Big Data Management Strategy for Continuous Pharmaceutical Manufacturing

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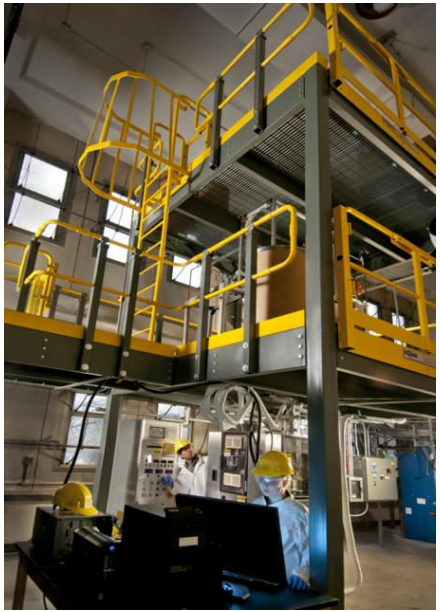
Outline

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

C-SOPS

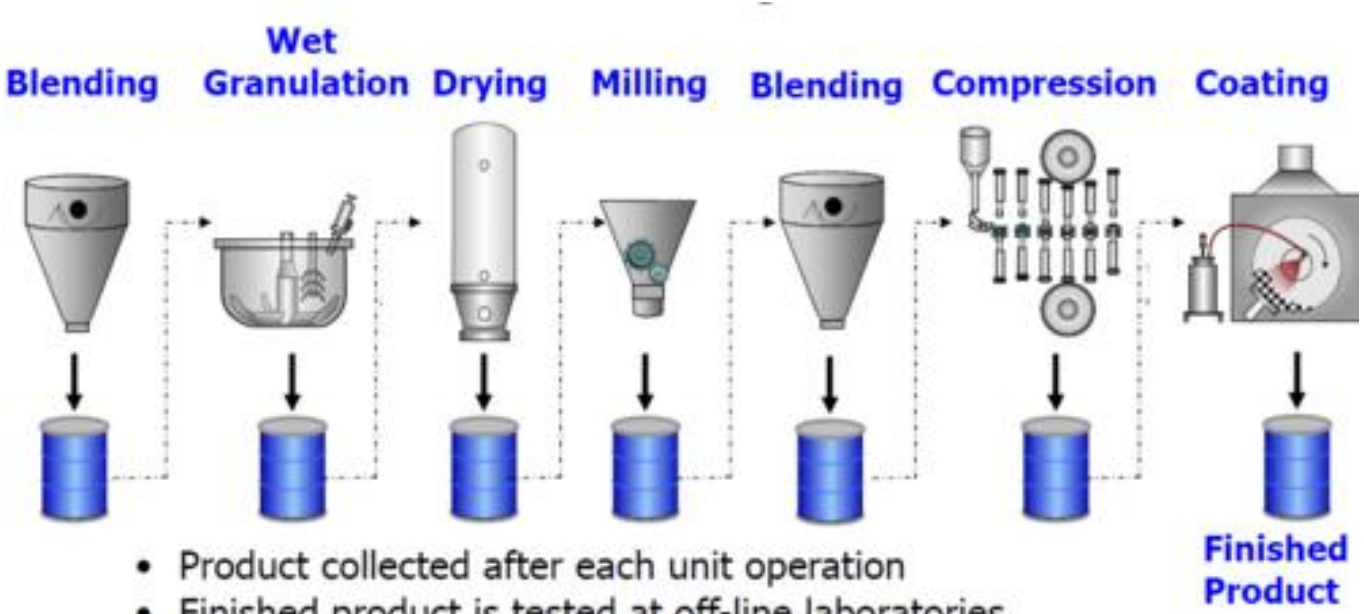
C-SOPS is the sandbox where academia, industry, and regulators meet (virtually) to develop and refine the next generation of advanced pharmaceutical manufacturing



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.

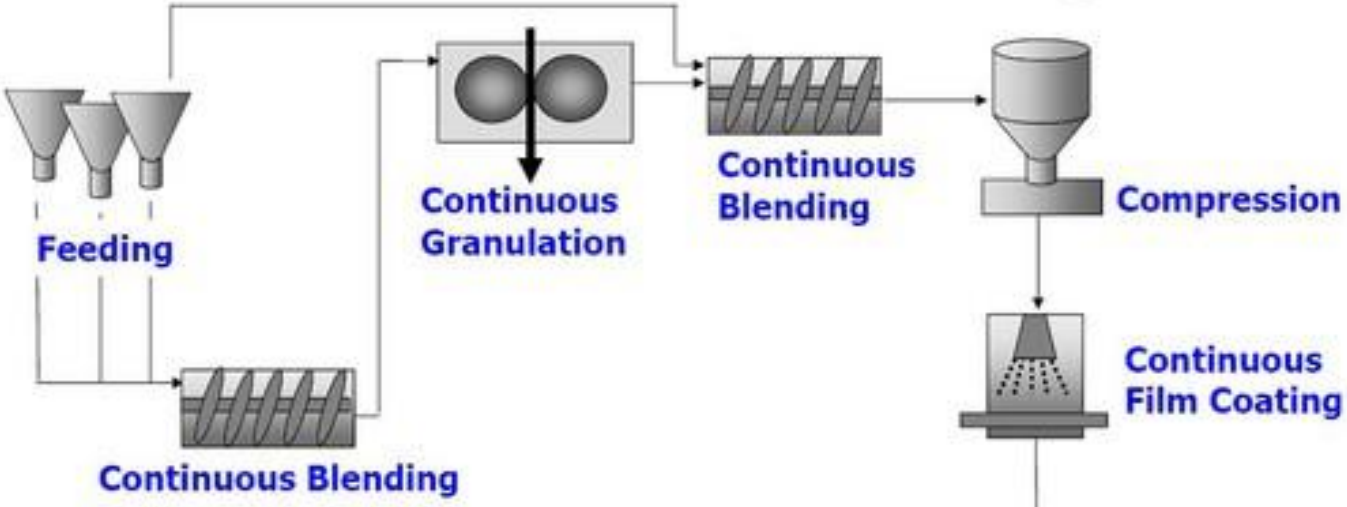
Current MFG in Pharma (Batch)



- Product collected after each unit operation
- Finished product is tested at off-line laboratories, after processing is complete
- Actual processing time = days to weeks

