



Lab to Patient Model Implementing a Recipe Based Framework to Support Product Lifecycle Management

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AGENDA

- The Burning Platform
 - Product Lifecycle Management
- Why & What of Recipe Framework
 - Content/Execution/Visualization
- What does success look like ?
- Transformation Needed
 - Not Just A Pharma Problem
 - How OSI Can help ?

My Journey with Recipe and How PI Fit In ?

Early 1990s - **POINTS**

- Excitement over 500, 2000 or more points
- Worrying what/why to promote to PI
- OSI – EA

Mid 1990s – **PLANTS**

- Utility & Alarm Monitoring
- Running Plants More Efficiently
- OSI – EA

Late 1990s/Early 2000s – **PROCESS**

- **S88** Standards for Select Process Segments (API)
- OSI - Process Book & EVT (Satyam !!)

My Journey with Recipe and How PI Fit In ?

The 2000s - **Batch**

- S88 Expanding into Other Areas (Drug Product)
- S95 Starting to Drive Interface Standards
- “Review by Exception”
 - non Process Data Needed to Release Batches
- OSI – Rt Reports, AF

Today – Product Life Cycle Management

- Need End to End Visibility of Product
 - From R&D Thru Commercial
 - From Raw Material to Patient
 - OSI - ???

The Numbers Game

➤ > 200

➤ > 2000

➤ >18000

➤ 29

➤ 130

➤ 0

Individual Product Families

SKUs

Raw Material SKUs

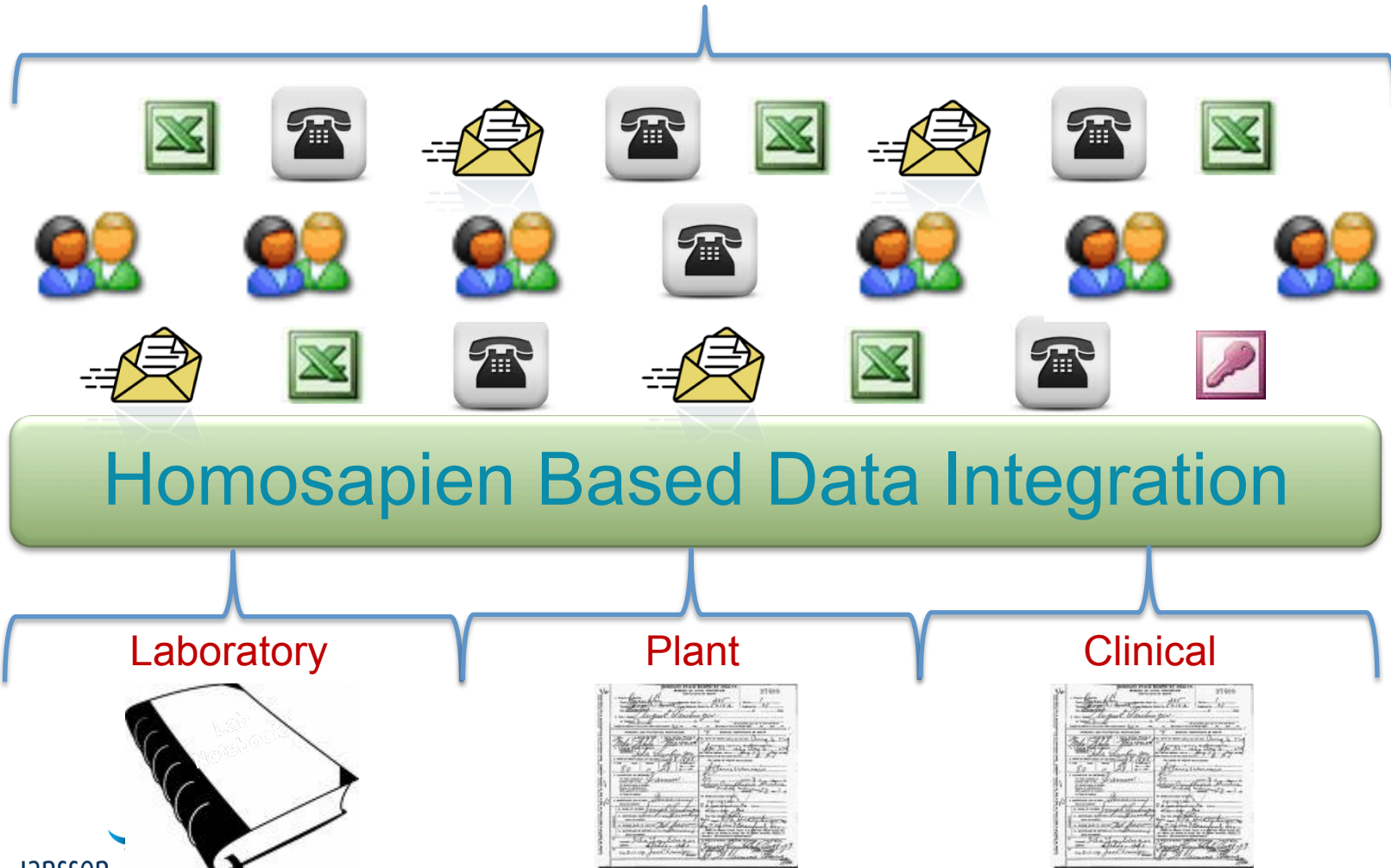
Internal Sites

External Sites

Products Made all Internally

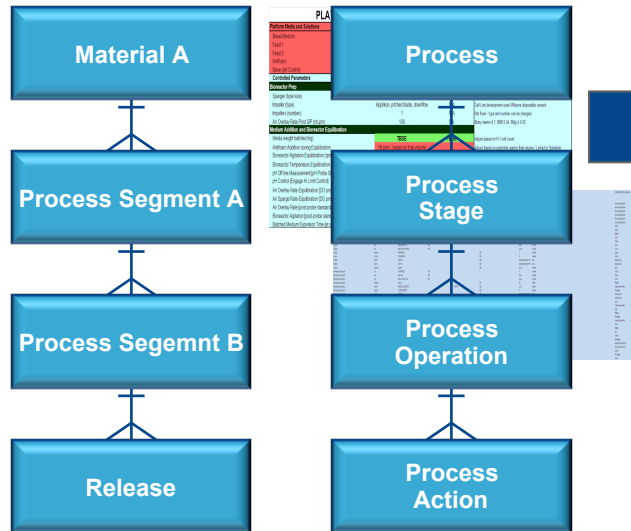
	External Mfg	Procurement	Total
