PI System for Academic Research in Continuous Pharmaceutical Manufacturing

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Vision

Science and risk based manufacturing for improved patient reach & healthcare supply

Goal

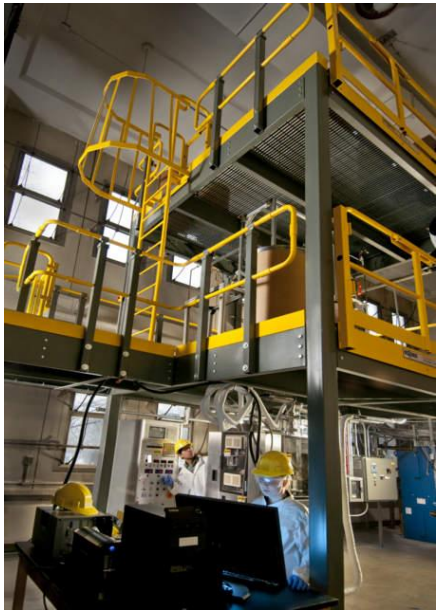
Real-time release testing in oral solid dose continuous manufacturing systems

Talk Agenda

- Continuous Pharmaceutical Manufacturing
- Role of PI System in CM Research & Education

C-SOPS

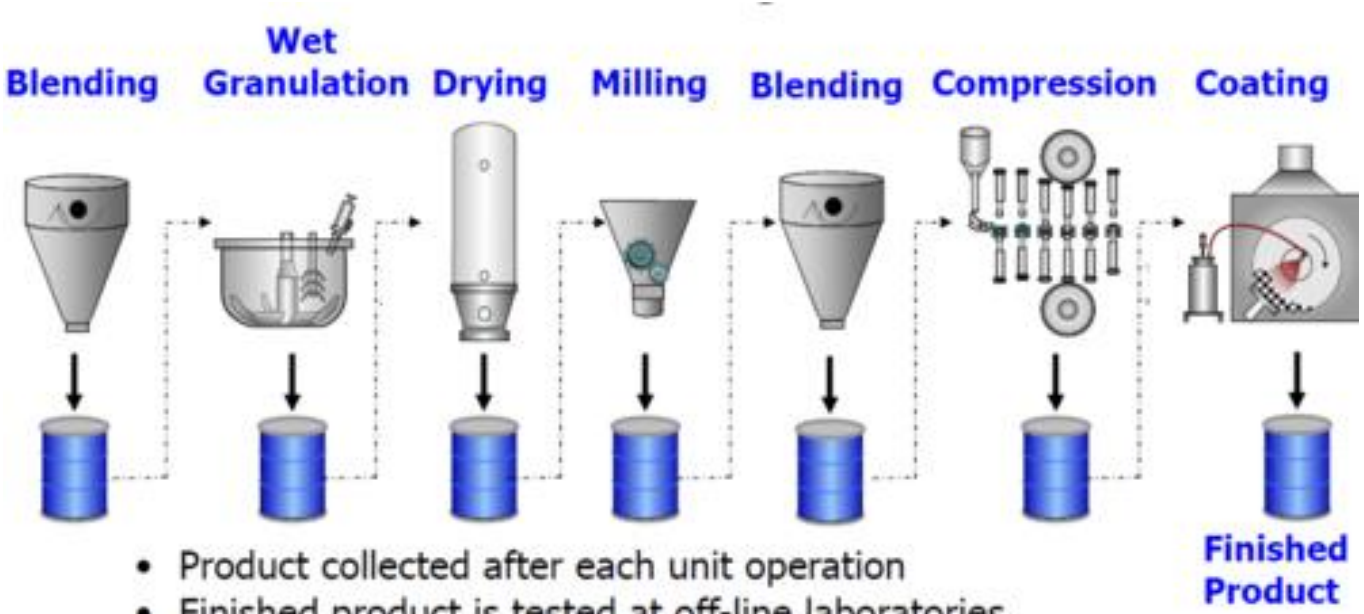
C-SOPS is the sandbox where academia, industry, and regulators meet (virtually) to develop and refine the next generation of advanced pharmaceutical manufacturing



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.

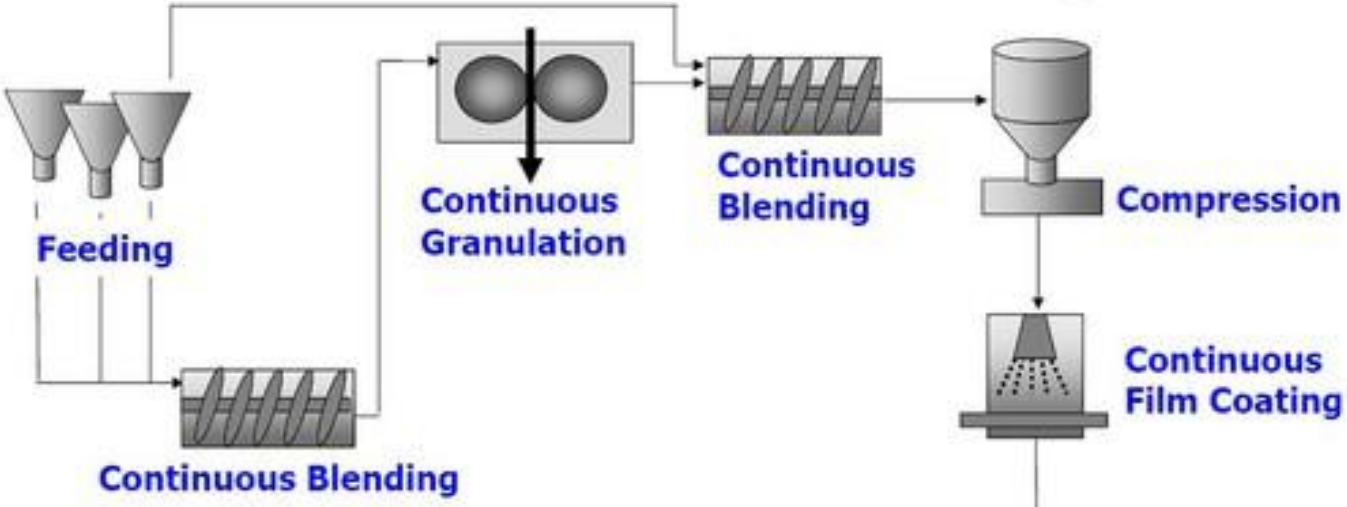
Current MFG in Pharma (Batch)



