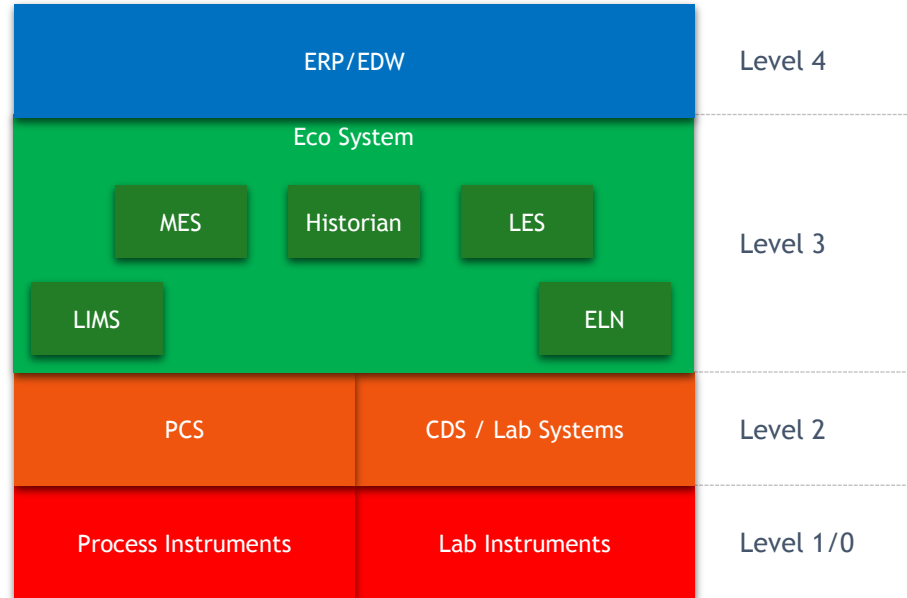


Material Handling
Particle Technology

Process
Analyzers
In-line, At-line &
Offline



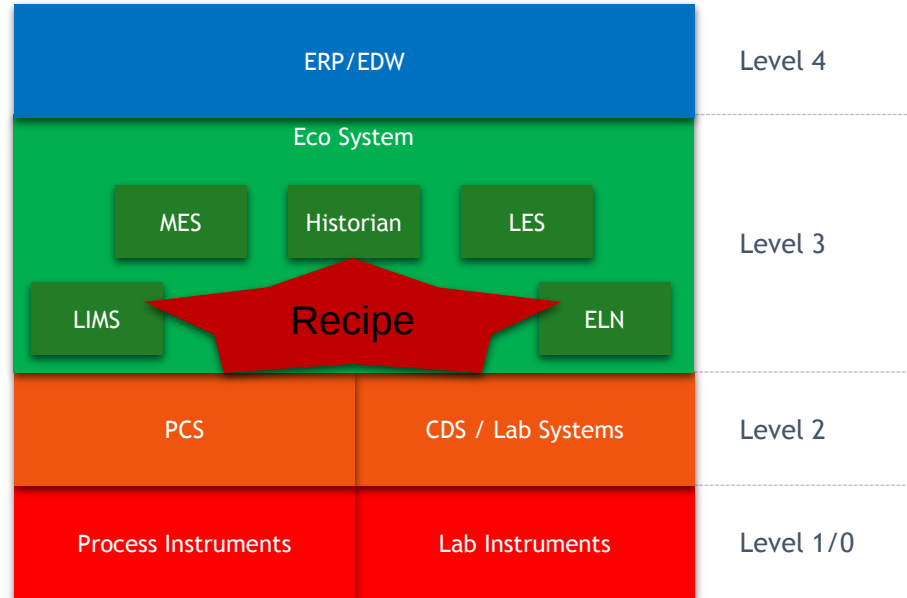
S95 Overall Architecture



CDS: Chromatography Data Software
ELN: Electronic Laboratory Notebook
ERP: Enterprise Resource Planning
LES: Laboratory Execution System

LIMS: Laboratory Information Management System
MES: Manufacturing Execution System
PCS: Process Control System