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

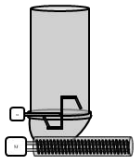
Figure courtesy of the FDA

C-SOPS Approach

Solid Dose Advanced Pharmaceutical Manufacturing

Material Properties

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



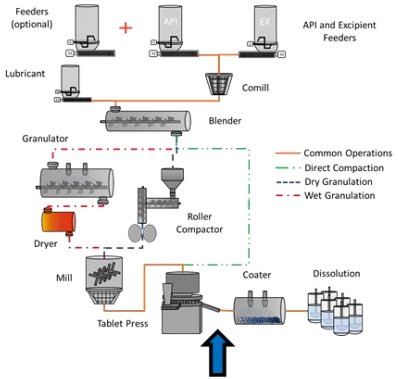
$$y = f(x,a,t,m,n)$$

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

Unit Ops Models

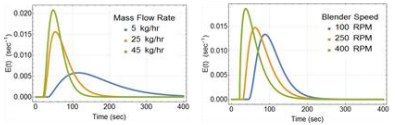
e.g., Feeders

Integrated Process Model "Flowsheets"

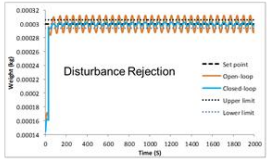


Experimental & Design Parameters

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 C*M 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