# of Partners	108	480	588
# of Sites	130	614	744
# of SKUs	2000	18,000	20,000

Our Response To Date



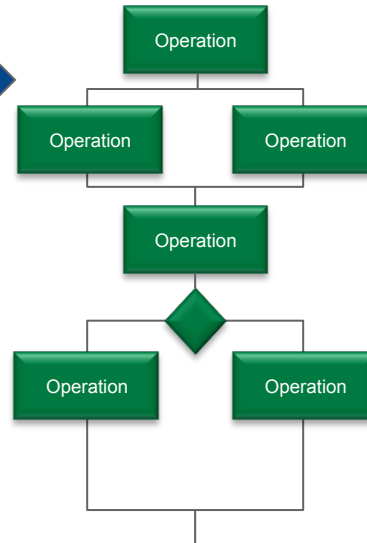
Recipe Framework

Content



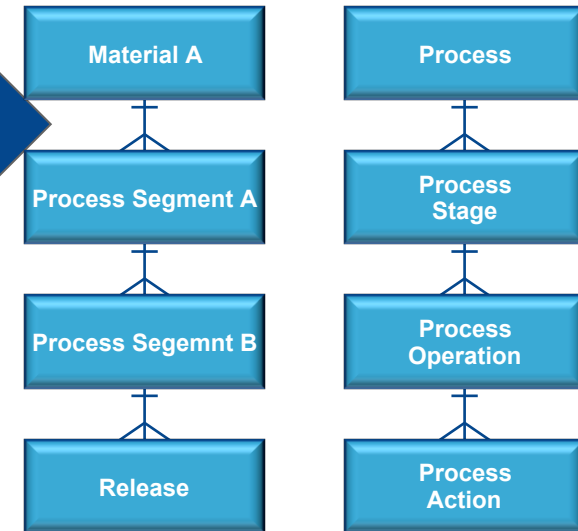
Product & Process Libraries

Execution



Recipe Based Workflows Lab & Plant

Visualization



Product & Process Analysis/Models

Consistent S88 Structure

Lab to Patient Execution Model – What does success look like ?

- End to End reproducible execution and therefore quality review by exception
 - Processes defined and orchestrated in a standard manner tied to regulatory filing
 - Checks and balances to ensure that the orchestration is completed as per agreed-to protocols
 - Practiced on all manufacturing floors, laboratories and clinical sites
 - End to End – From R&D thru Commercial
 - End to End – From raw material to Patient
 - Data not Document Centric
- CPP/CQA of Product and Safety/Efficacy data from clinical in context for QbD
- Process Defined by a Recipe from Global Library of Products, unit operations, equipment & materials
- Integration of information between systems will be implemented using industry standards (S95) – KISS
- Start-up and implementation will be order of days not years ! Product not system engineering focused !
- Reduction in SOPs since activities now expressed as modular/repeatable S88 unit procedures
- Real-time access to events and data for production review (troubleshooting, process optimization, etc.)
- Real Time Quality review (recurring issues, batch release, etc.)