- 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

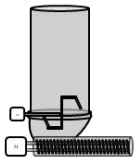
Figure courtesy of the FDA

C-SOPS Approach

Solid Dose Advanced Pharmaceutical Manufacturing

Material Properties

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



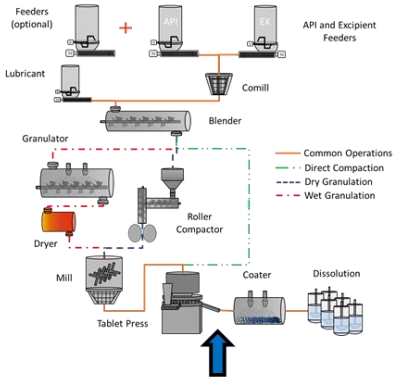
$$y = f(x,a,t,m,n)$$

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

Unit Ops Models

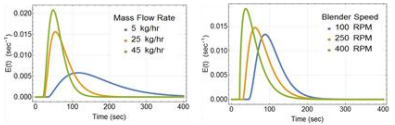
e.g., Feeders

Integrated Process Model "Flowsheets"

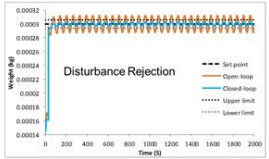


Experimental & Design Parameters

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

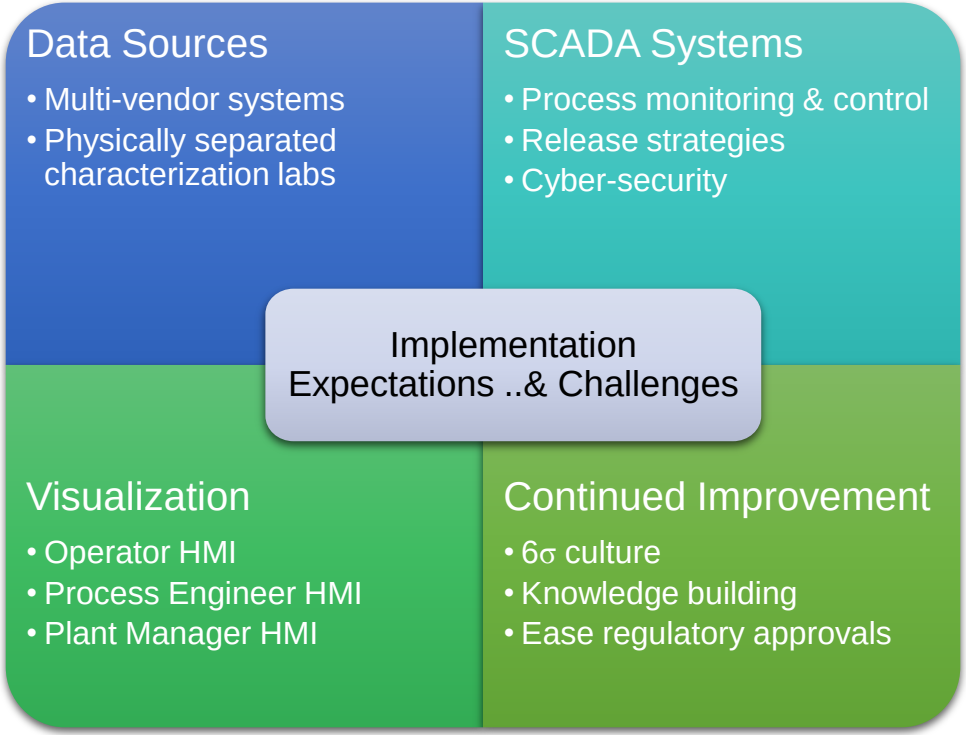
- 5 vendors now offer an integrated solution: GEA, Glatt, Bohle, Powrex, Bosch