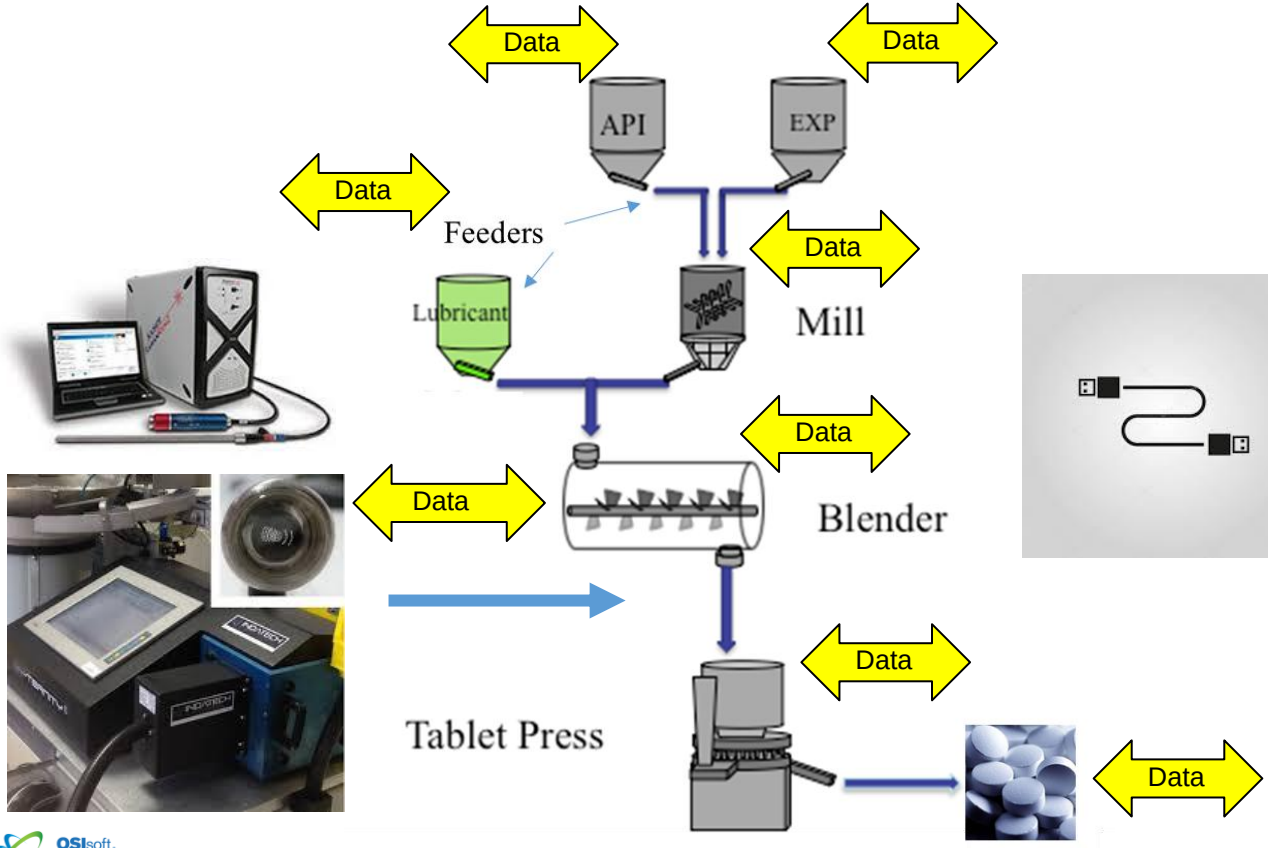
Generics

- 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

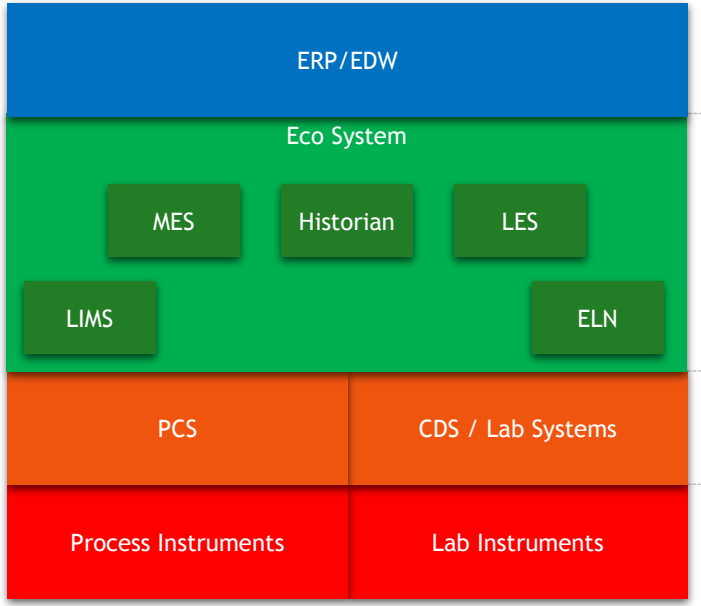


Material Handling
Particle Technology

Process
Analyzers
In-line, At-line &
Offline

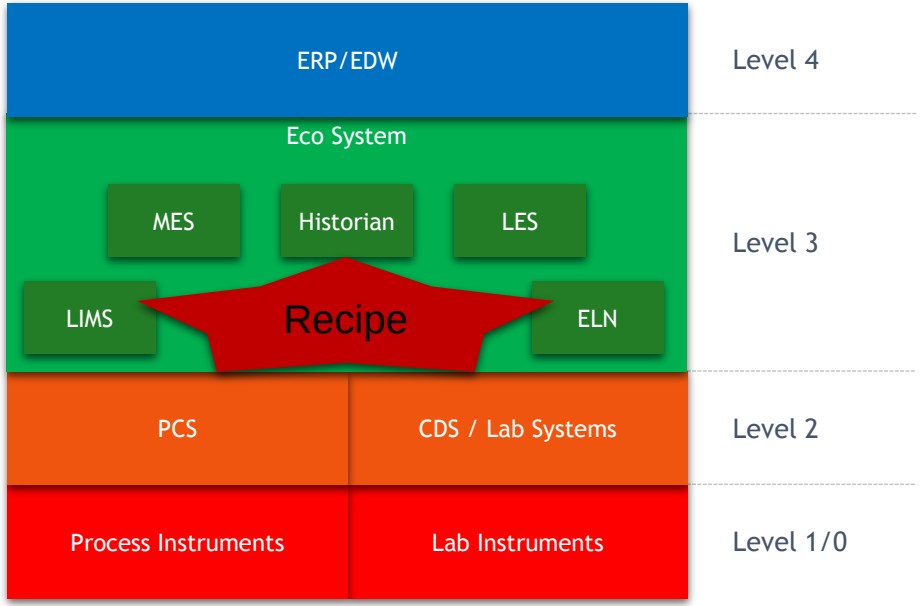
Process Systems
Engineering

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



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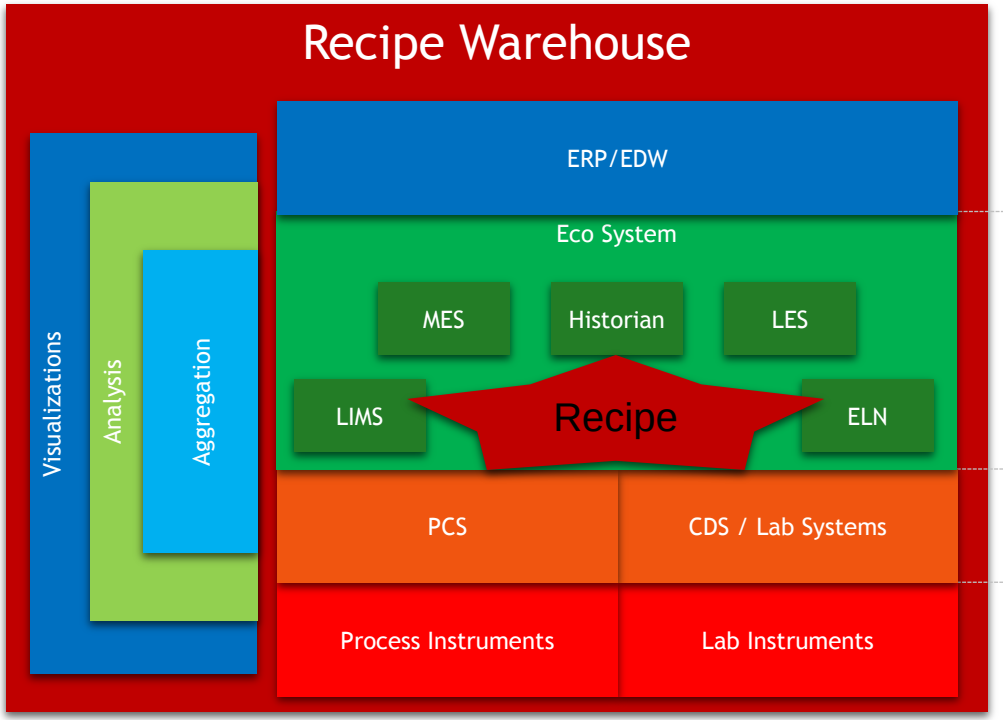
S88/S95 ‘Big Data’ Recipe Architecture



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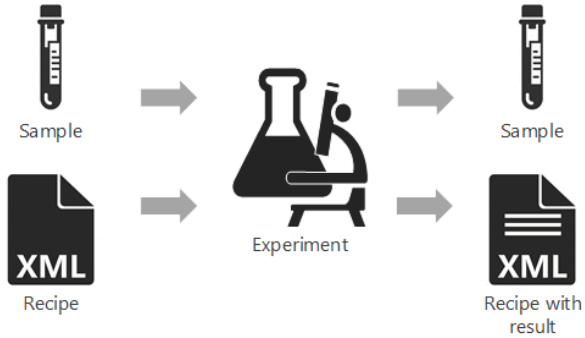
Recipe Model Implementation

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

➢ Steps

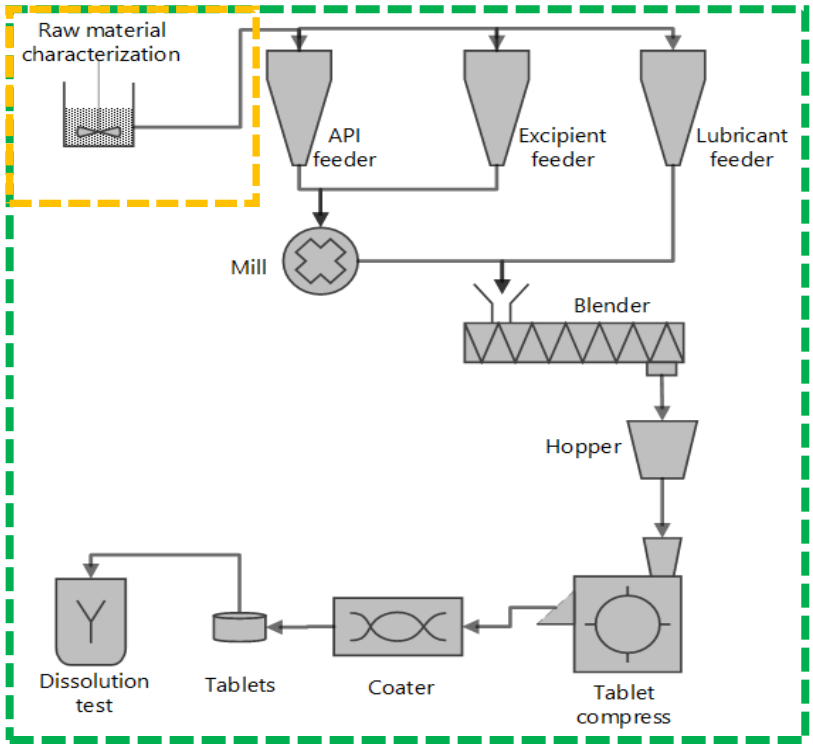
1. ISA-88 applicable area identification
   - Continuous manufacturing and analytical process
2. Recipe structure definition
   - XML Schema Definition (XSD)
3. Process analysis
   - Recipe modules
4. Process mapping
   - Recipe development