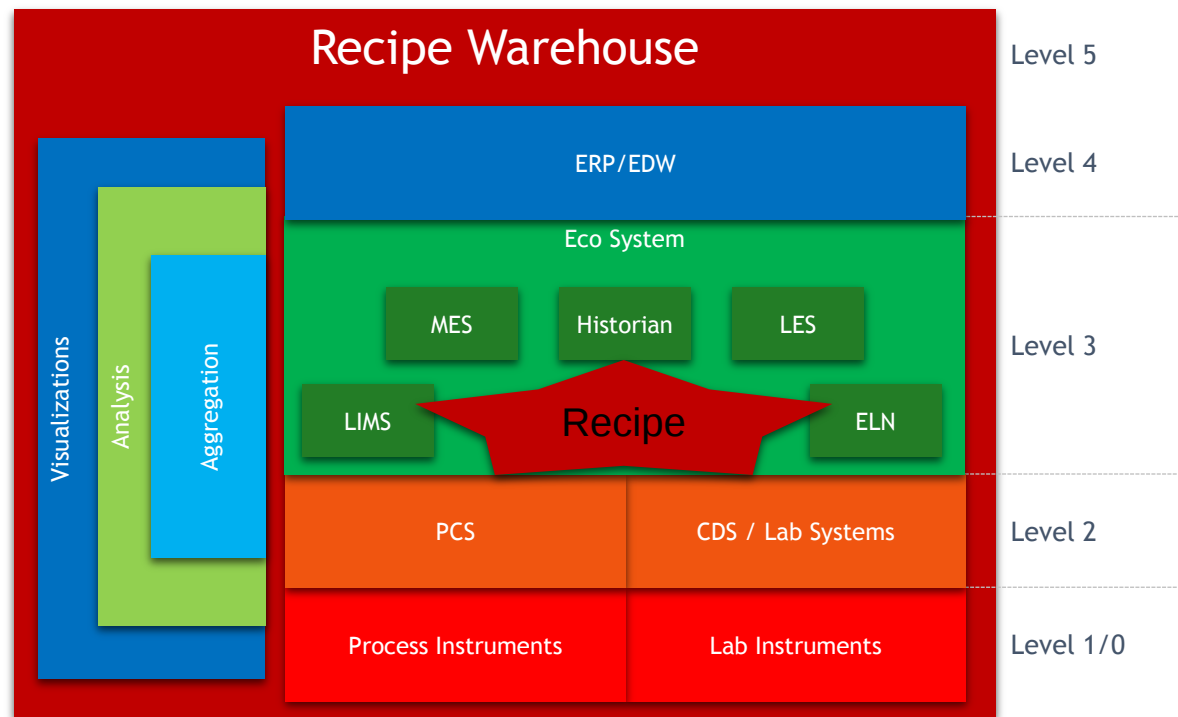
S88/S95 Overall Architecture



CDS: Chromatography Data Software
ELN: Electronic Laboratory Notebook
ERP: Enterprise Resource Planning
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LIMS: Laboratory Information Management System
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S88/S95 'Big Data' Recipe Architecture



CDS: Chromatography Data Software
ELN: Electronic Laboratory Notebook
ERP: Enterprise Resource Planning
LES: Laboratory Execution System

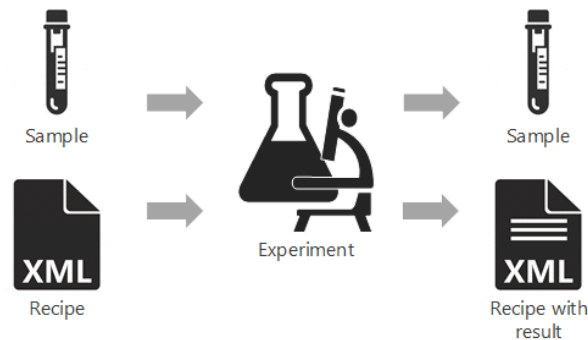
LIMS: Laboratory Information Management System
MES: Manufacturing Execution System
PCS: Process Control System

Recipe Model Implementation

- Precondition: The reference model and guideline recommended in the ISA-88 standard are not to be strictly normative.

➤ Steps

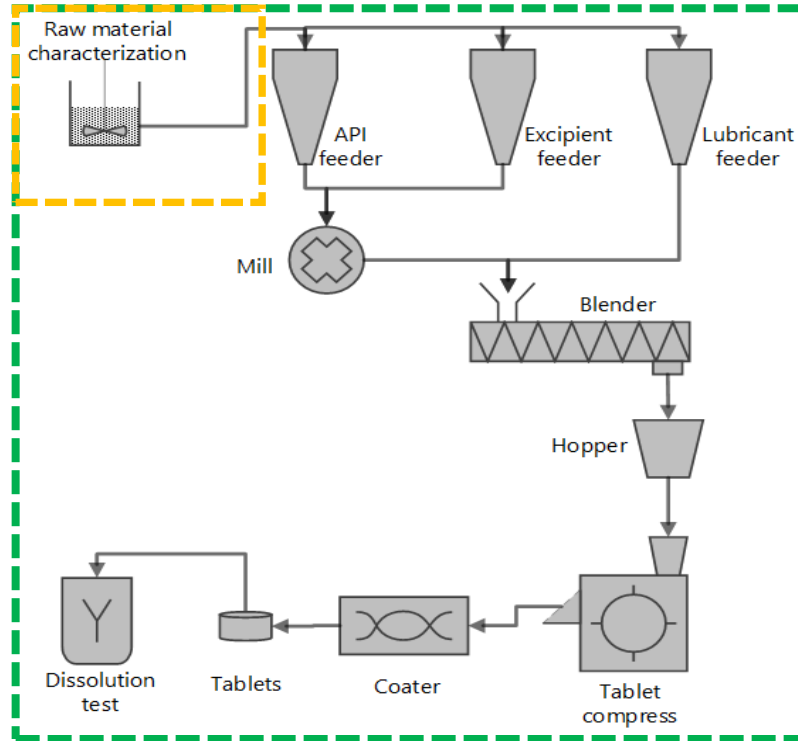
1. ISA-88 applicable area identification
 - Continuous manufacturing and analytical process
2. Recipe structure definition
 - XML Schema Definition (XSD)
3. Process analysis
 - Recipe modules
4. Process mapping
 - Recipe development



Results

Case I

Case II



Continuous Pharmaceutical Process

Case I: Recipe Based ELN System

- ELN ¹ system is developed and implemented for data management in raw material characterization laboratories.
- A custom module for Drupal - an open source CMS ² written in PHP.
- Installed and maintained on Amazon Web Service - cloud computing service.