Current focus

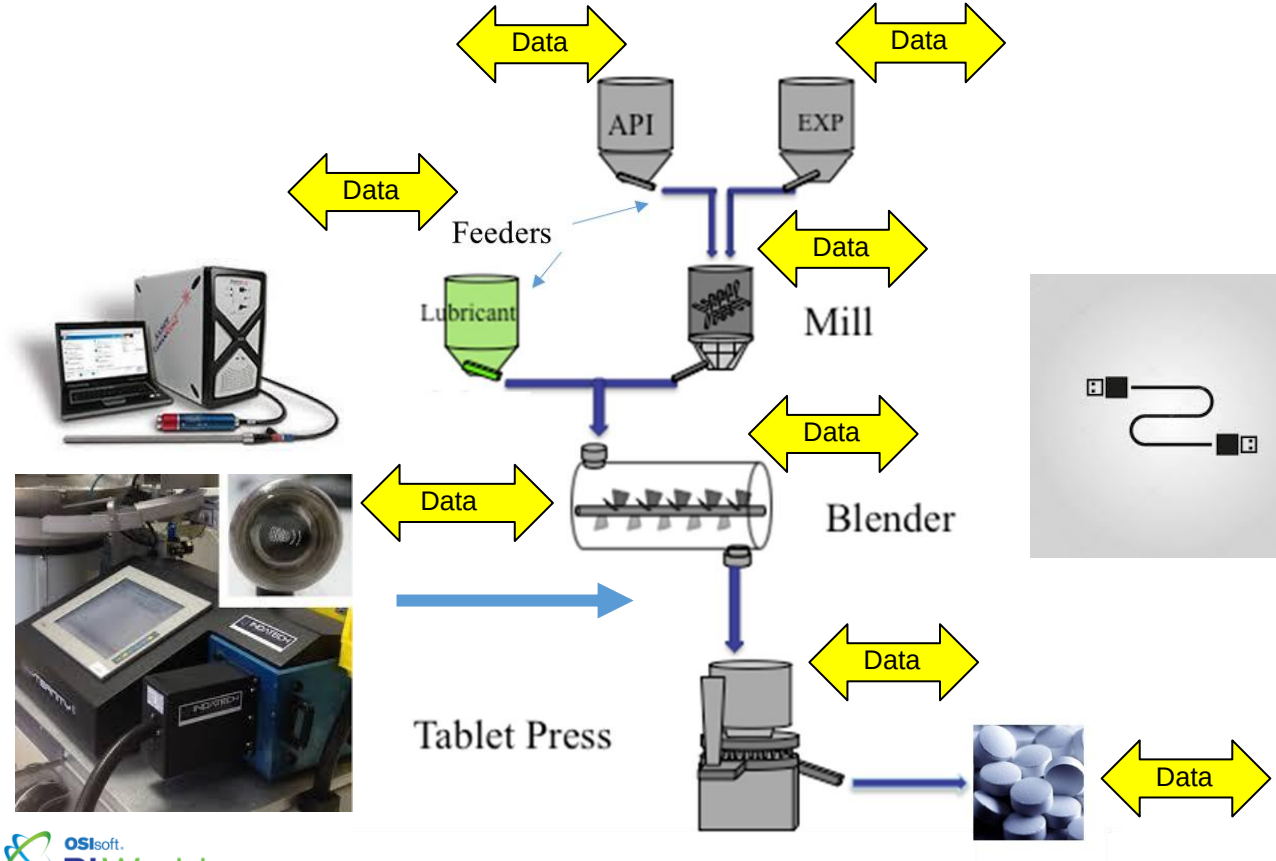
Industry 4.0 in pharma development and manufacturing

- Leverage interconnected systems, process and product knowledge for real-time release testing, process intensification and safety
- Continued Verification & Improvements
- Material tracking
- Risk assessment
- Visualization

Grant U01FD006487 (2018)