Results

Case I

Case II



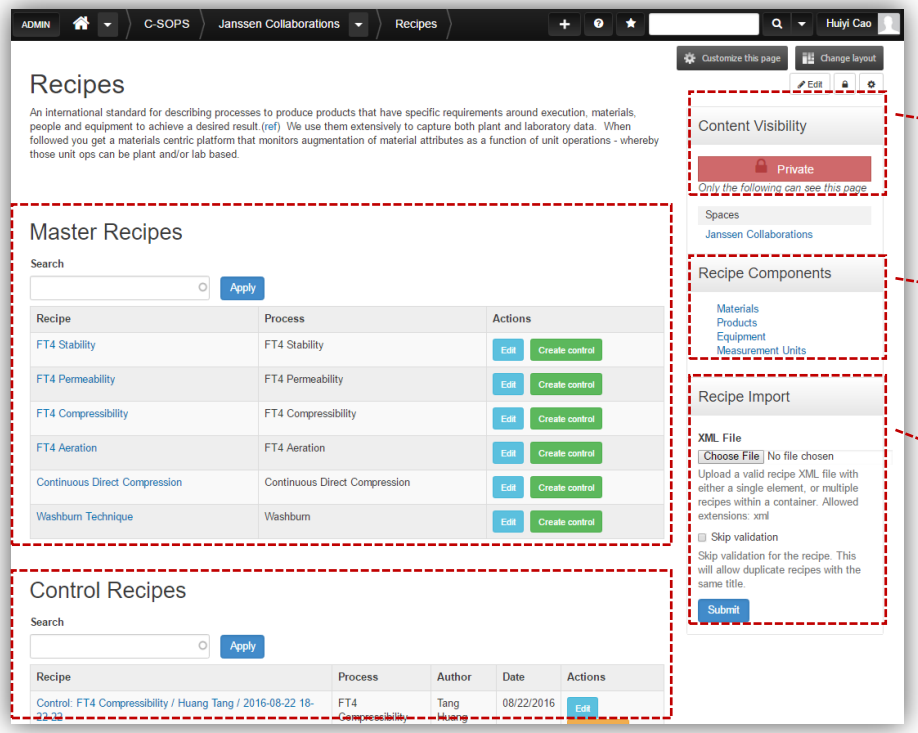
Continuous Pharmaceutical Process

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.

1. ELN: Electronic Laboratory Notebook
2. CMS: Content Management System

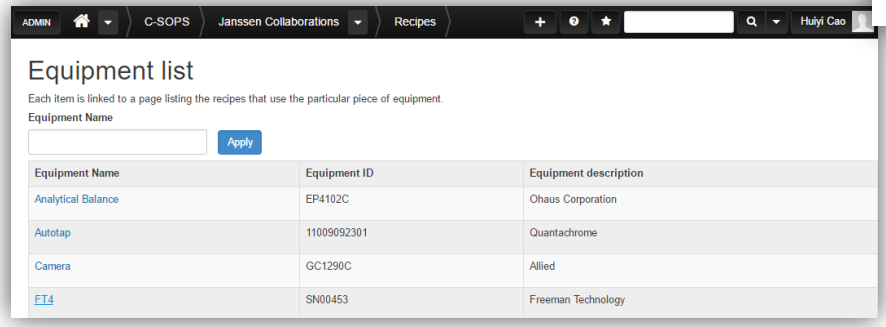
ELN Web Interface

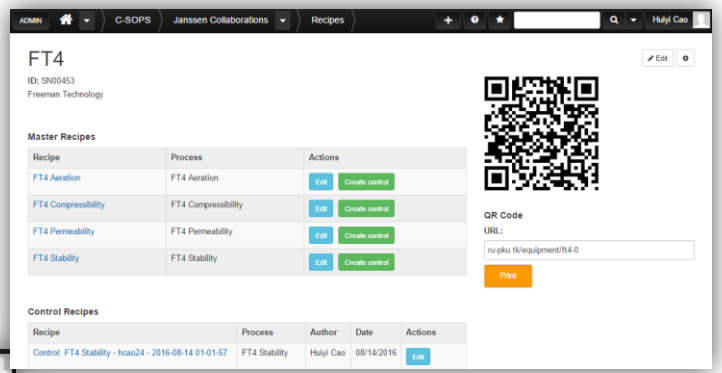


Drupal ELN interface

ELN Features

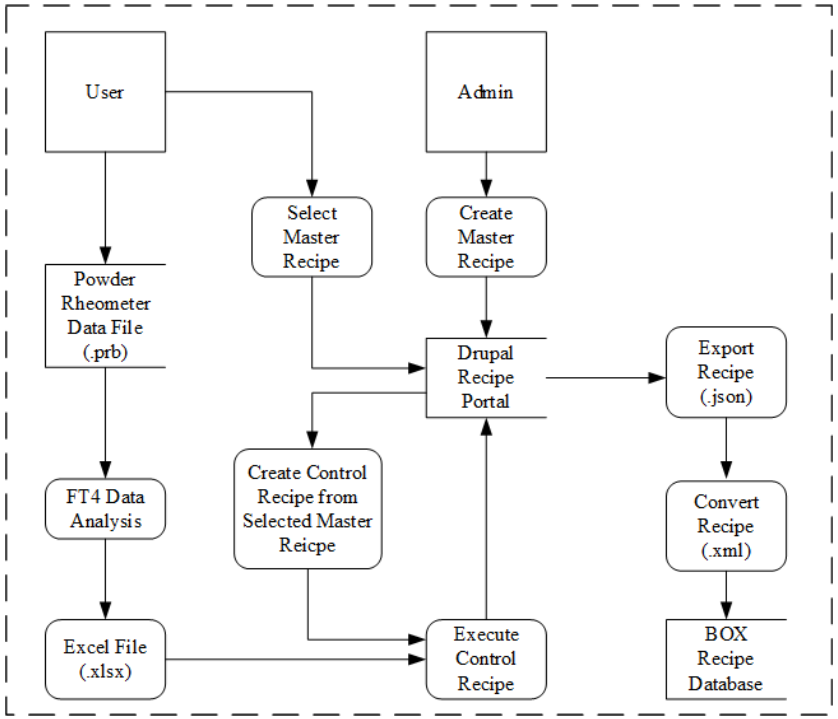
- Excel file parsing
- Recipe conversion and output
- Equipment and material management
- Barcode generating and printing





