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
- Flow, Bulk Density, Angle of Repose

Integrated Process Model
"Flowsheets"

Experimental & Design Parameters
- $y = f(x,a,t,m,n)$
- $\frac{dy}{dt} = g(x,a,t,m,n)$

Unit Ops Models
- Feeders

Predictive Modeling
- Mass Flow Rate vs Time

Control Design
- Disturbance Repetition

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• FDA actively promoting it (advanced controls and enhanced process understanding required), strong proponent, draft guidance document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

Process Systems
Engineering

Data

Data

Data

Data

Data

Data

Data
**S95 Overall Architecture**

- **Level 4**: ERP/EDW
- **Level 3**: Eco System
  - MES
  - Historian
  - LES
  - LIMS
  - ELN
- **Level 2**: PCS
  - CDS / Lab Systems
- **Level 1/0**: Process Instruments
  - Lab Instruments

**Acronyms**
- 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
LES: Laboratory Execution System
LIMS: Laboratory Information Management System
MES: Manufacturing Execution System
PCS: Process Control System

Recipe
S88/S95 ‘Big Data’ Recipe Architecture

Recipe Warehouse

- **Level 5**: Visualizations
- **Level 4**: Analysis
- **Level 3**: Aggregation
- **Level 2**: Recipe
- **Level 1/0**: Lab Instruments, Process Instruments, CDS / Lab Systems

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
- Raw material characterization
- API feeder
- Excipient feeder
- Lubricant feeder
- Mill
- Blender
- Hopper
- Tablet compressor
- Tablets
- Coater
- Dissolution test

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.

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

• Excel file parsing
• Recipe conversion and output
• Equipment and material management
• Barcode generating and printing
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
Data Flow in Pilot Plant

Level 3

Level 2

Level 1

ISA-88 Recipe Model

Cloud Storage

Process Control System

Process Equipment

PAT Data Management

PAT Sensor
DeltaV Recipe Model
OSI-PI Recipe Structure

PI system structure
PI Asset Framework

PI AF explorer
PI Event Frame

Recipe Structure

PI EF explorer
PI Vision
Individual equipment & sensors

Operations configuration

Setup PI System

Visualization & additional systems

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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.
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