Linkage to QbD: ICH Q8-Q11

- A harmonized pharmaceutical quality **system** applicable across the **life cycle** of the product emphasizing an **integrated** approach to **quality risk management and science**
 - New ICH guidelines (High level guidelines, more visionary, less prescriptive, flexible regulatory approaches)
 - Pharmaceutical Development (Q8)
 - Quality Risk Management (Q9)
 - Pharmaceutical Quality Systems (Q10)
 - Continuous Validation (Q11)
- Focused on defining **design space** and proposed methods to ensure product is maintained in the intended multivariate specifications



Product & process

Critical Parameters & Steps

Structured in S88 Format

3.2.5.2.1 Description of Manufacturing Process and Process Controls

Figure 1: Preparation of Formulated Bulk

Process Steps	In-Process Control ^a
Stage 1 Preculture and Expansion	Microscopic examination
Stage 2 Bioreactor Production	Mycoplasma, Acidfastness, Bioterrorism, Endotoxin
Stage 3 Direct Product Capture (DPC)	Bioterrorism, Endotoxin, ATP, pH, Protein concentrations
Stage 4 Thaw and Pooling of DPC Isolates	Bioterrorism, Endotoxin
Stage 5 Low pH Hold	Bioterrorism, Endotoxin
Stage 6 Cation Exchange Chromatography	Bioterrorism, Endotoxin

2. BIOREACTOR

2.1. Stage 2. Bioreactor Production

Stage 2 is in phase 3 clinical production process is the growth of C137B cells and production of unimatrix in the 100L+ perfusion bioreactor, as described in Figure 3.

Figure 3: Process Flow Diagram

```

graph TD
    A[Inoculate the production bioreactor to a target seedling volume (cell density of 4x10^6 VCM). Test postconcentration volume of 100] --> B[Fed with CB8-417 and initiate ATP perfusion. Withdraw harvest control the bioreactor volume at a target of 1000L.]
    B --> C[On Day 7 switch feed to CB8-G medium.]
    C --> D[Terminate the production bioreactor Day 50 postinoculation.]
    D --> E[Operation]
    E --> F[Operation]
    F --> G[Operation]
    G --> H{ }
    H --> I[Operation]
    H --> J[Operation]
  
```

3.2.5.2.2 Description of Manufacturing Process and Process Controls

3.2.5.2.3 CONTROL OF MATERIALS

f. RAW MATERIALS

Table 1: Compendial Raw Materials

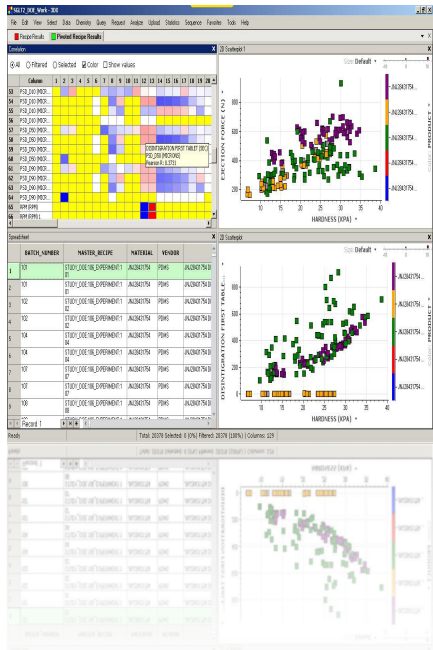
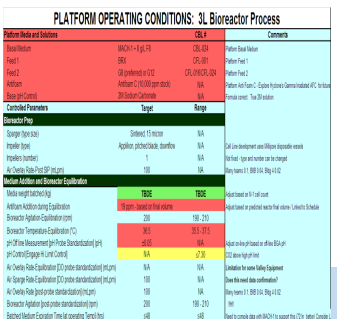
Raw Materials	Compendial Codes
Amino Acids: Glutamic Acid	C137B, Inc.
Citric Acid Monohydrate	C137B, Inc.
Glycerol	C137B, Inc.
Oxygen Liquid	C137B, Inc.
Potassium Phosphate (K ₂ HPO ₄)	WATCO, Inc.
Proteinase K	C137B, Inc.
Sodium Acetate Trihydrate	C137B, Inc.
Sodium Calcium Oxide/Bicarbonate	WATCO, Inc.
Sodium Chloride	C137B, Inc.
Sodium Citrate Dihydrate	C137B, Inc.
Sodium Hydrogen Carbonate	C137B, Inc.
Sodium Hydroxide	C137B, Inc.
Sodium Phosphate Dibasic Dihydrate	C137B, Inc.
Sodium Phosphate Monobasic Monohydrate	C137B, Inc.
Sulfuric Acid	Rohm & Haas Co.
Sodium Salt of Ethylenediaminetetraacetic Acid (EDTA)	C137B, Inc.
Transferrin (Tn)	C137B, Inc.
Water for Injection (WFI)	C137B, Inc.