ELN Web Interface

Master
Recipe

Control
Recipe

The screenshot displays the ELN Web Interface with a navigation bar at the top containing 'ADMIN', 'C-SOPS', 'Janssen Collaborations', and 'Recipes'. The main content area is titled 'Recipes' and includes a description: 'An international standard for describing processes to produce products that have specific requirements around execution, materials, people and equipment to achieve a desired result (ref). We use them extensively to capture both plant and laboratory data. When followed you get a materials centric platform that monitors augmentation of material attributes as a function of unit operations - whereby those unit ops can be plant and/or lab based.'

The interface is divided into three main sections, each highlighted with a red dashed box and a corresponding label:

- Master Recipes:** This section features a search bar with an 'Apply' button and a table of recipes. The table has columns for 'Recipe', 'Process', and 'Actions'. The recipes listed are FT4 Stability, FT4 Permeability, FT4 Compressibility, FT4 Aeration, Continuous Direct Compression, and Washburn Technique. Each recipe has 'Edit' and 'Create control' buttons.
- Control Recipes:** This section also has a search bar with an 'Apply' button and a table of control recipes. The table has columns for 'Recipe', 'Process', 'Author', 'Date', and 'Actions'. The control recipe listed is 'Control: FT4 Compressibility / Huang Tang / 2016-08-22 18-22-30'. It has an 'Edit' button.
- Recipe Import:** This section includes a 'Content Visibility' dropdown set to 'Private', a 'Recipe Components' list (Materials, Products, Equipment, Measurement Units), and an 'XML File' upload section. The XML File section has a 'Choose File' button and a 'Submit' button.

Visibility

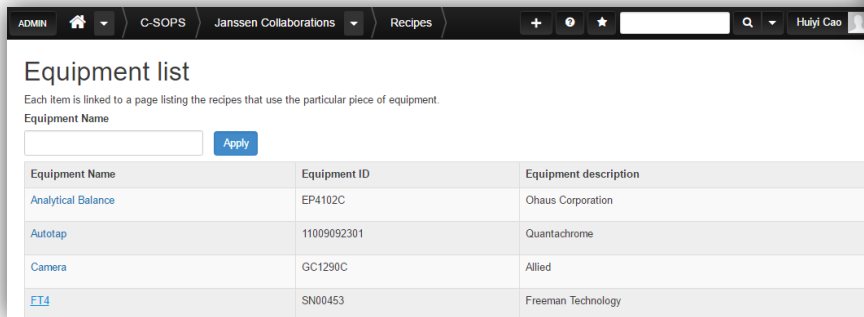
Recipe
Components

Recipe Import

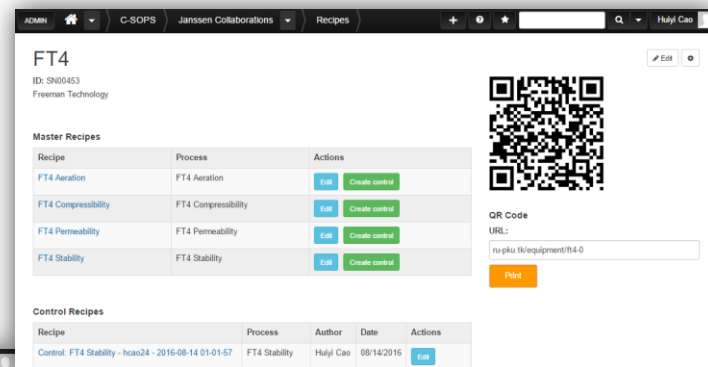
Drupal ELN interface

ELN Features

- Excel file parsing
- Recipe conversion and output
- Equipment and material management
- Barcode generating and printing



Equipment Name	Equipment ID	Equipment description
Analytical Balance	EP4102C	Ohaus Corporation
Autotap	11009092301	Quantachrome
Camera	GC1290C	Allied
FT4	SN00453	Freeman Technology



FT4
ID: SN00453
Freeman Technology

QR Code
URL: [https://equipment/ft4-0](#)
[Print](#)