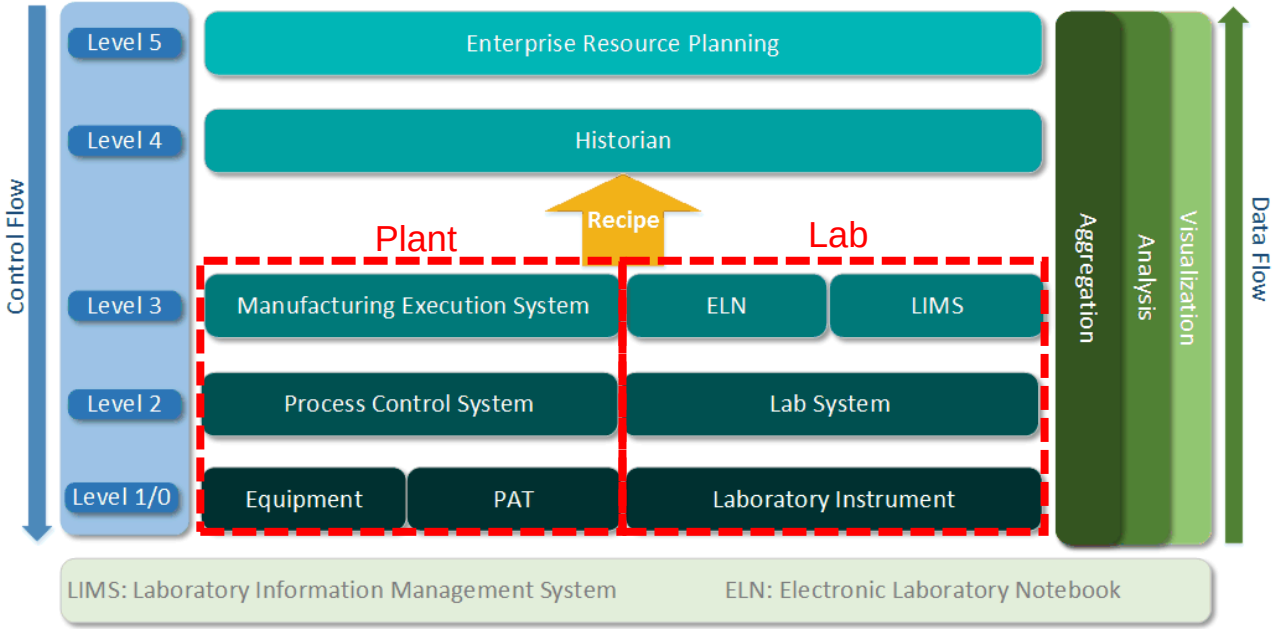
Left: ELN equipment list
Right: ELN equipment info

Data Flow in ELN



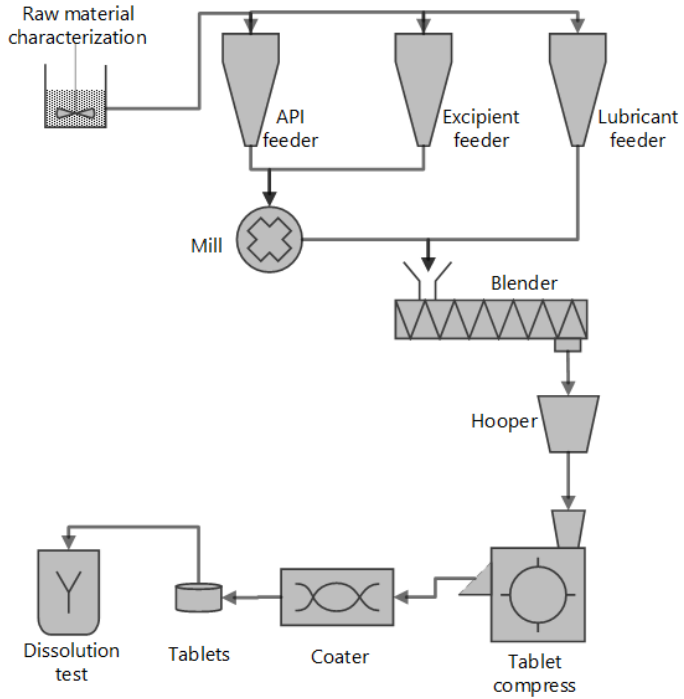
ELN data flow (FT4)