Site Executable Recipe

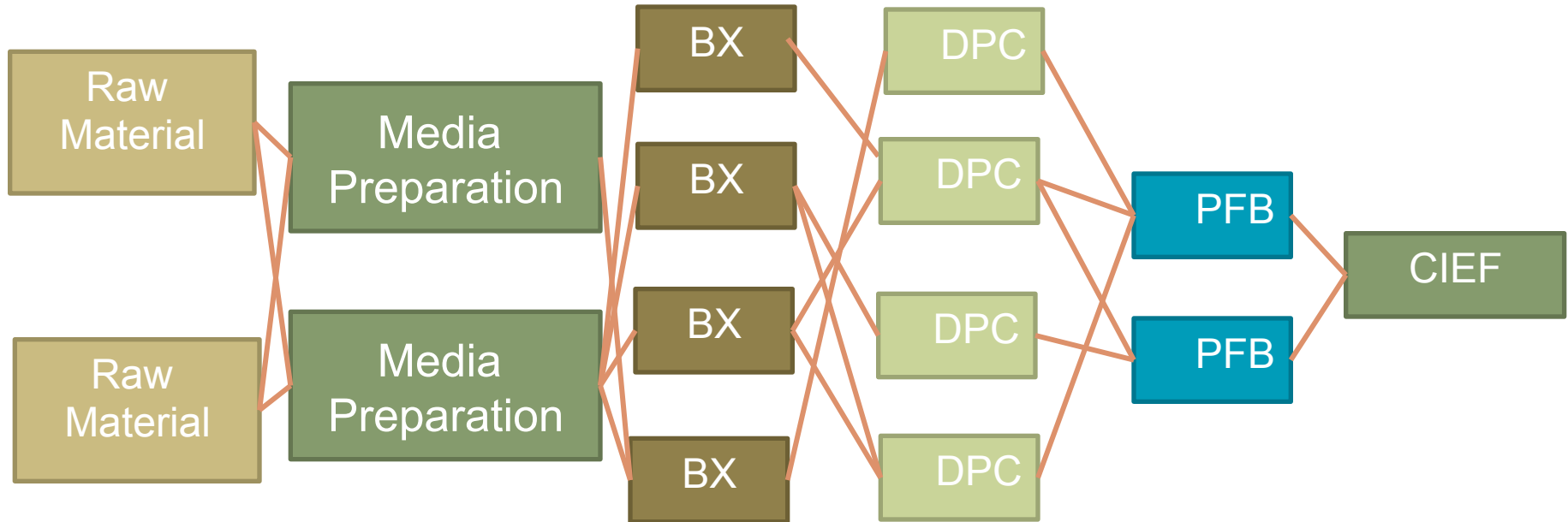
EXECUTION
Data generated in S88 Format
Contains additional site details