Master Recipes

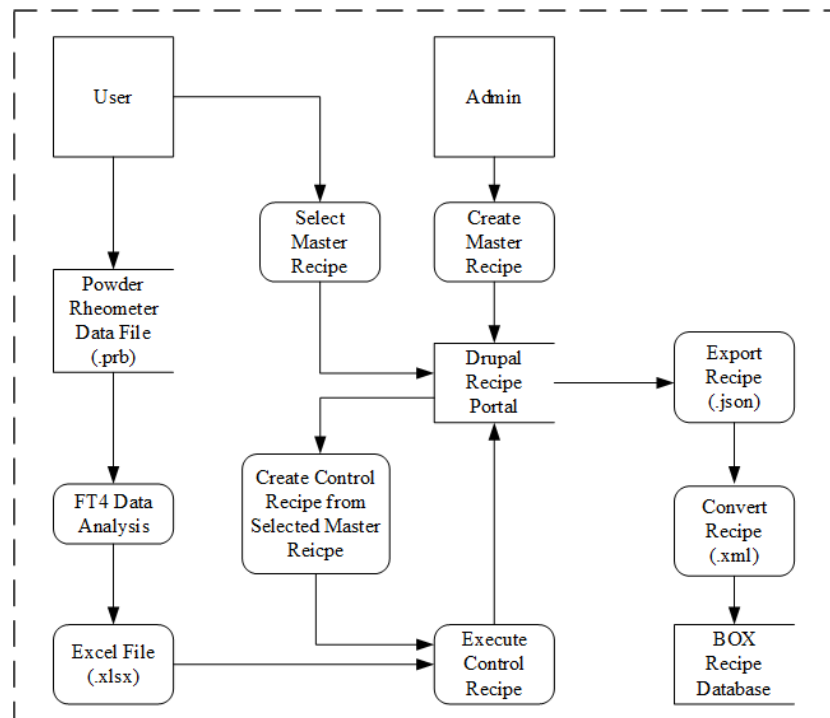
Recipe	Process	Actions
FT4 Aeration	FT4 Aeration	Edit Create control
FT4 Compressibility	FT4 Compressibility	Edit Create control
FT4 Permeability	FT4 Permeability	Edit Create control
FT4 Stability	FT4 Stability	Edit Create control

Control Recipes

Recipe	Process	Author	Date	Actions
Control FT4 Stability - hcao24 - 2016-08-14 01-01-57	FT4 Stability	Huiyi Cao	08/14/2016	Edit

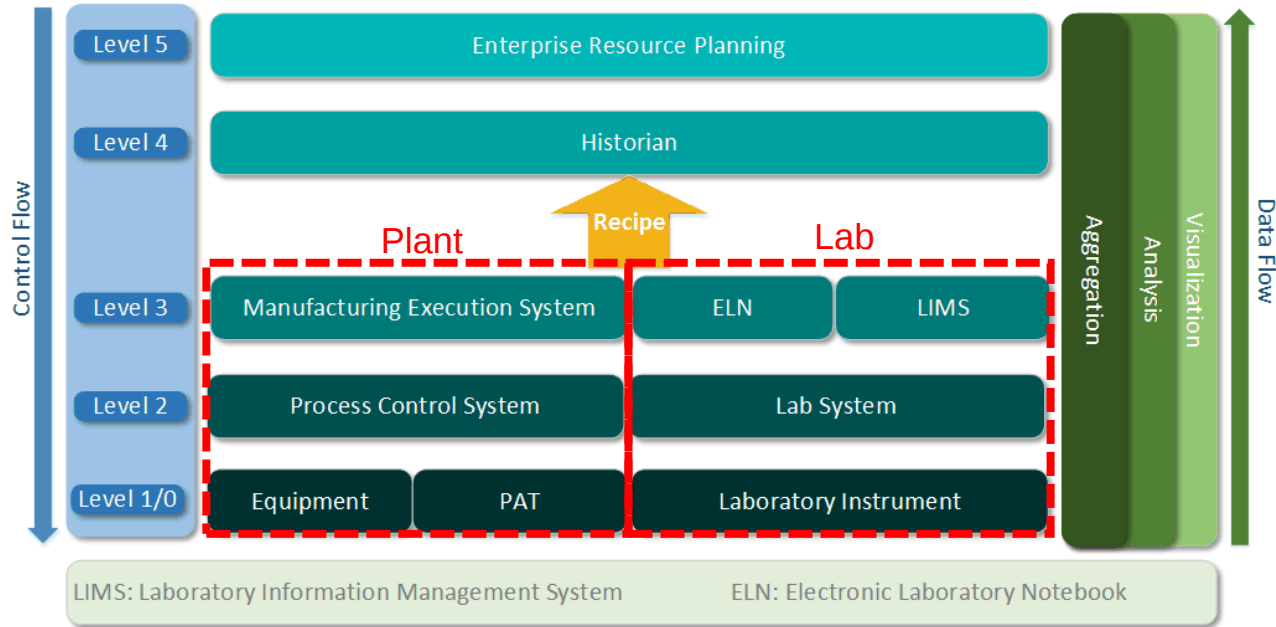
Left: ELN equipment list
Right: ELN equipment info