Architecture of Data Integration



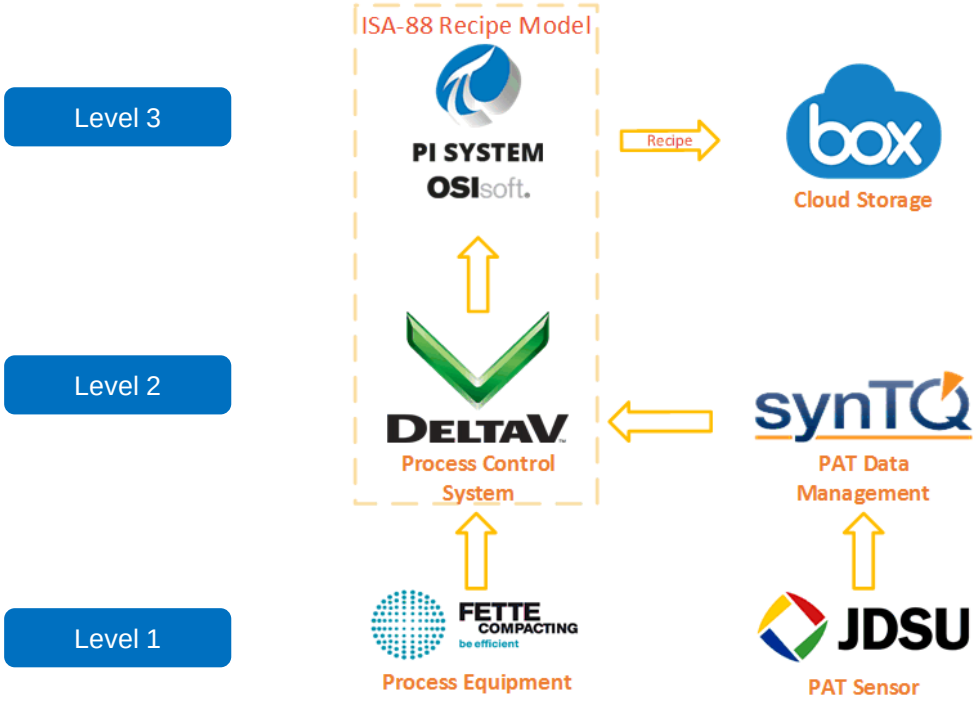
Architecture of control and data flows

Case II: Data Integration in Continuous Direct Tablet Compaction Process

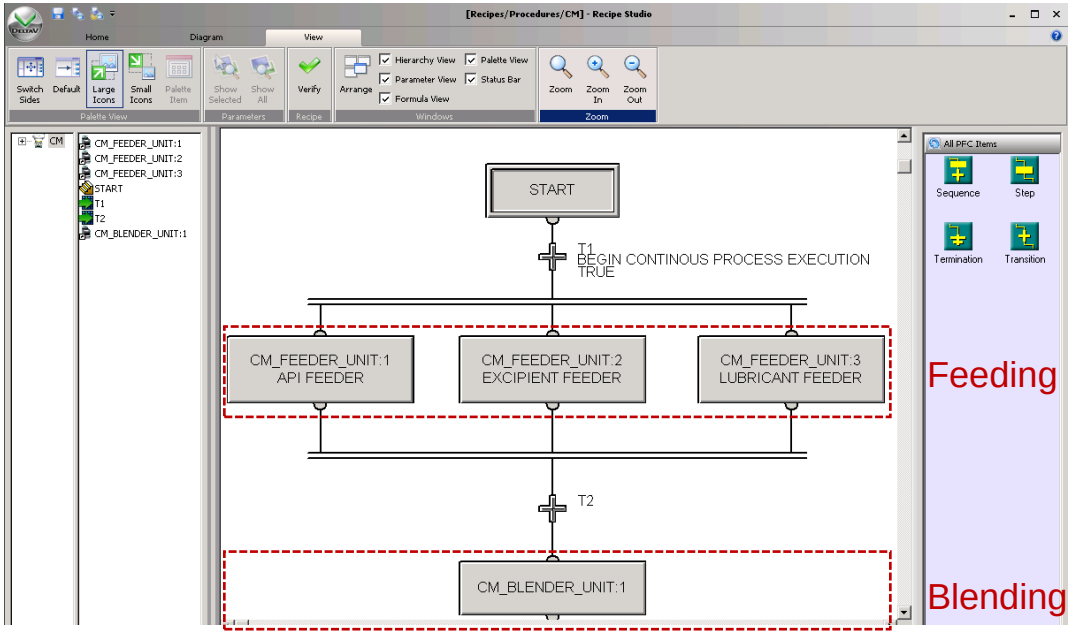


Continuous tablet compaction process

Data Flow in Pilot Plant

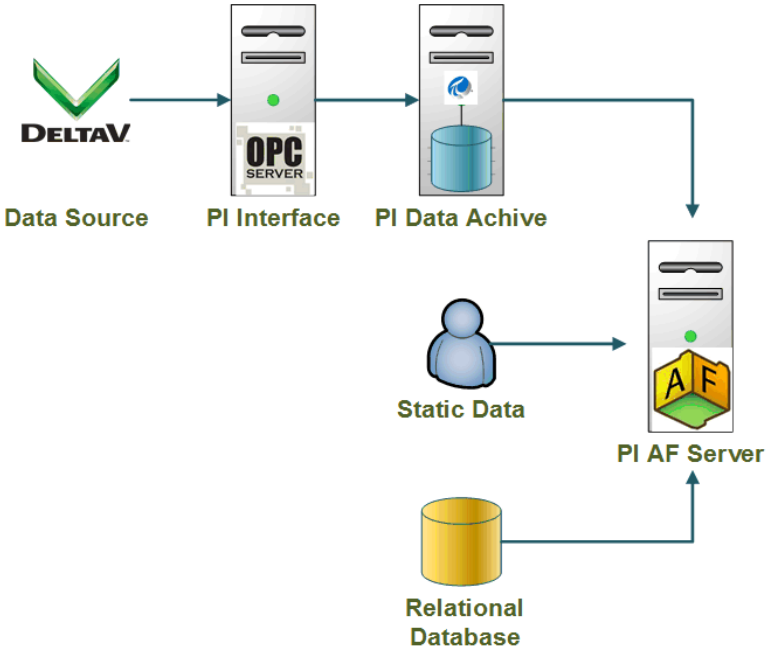


DeltaV Recipe Model



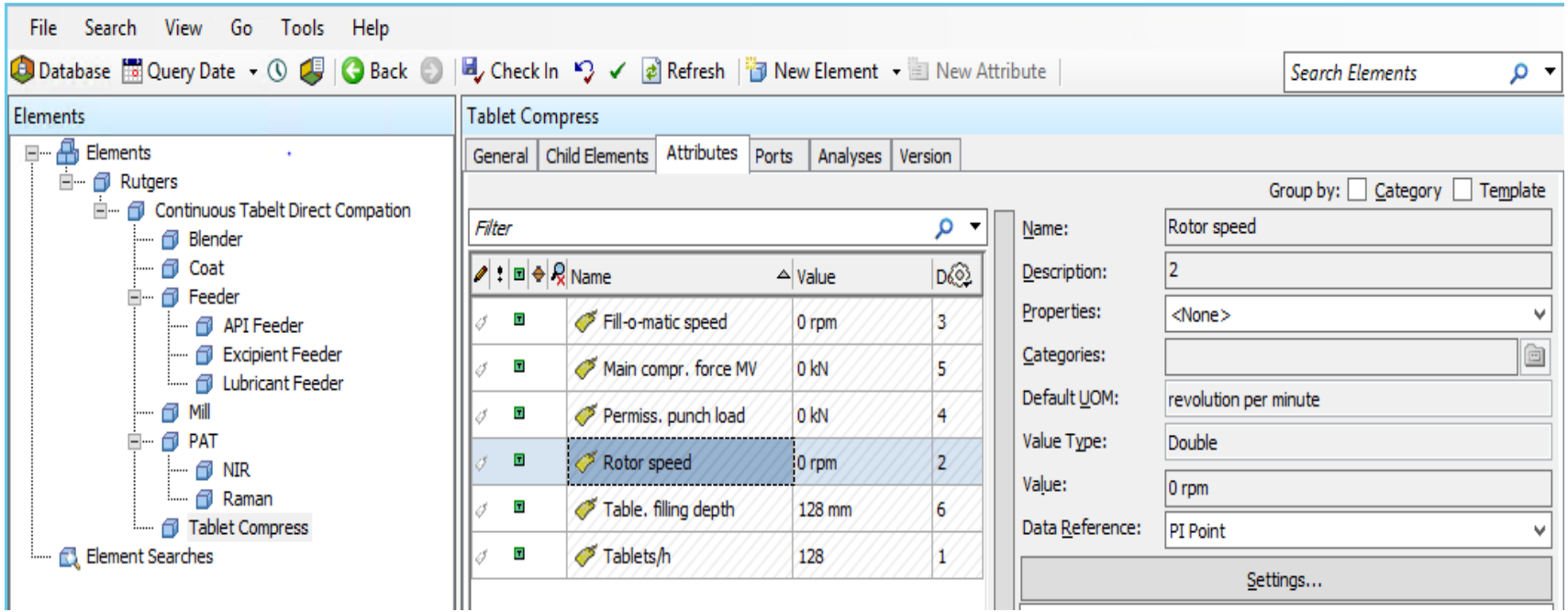
DeltaV Recipe Studio interface

OSI-PI Recipe Structure



PI system structure