VISUALIZATION

- Critical Parameters & Steps
- Context rich data

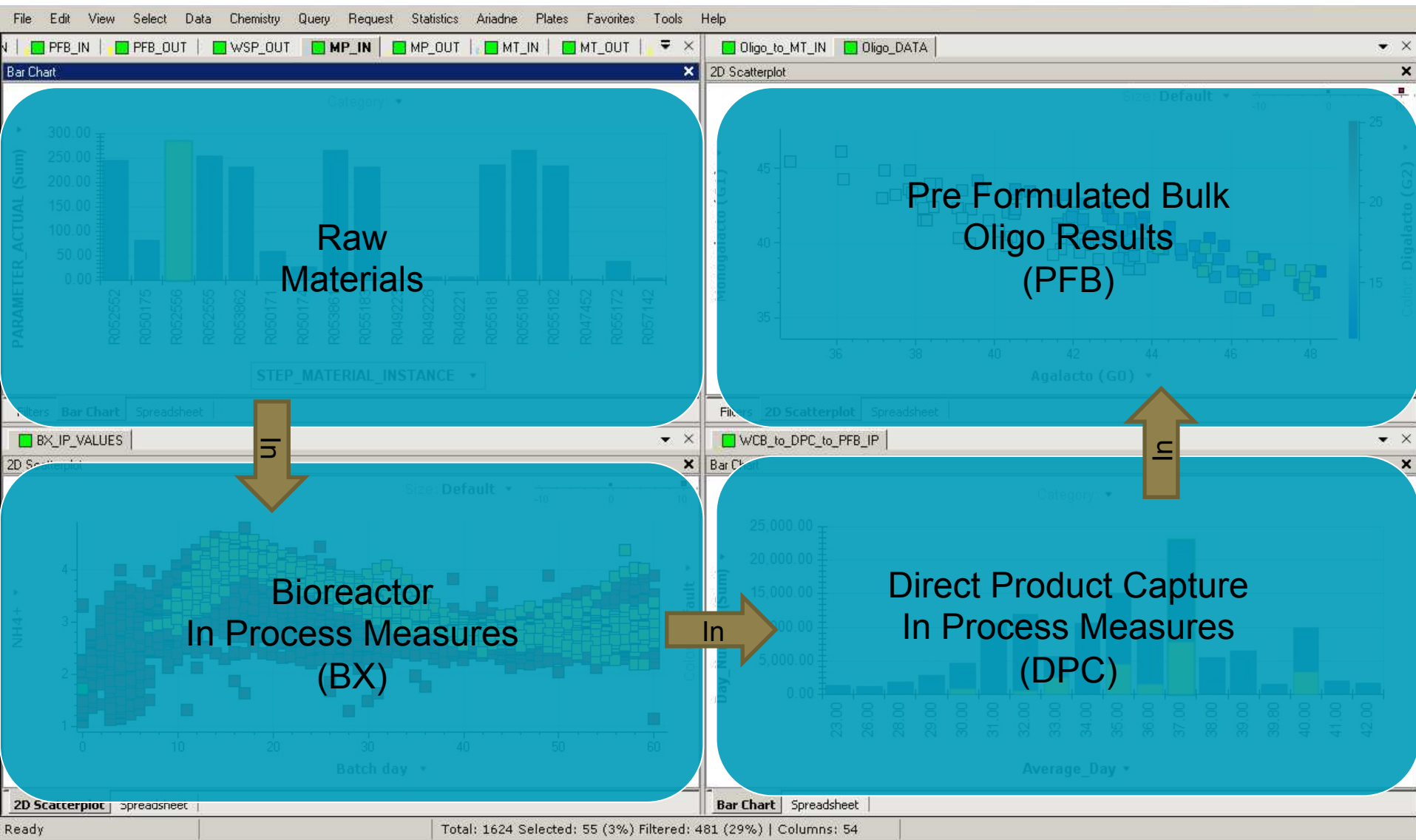


Recipe Framework Enables Genealogy Insight

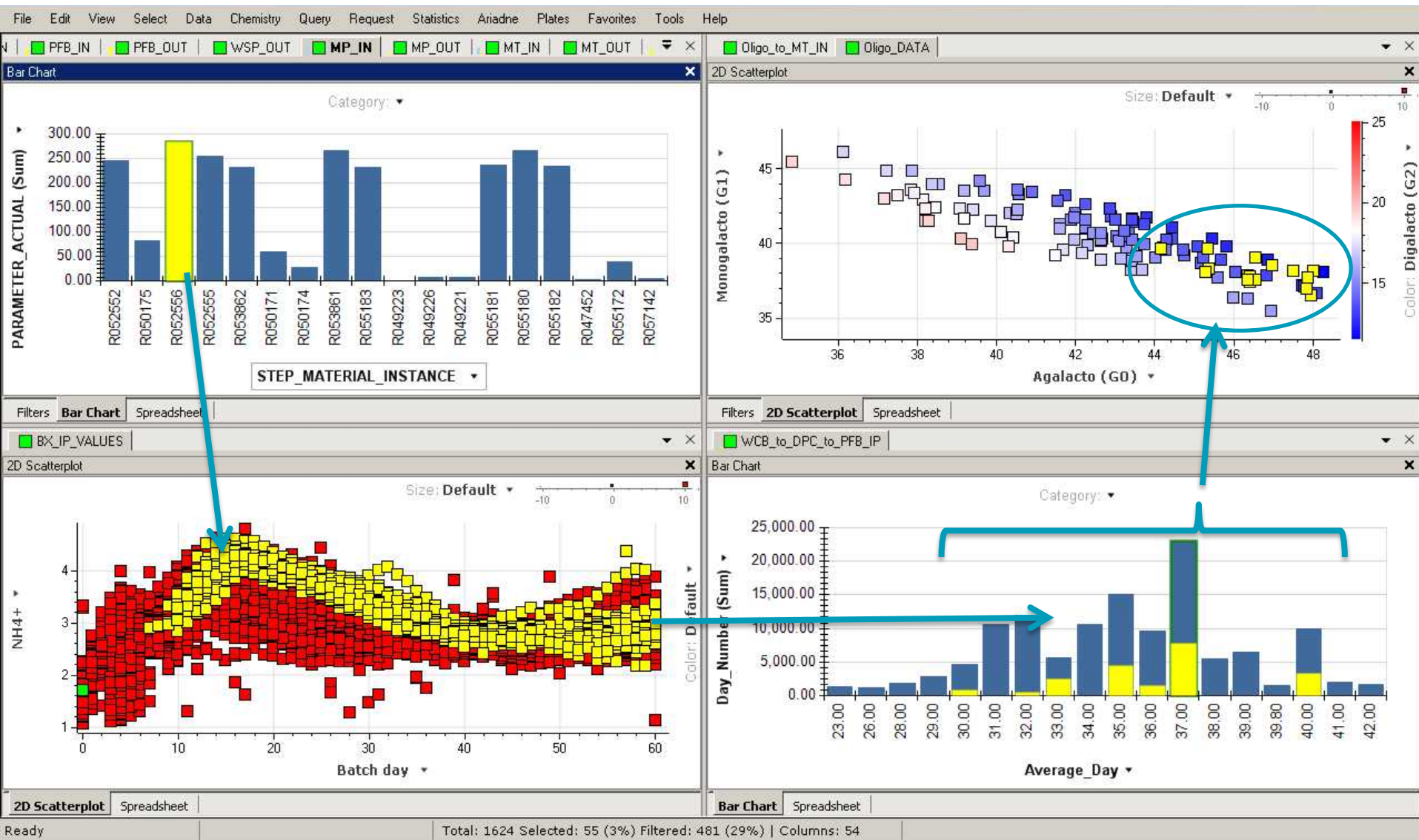


- Linking results from QC lab to Raw Material inputs +
 - Multi site implementation+
 - In process equipment variations +
 - In process analytical measures (Bioreactor, DPC performance)