Data Flow in ELN



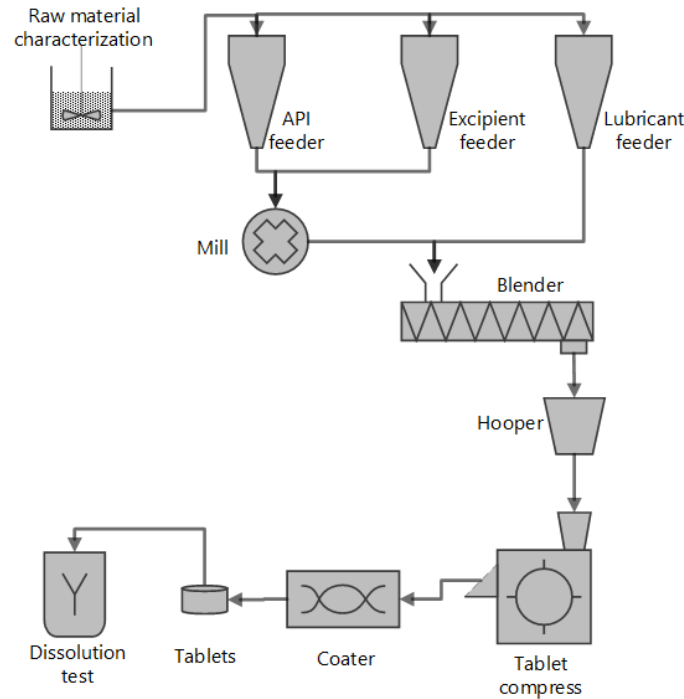
ELN data flow (FT4)