Rutgers Direct Compression (DC) CM Line

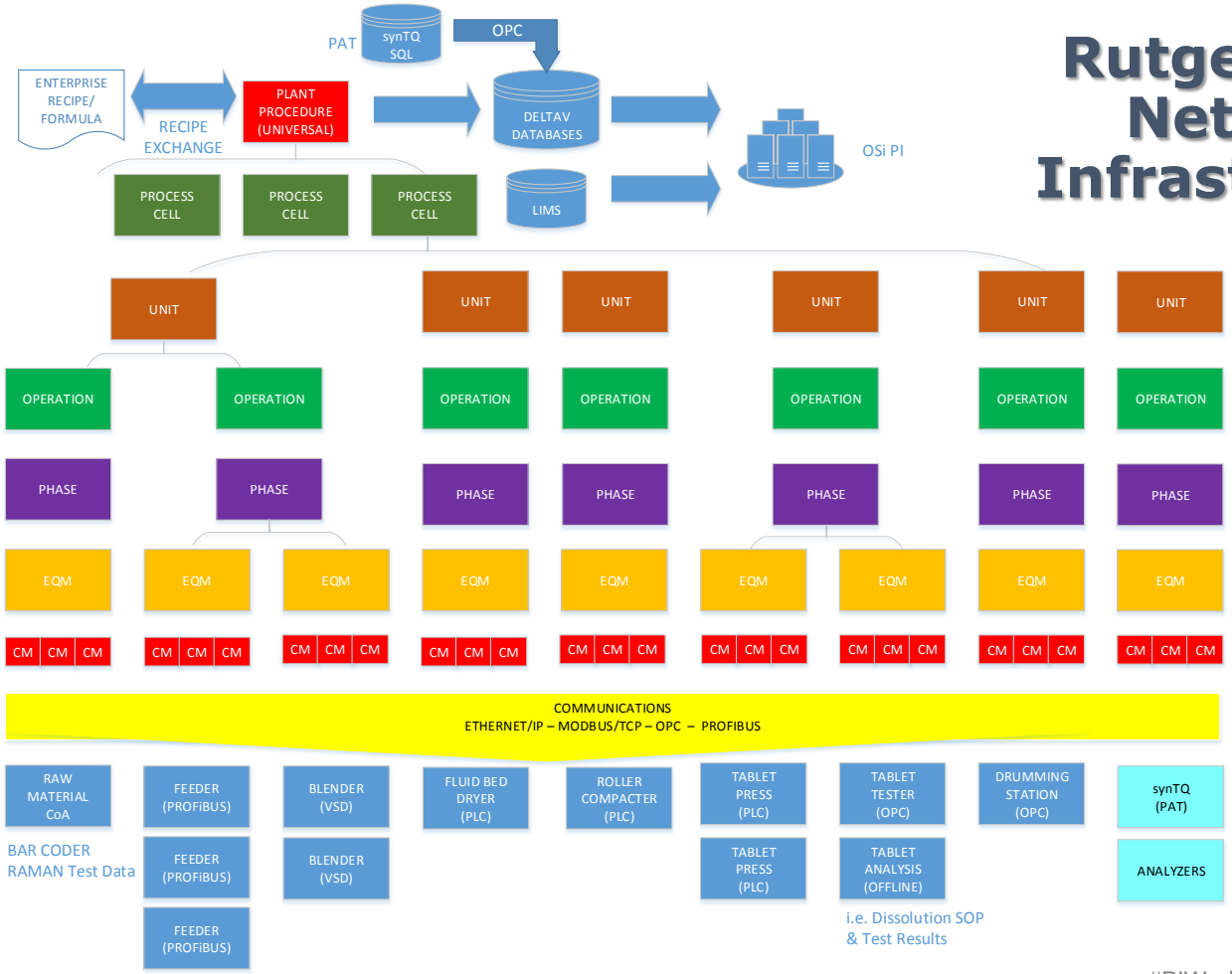


Material Handling
Particle Technology

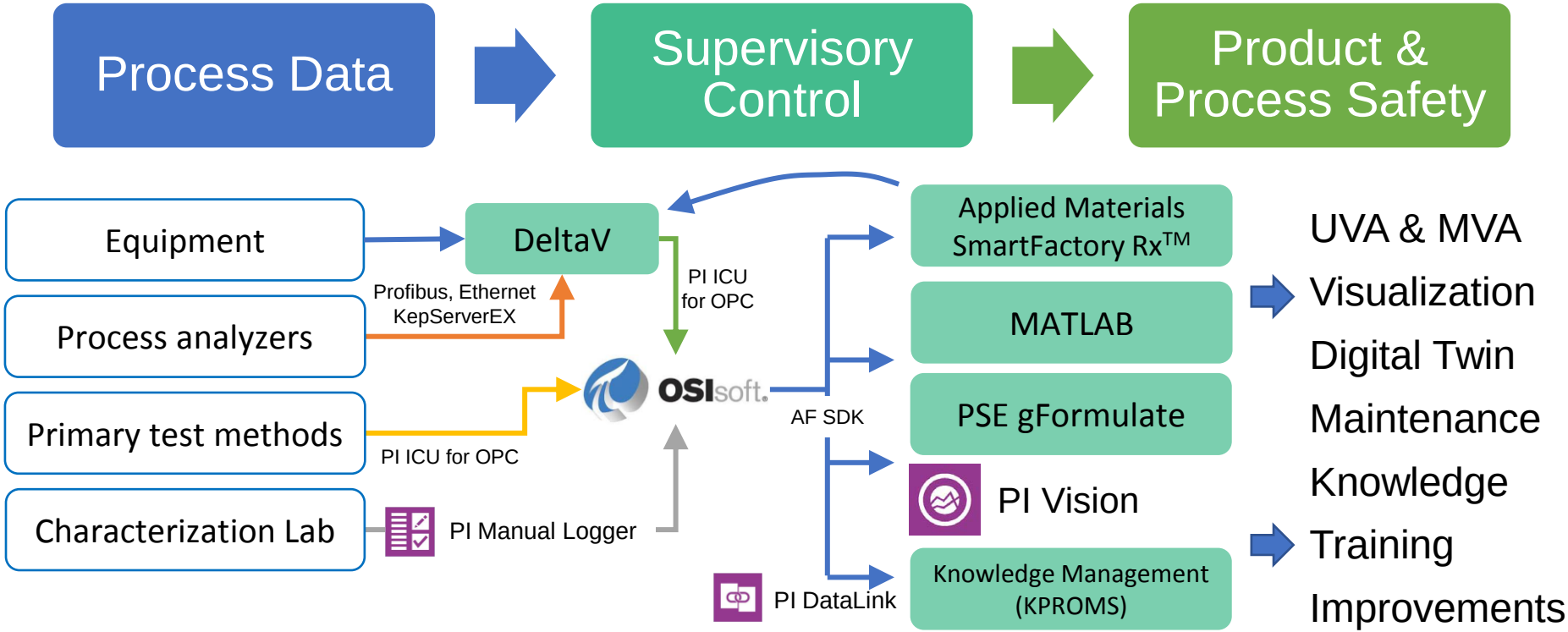
Process
Analyzers
In-line, At-line &
Offline