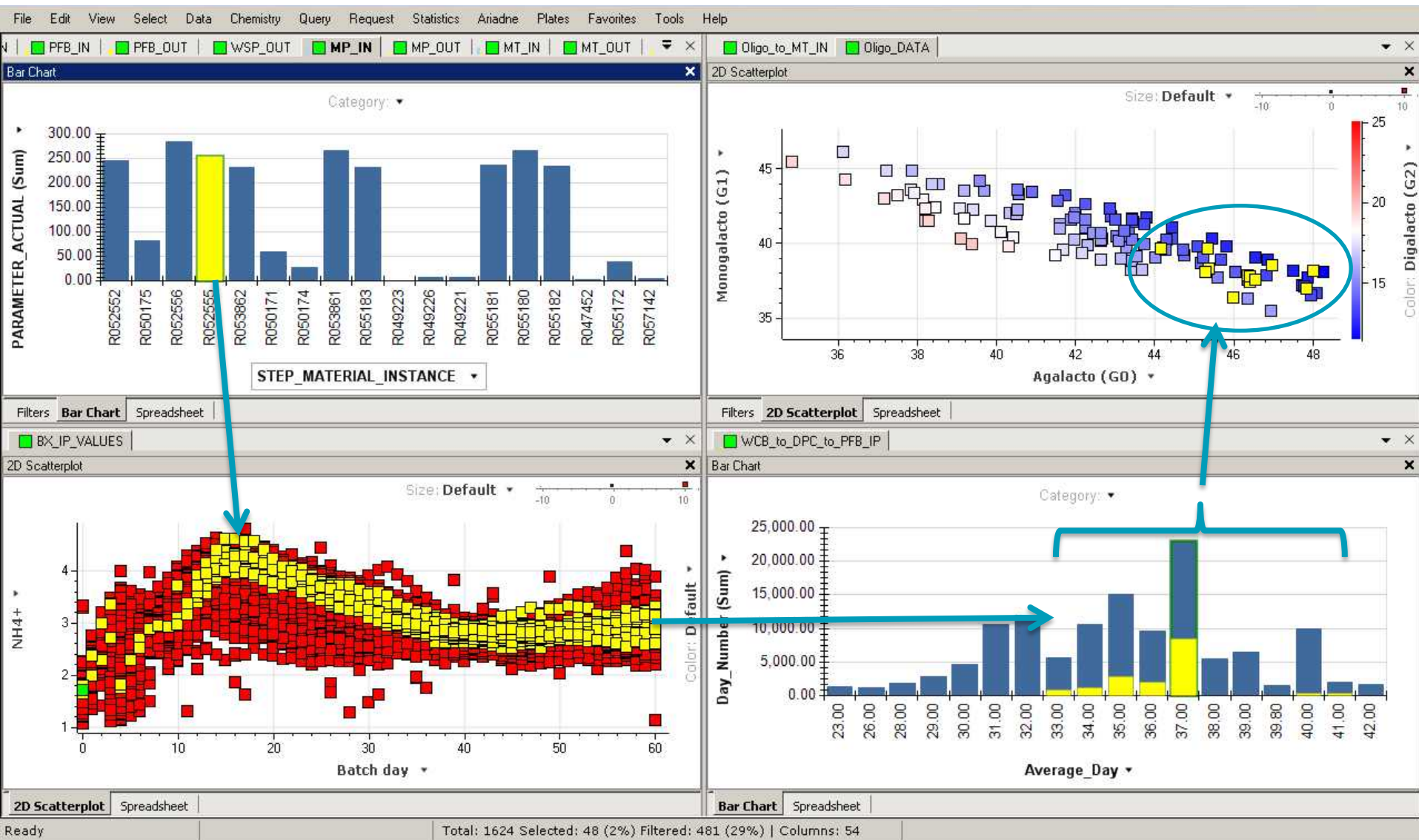
Interactive Control Panel



Interactive Control Panel

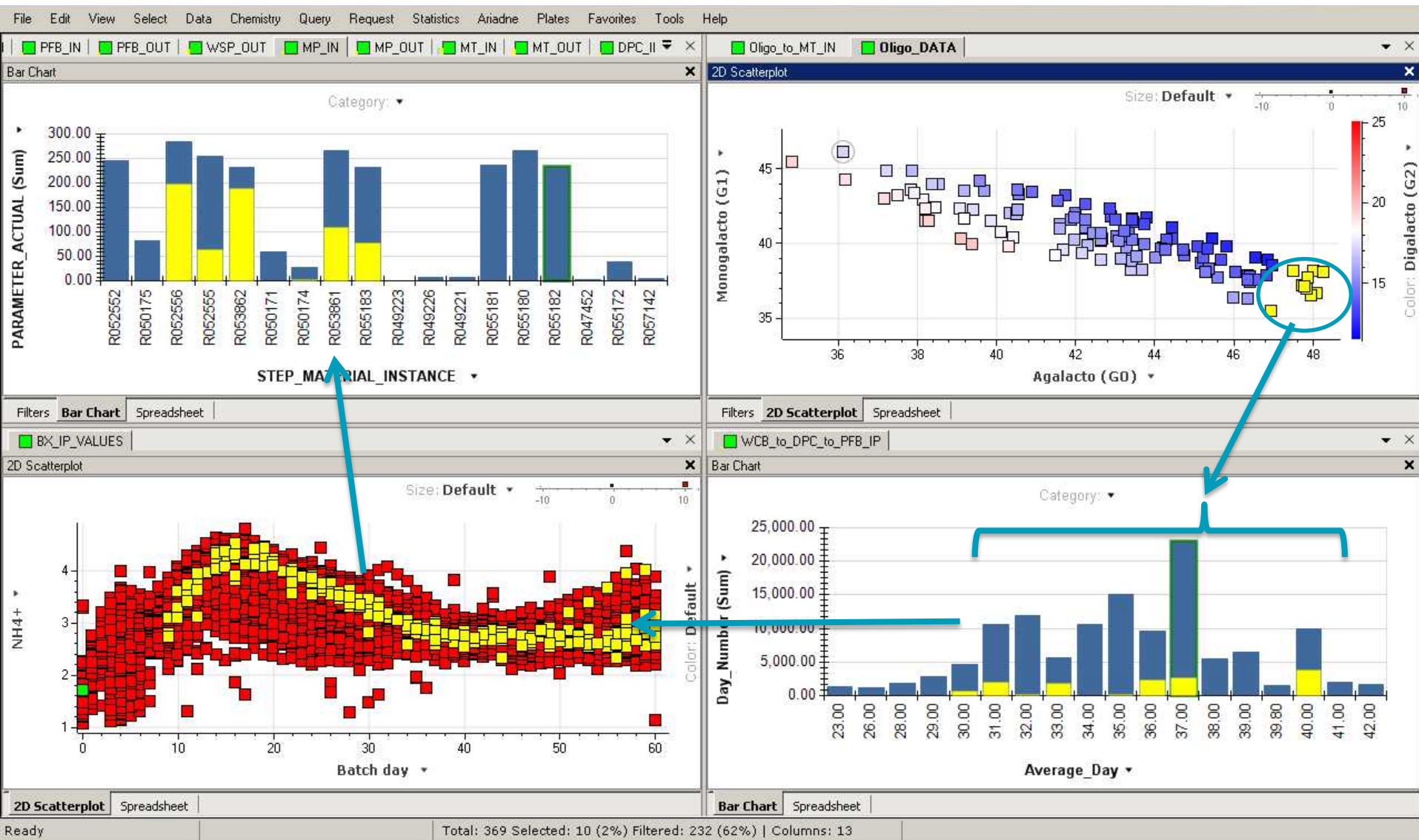