Architecture of Data Integration



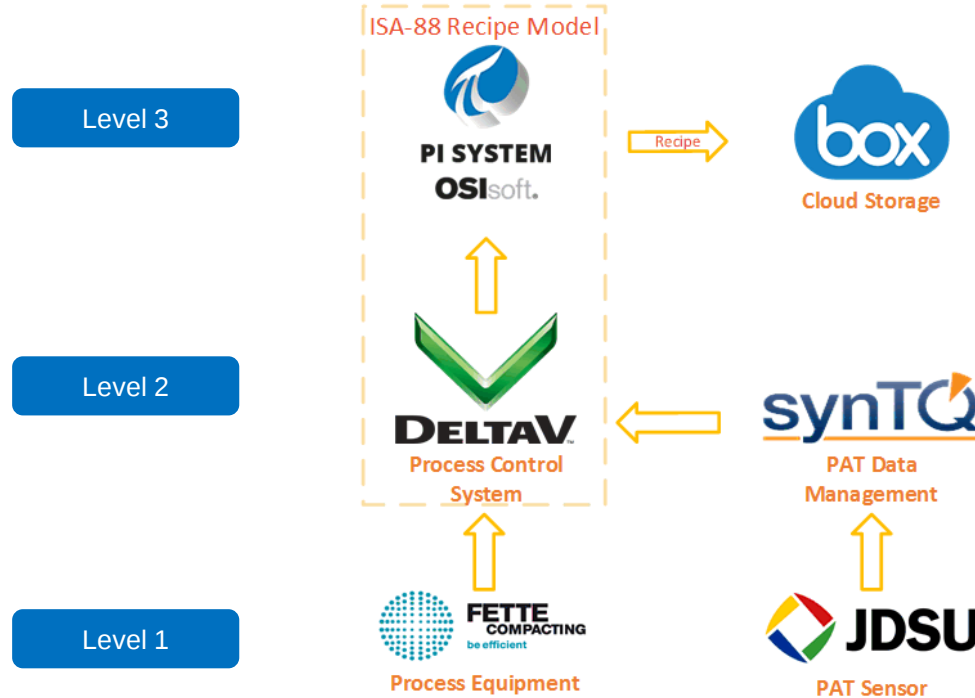
Architecture of control and data flows

Case II: Data Integration in Continuous Direct Tablet Compaction Process

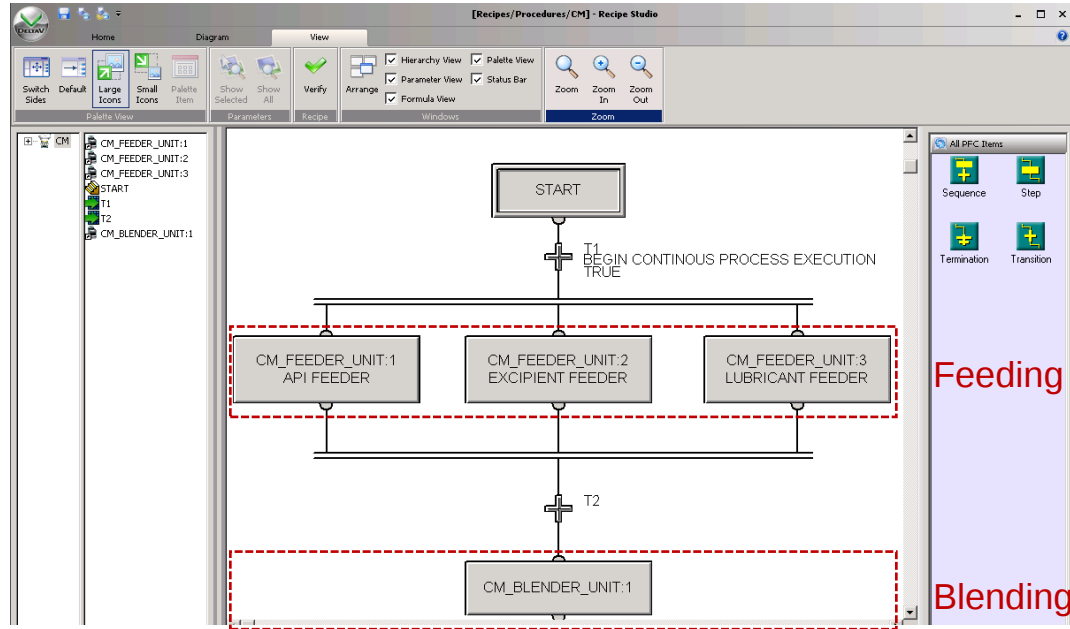


Continuous tablet compaction process

Data Flow in Pilot Plant

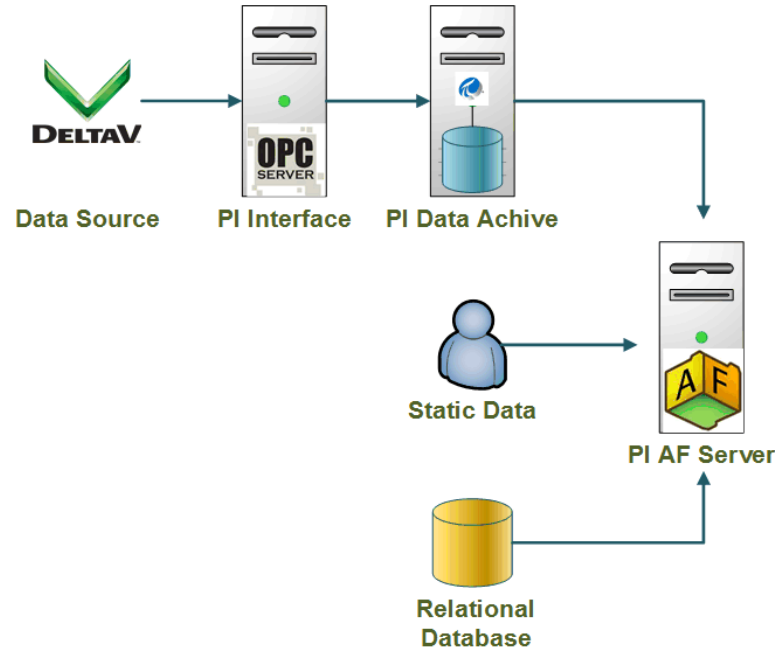


DeltaV Recipe Model



DeltaV Recipe Studio interface

OSI-PI Recipe Structure



PI system structure

PI Asset Framework

File Search View Go Tools Help

Database Query Date Back Check In Refresh New Element New Attribute Search Elements

Elements

- Elements
 - Rutgers
 - Continuous Tabetl Direct Compation
 - Blender
 - Coat
 - Feeder
 - API Feeder
 - Excipient Feeder
 - Lubricant Feeder
 - Mill
 - PAT
 - NIR
 - Raman
 - Tablet Compress
- Element Searches

Tablet Compress

General Child Elements Attributes Ports Analyses Version

Filter

Name	Value	Dk
Fill-o-matic speed	0 rpm	3
Main compr. force MV	0 kN	5
Permiss. punch load	0 kN	4
Rotor speed	0 rpm	2
Table, filling depth	128 mm	6
Tablets/h	128	1

Group by: ☐ Category ☐ Template

Name: Rotor speed

Description: 2

Properties: <None>

Categories:

Default UOM: revolution per minute

Value Type: Double

Value: 0 rpm

Data Reference: PI Point

Settings...

PI AF explorer

PI Event Frame

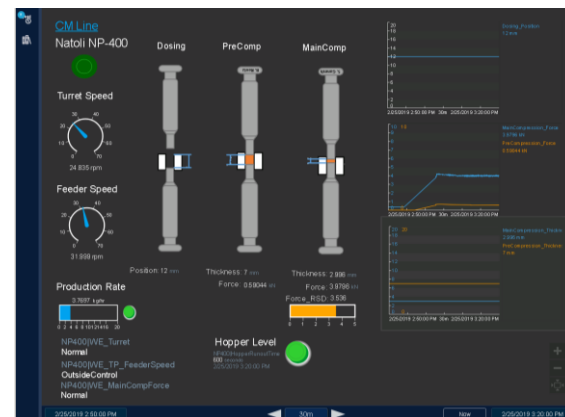
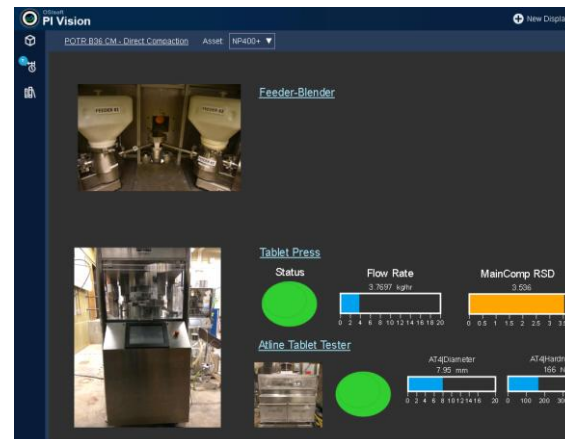
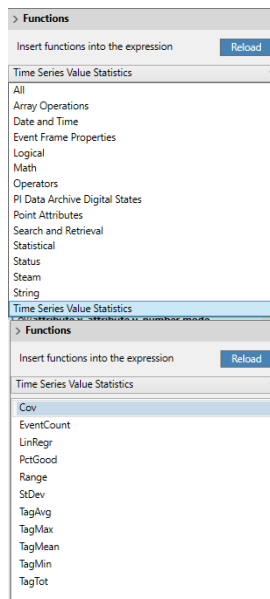
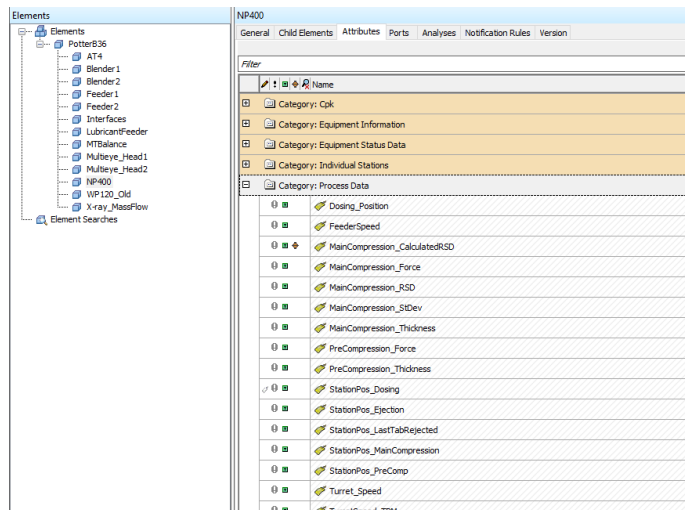
PSOA