Process Systems
Engineering

Rutgers Line Network Infrastructure



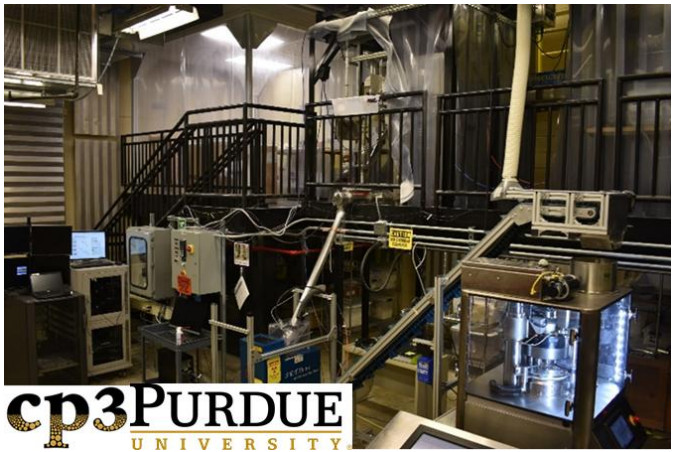
Process operations implementation



Networked following ISA-95

150 YEARS OF GIANT LEAPS™
PURDUE UNIVERSITY

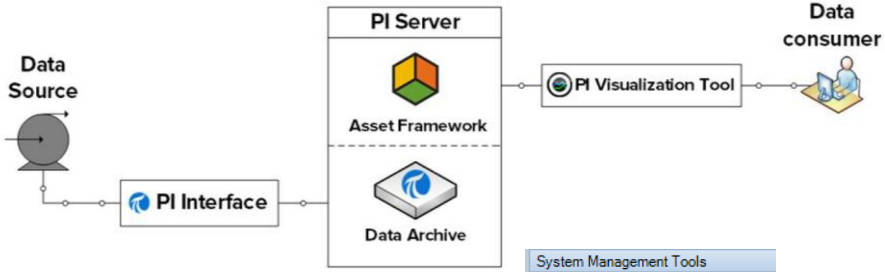
- Davidson School of Chemical Engineering
- Center for Particulate Products & Processes (Purdue CP3)
  - Solids processing research and education
  - Pharma, consumer products, agriculture, chemicals, food, ceramics etc.
  - Solids characterization facility
  - OSD continuous manufacturing pilot plant
- Commissioned PI System in Oct 2018

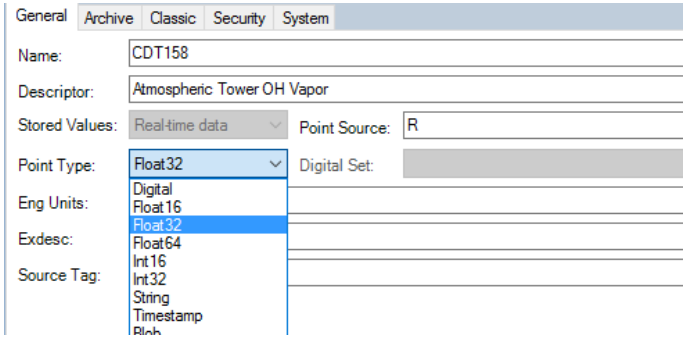


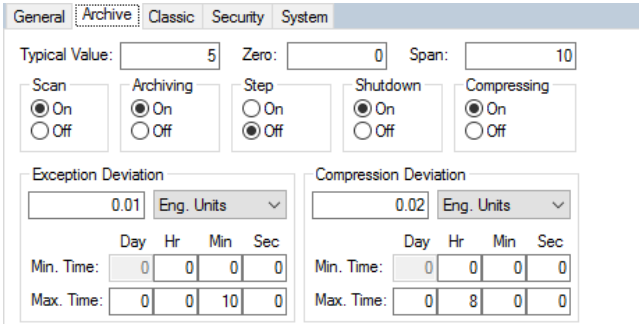
Role of PI System

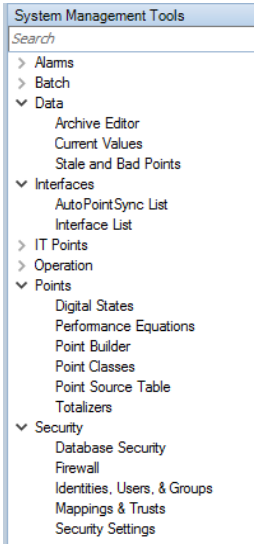
Step 1: Get the data!

- PI SMT, PI ICU
  - Archiving – data source, rate of acquisition, data types, precision
  - Control database access
- PI Manual Logger