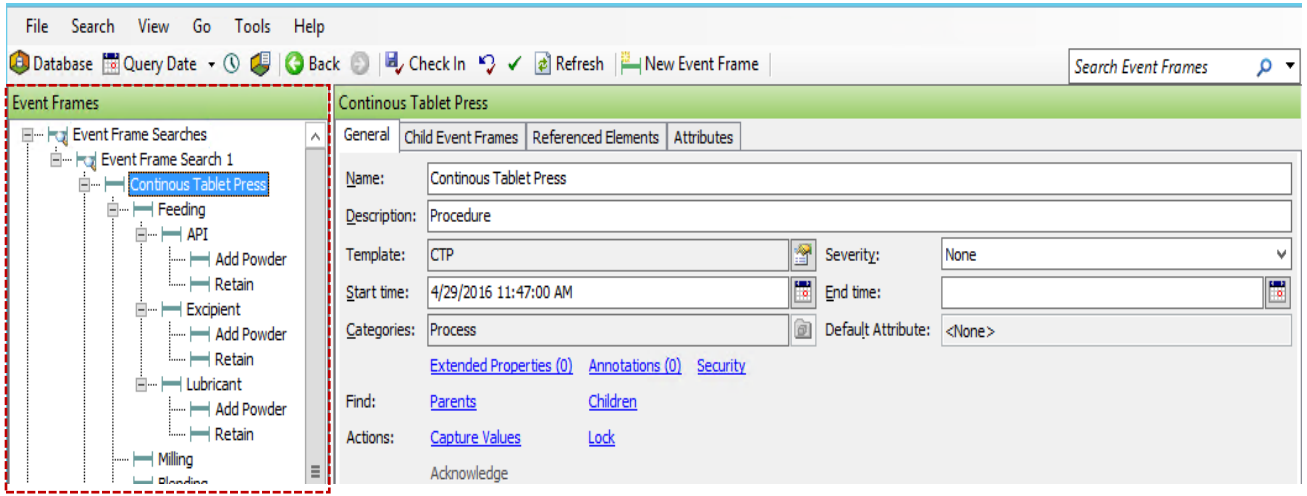
PI Asset Framework



PI AF explorer

PI Event Frame

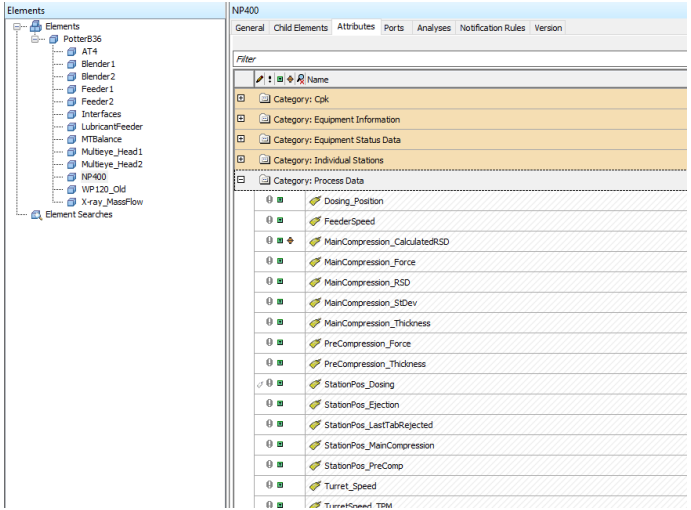
P
S
O
A

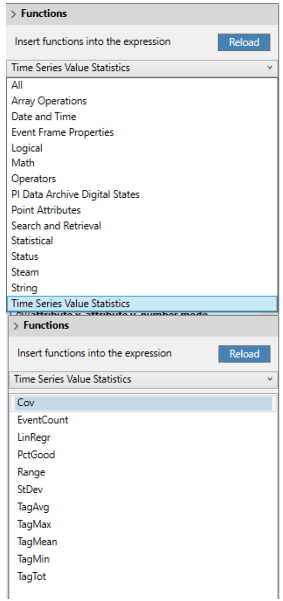


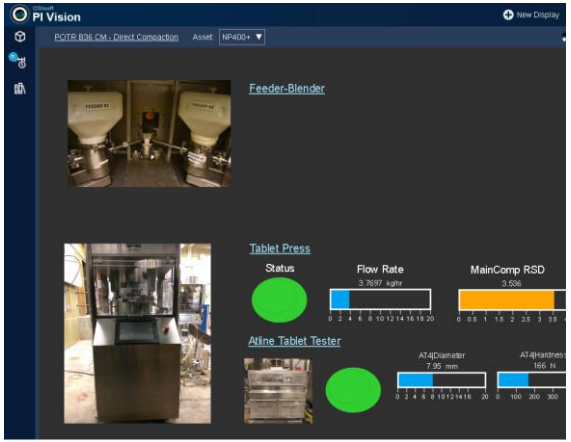
Recipe Structure

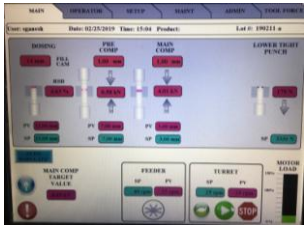
PI EF explorer

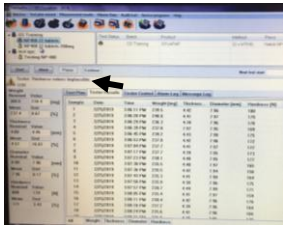
PI Vision



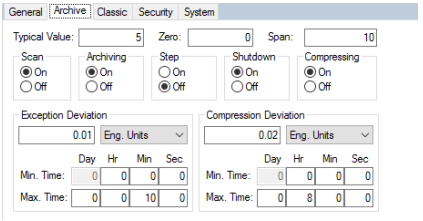


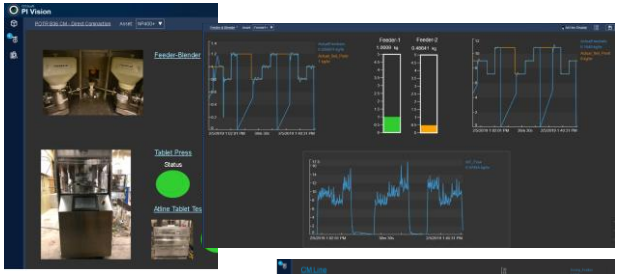


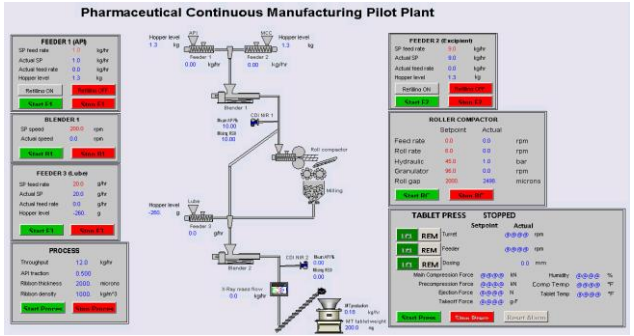