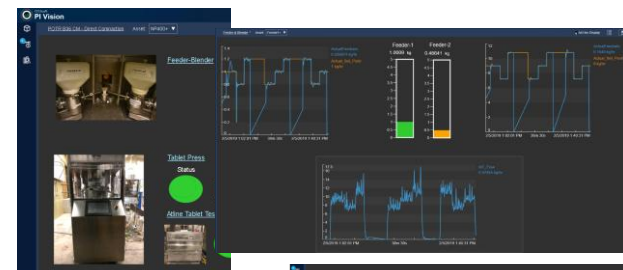
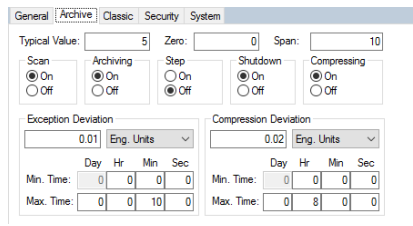
The screenshot displays the PI Event Frame Explorer application. On the left, a tree view under 'Event Frames' shows a hierarchy: 'Event Frame Searches' > 'Event Frame Search 1' > 'Continuous Tablet Press' (highlighted with a red dashed box). Below this, a sequence of steps is listed: Feeding, API, Add Powder, Retain, Excipient, Add Powder, Retain, Lubricant, Add Powder, Retain, and Milling. On the right, the 'Continuous Tablet Press' event frame details are shown. The 'General' tab is active, displaying fields for Name, Description, Template, Start time, End time, Categories, and Default Attribute. The 'Find' section includes links for 'Parents' and 'Children', and the 'Actions' section includes 'Capture Values' and 'Lock'. A search bar at the top right is labeled 'Search Event Frames'.

Recipe Structure

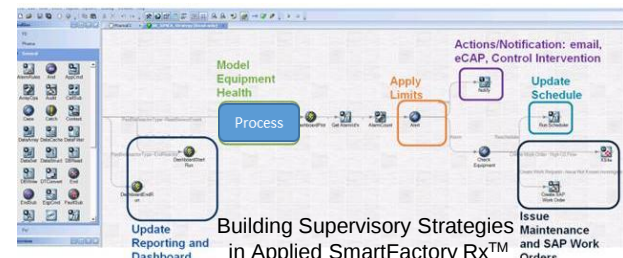
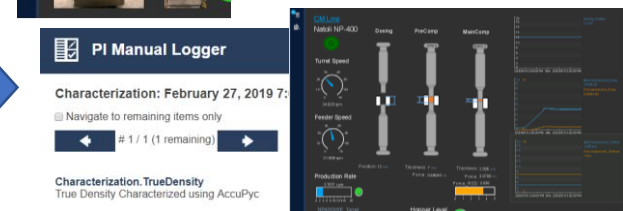
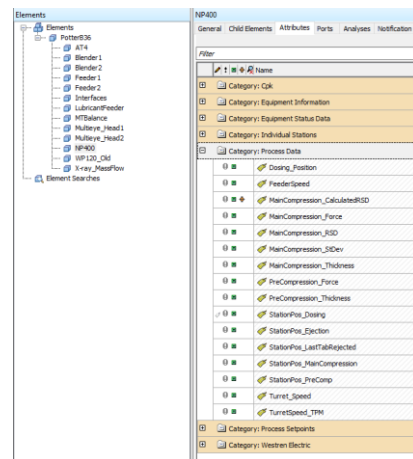
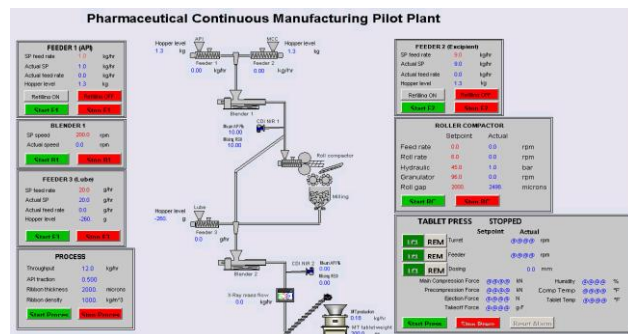
PI EF explorer