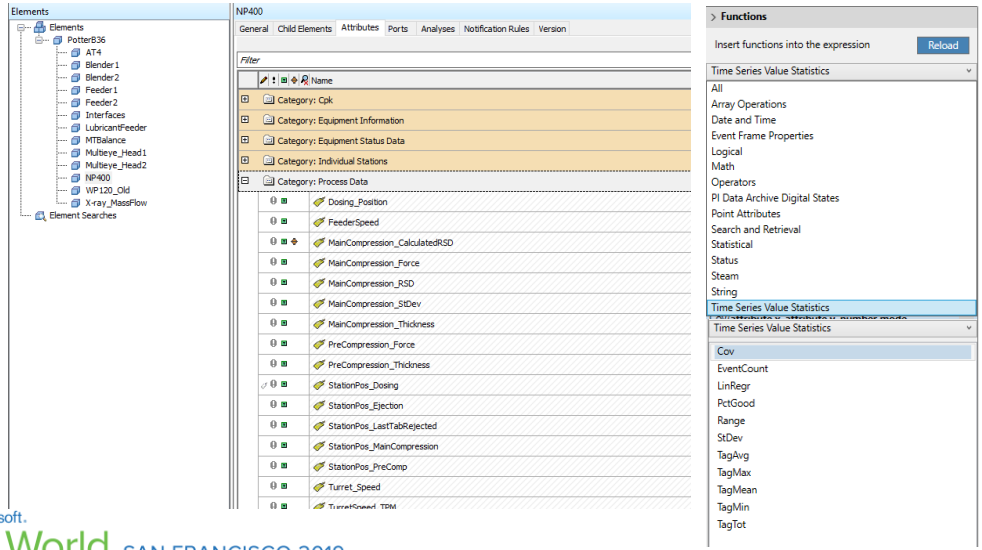


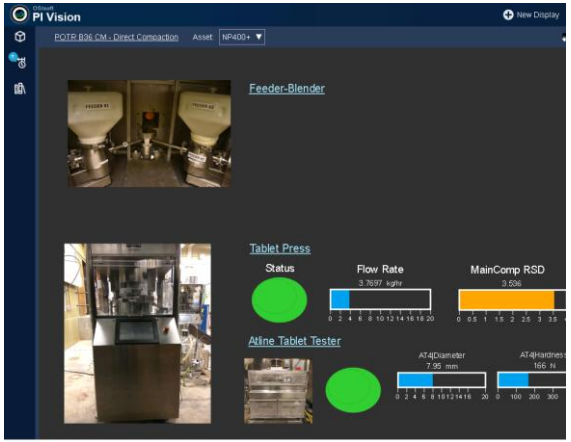


Role of PI System

Step 2: Contextualize the data

- PI Asset Framework
  - Map assets, define events
- PI Vision – real-time visualization





Role of PI System

Step 3: Interface with data consumers for advanced analytics

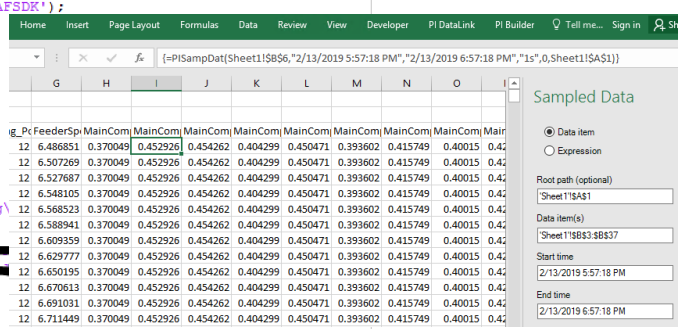
- AF SDK
  - MATLAB
  - Applied SmartFactory Rx™
- PI DataLink in Excel
  - Experimental records
  - Testing new analyses
  - Collaborations, education
- Consistent tag naming helps!

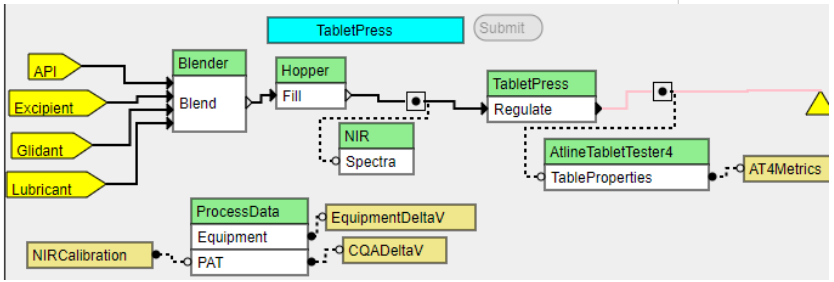
```
%add OSIsoft .NET references to be able to use them
afsdk = NET.addAssembly('OSIsoft.AFSDK');
import OSIsoft.AF.*;
import OSIsoft.AF.Asset.*;
import OSIsoft.AF.Time.*;
import OSIsoft.AF.Data.*;
import OSIsoft.AF.PI.*;
import System.*

% connect to Purdue PI AF server
piSystems = OSIsoft.AF.PISystems;
fprintf('Connecting and refreshing\

af_svr = piSystems.Item('[redacted]
af_db = af_svr.Databases.Item('[redacted]

% confirm database connection
af_db.Refresh();
fprintf('\nConnected\n');
```

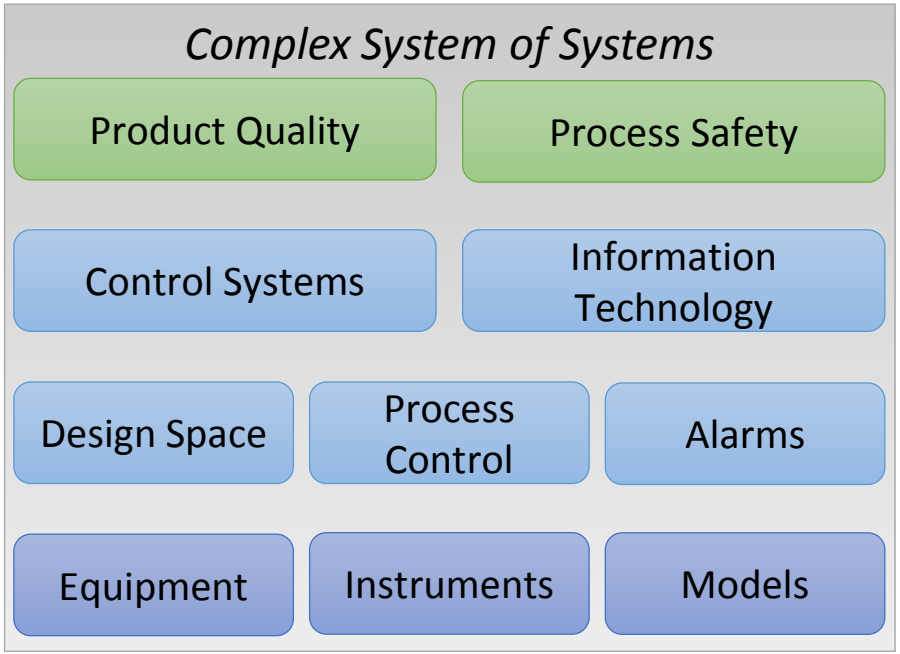




Knowledge Provenance Mgmt. System (HUBZero)

QbD to operational excellence

Reliable process operations in OSD CM



What if… sensors fail?