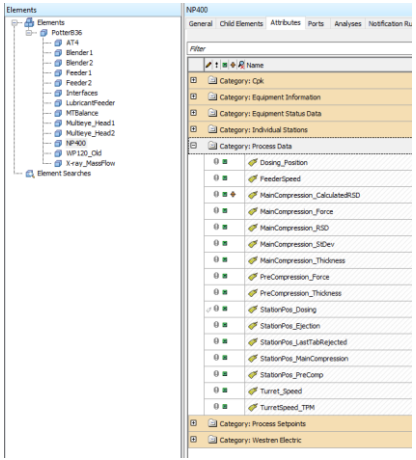
Individual equipment & sensors



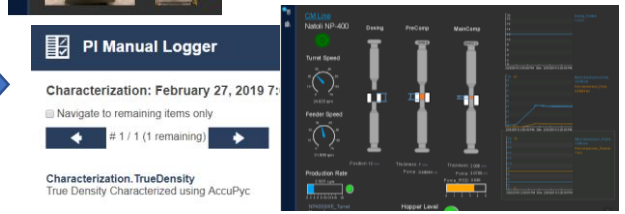


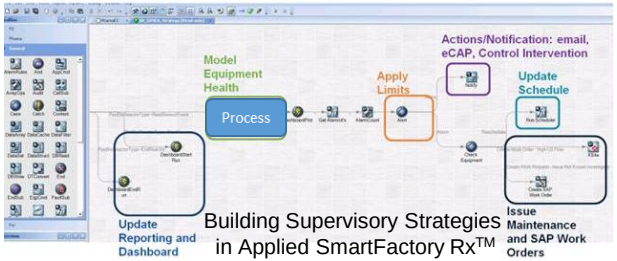


Operations configuration



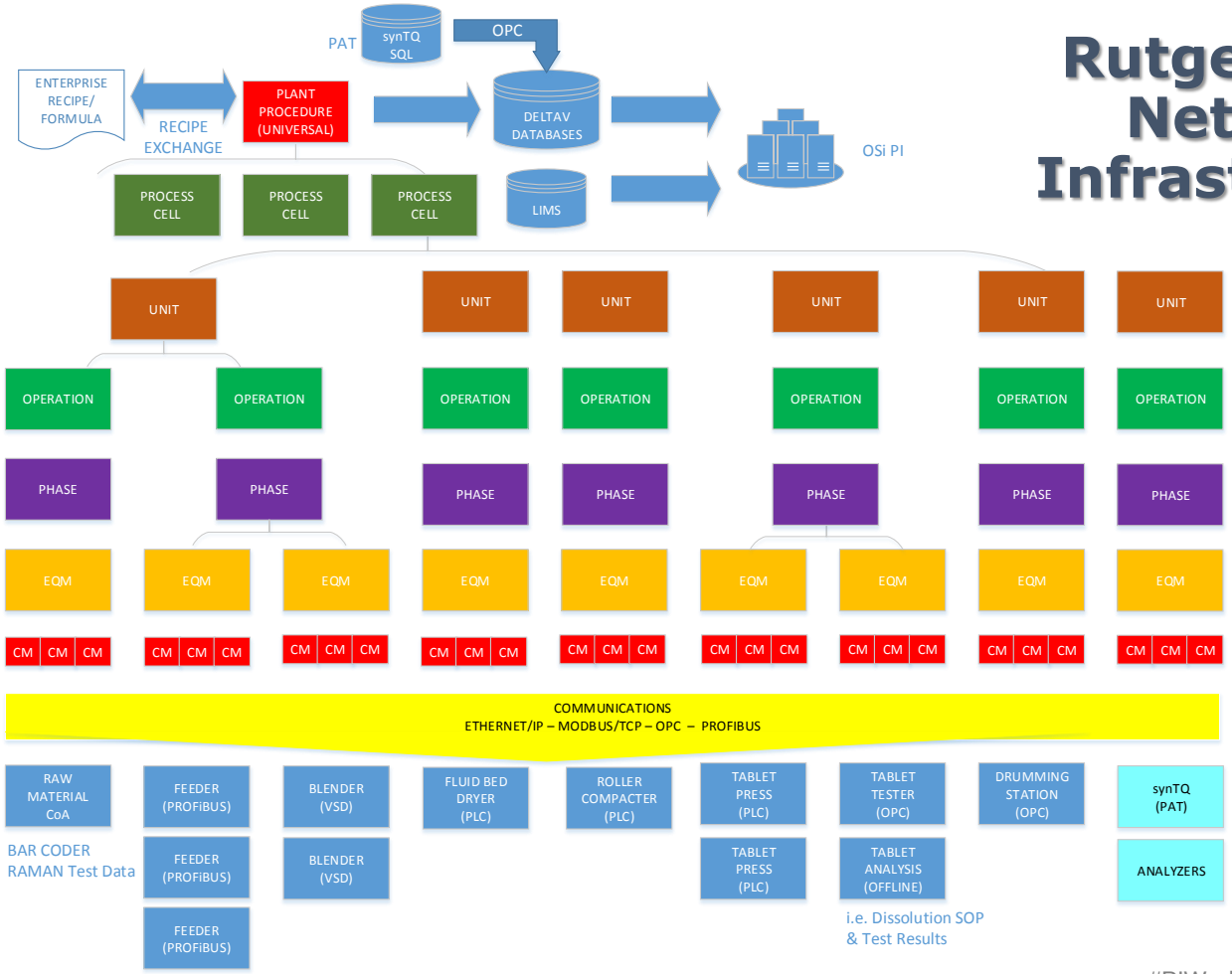
Setup PI System





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

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- Associate Director, C-SOPS
- Rutgers University

Questions?

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