PI Vision





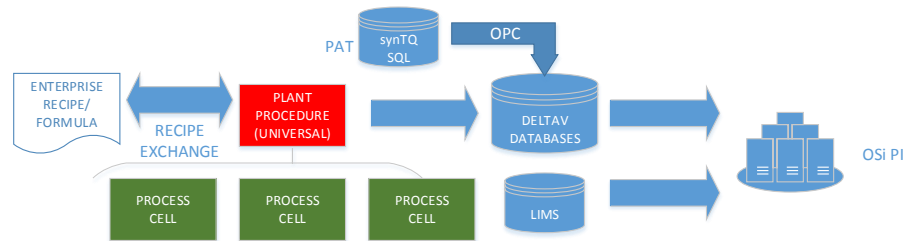
Individual equipment & sensors



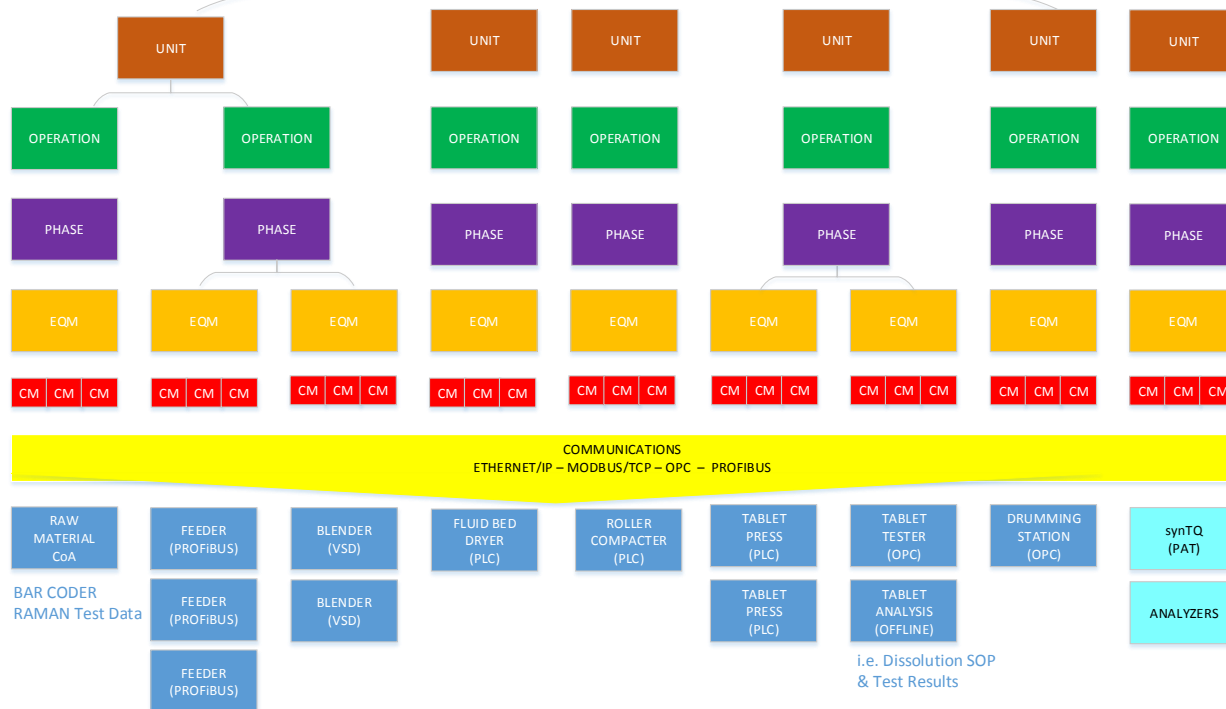
Operations configuration

Setup PI System

Visualization & additional systems



Rutgers Line Network Infrastructure



Conclusion

- ISA-88 Batch Control Standard is adopted to continuous manufacturing in order to provide a design philosophy for data structure, as well as reference models.
- A recipe based ELN system is in charge of capturing data from various analytical platforms.
- Recipe model implemented in PCS and Data Historian
- Data integration is set up to provide real-time data from the continuous manufacturing plant.

Acknowledgement

- Huiyi Cao
- OSIsoft PI System Academic Team
- Janssen Pharmaceutical
- Emerson, Control Associates, QbD Process Control
- Rutgers Colleagues; Ravendra Singh, Rohit Ramachandran, Marianthi Ierapetritou, Shantenu Jha



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name & company



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