Failure/gross error causes:
Communication, fouling, orientation, calibration, device life

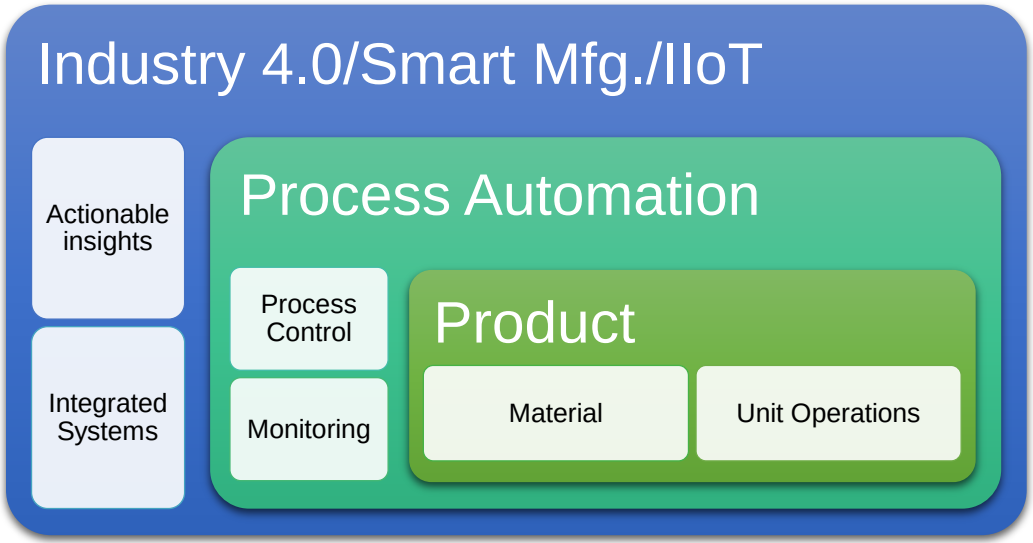
Impacts Quality & Consumer Reach

- Increased offline quality testing
- Diminished competitive advantage
- Limits/Questions use of technology

QbD to operational excellence

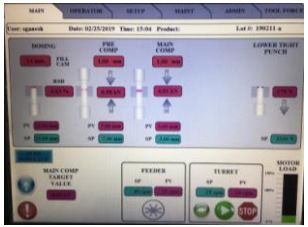
Reliable process monitoring in OSD CM

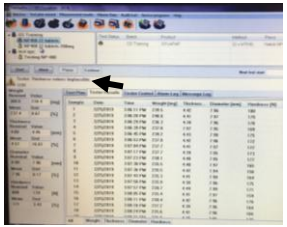
Objective: Condition-based maintenance for sensor network reliability in OSD CM



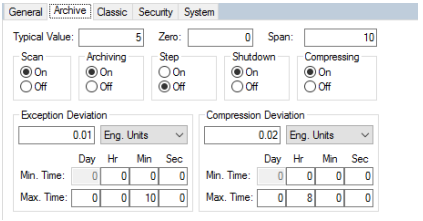
- SPC - UVA & MVA
- Data reconciliation
- Fault diagnosis
- Maintenance action
- Standards & guidelines

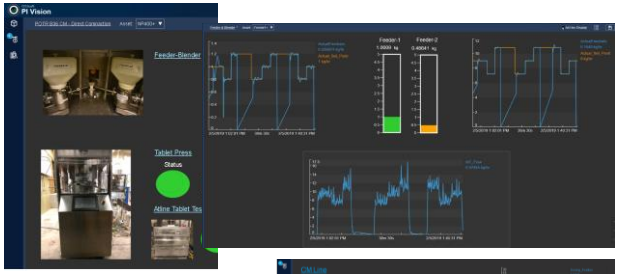
From device data to supervisory strategies

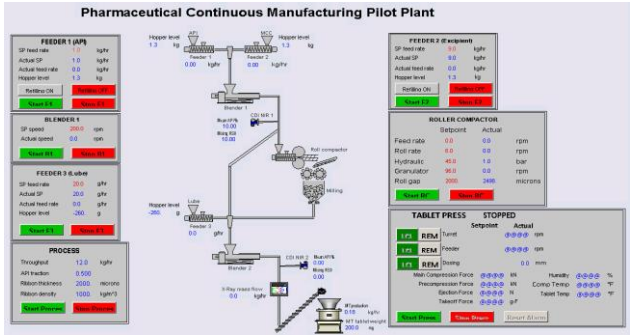




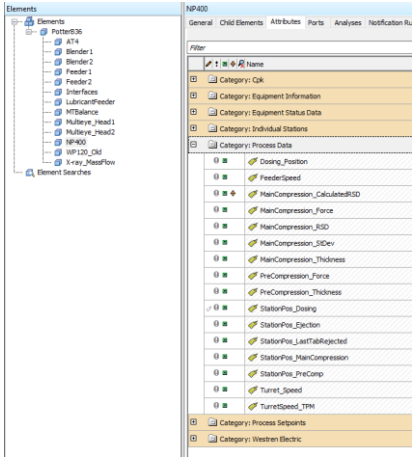
Individual equipment & sensors



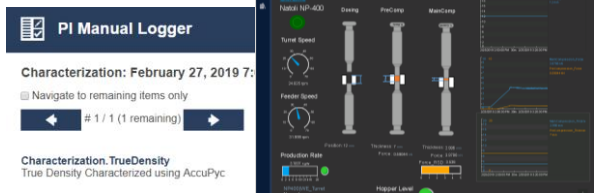


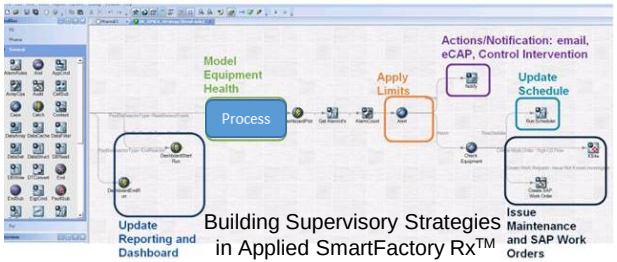


Operations configuration



Setup PI System



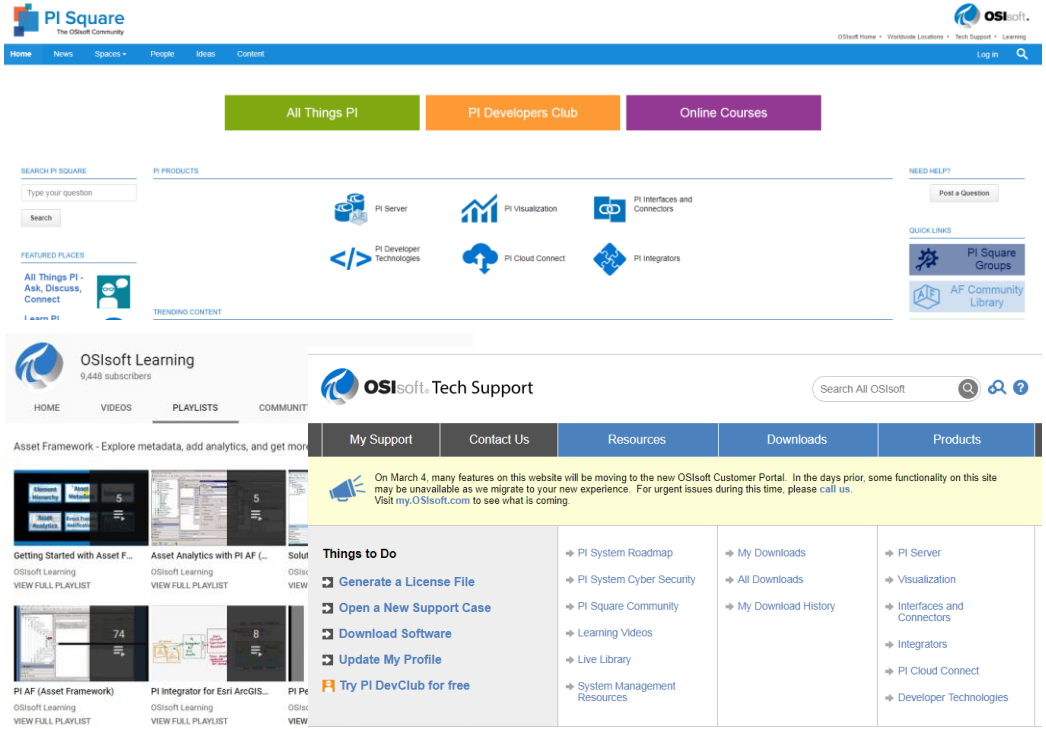


Visualization & additional systems

Setup, training and continued learning

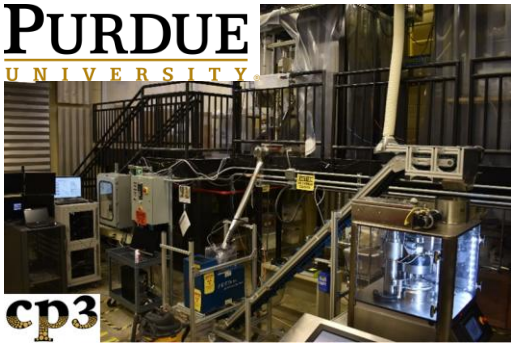
Resources for independent and intuitive learning

- Understand your data
- YouTube
- PI Square training modules
- Documentation
- PI World presentations
- Tech support
- White papers



Purdue University Center for Particulate Products and Processes (CP3)

Process analytics research and education using PI System in OSD CM & solids processing pilot plant



CHALLENGE

Systems Integration & Operational reliability for real-time release in OSD CM systems

- Product quality tracking & release
- Manage systemic risks – sensor & equipment failure, cybersecurity

SOLUTION

PI System commissioned for data integration & enabling advanced analytics

- ICU, Manual Logger, Vision, Asset Analytics, Event Frames, DataLink
- AF SDK used to interface with Matlab, AMAT SmartFactory Rx™

RESULTS

Insights for predictive analytics - supervisory control, release strategies, maintenance etc.

- Advancing pharmaceutical manufacturing
- Data science research & education using real-world examples

Acknowledgement

- OSIsoft Academic Team - Mike Mihuc, Erica Trump
- OSIsoft Tech Support
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  - Profs Rex Reklaitis, Zoltan Nagy
- Our supporters and partners, and the community interactions

PI System in Continuous Pharmaceutical Manufacturing

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Questions?

Please wait for the **microphone**

State your **name & company**

Please remember