Interactive Control Panel



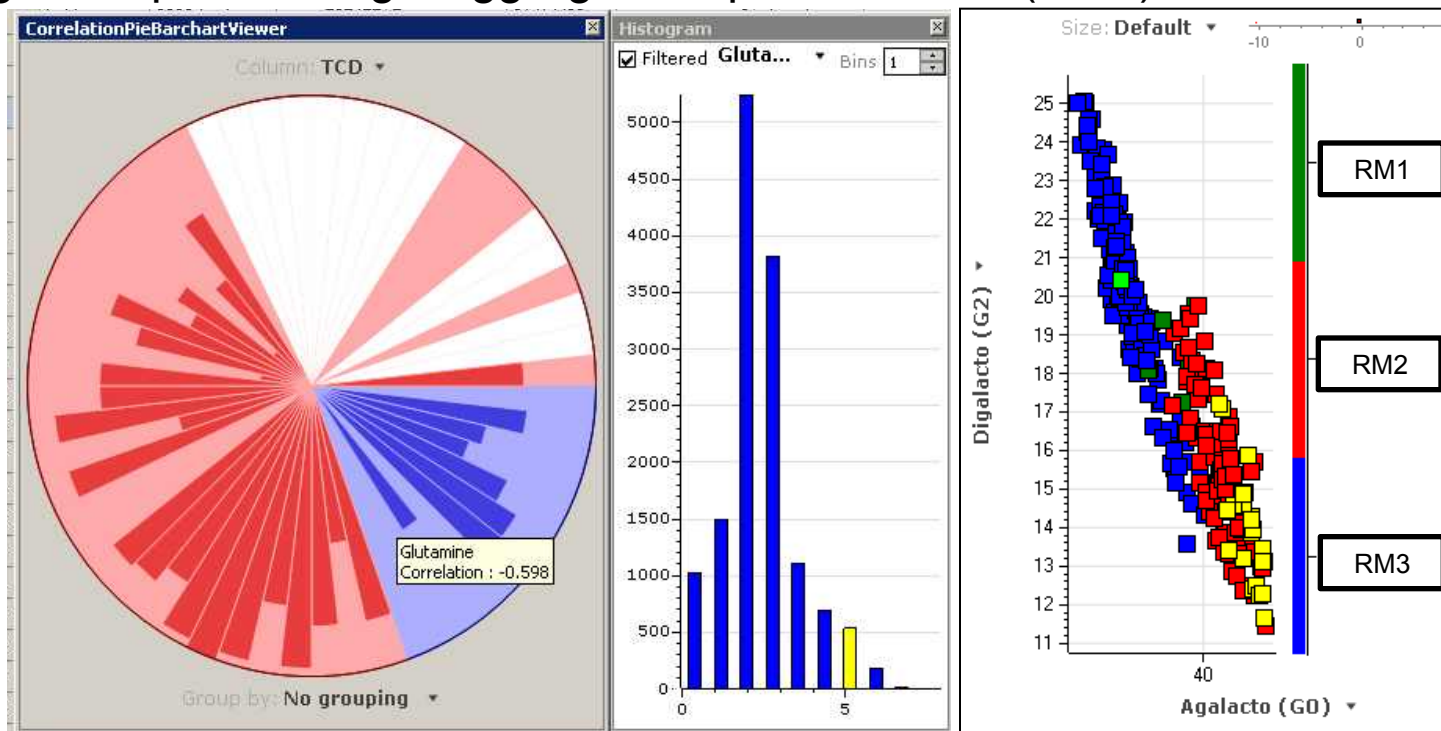
Interactive Control Panel

We can go in Reverse!



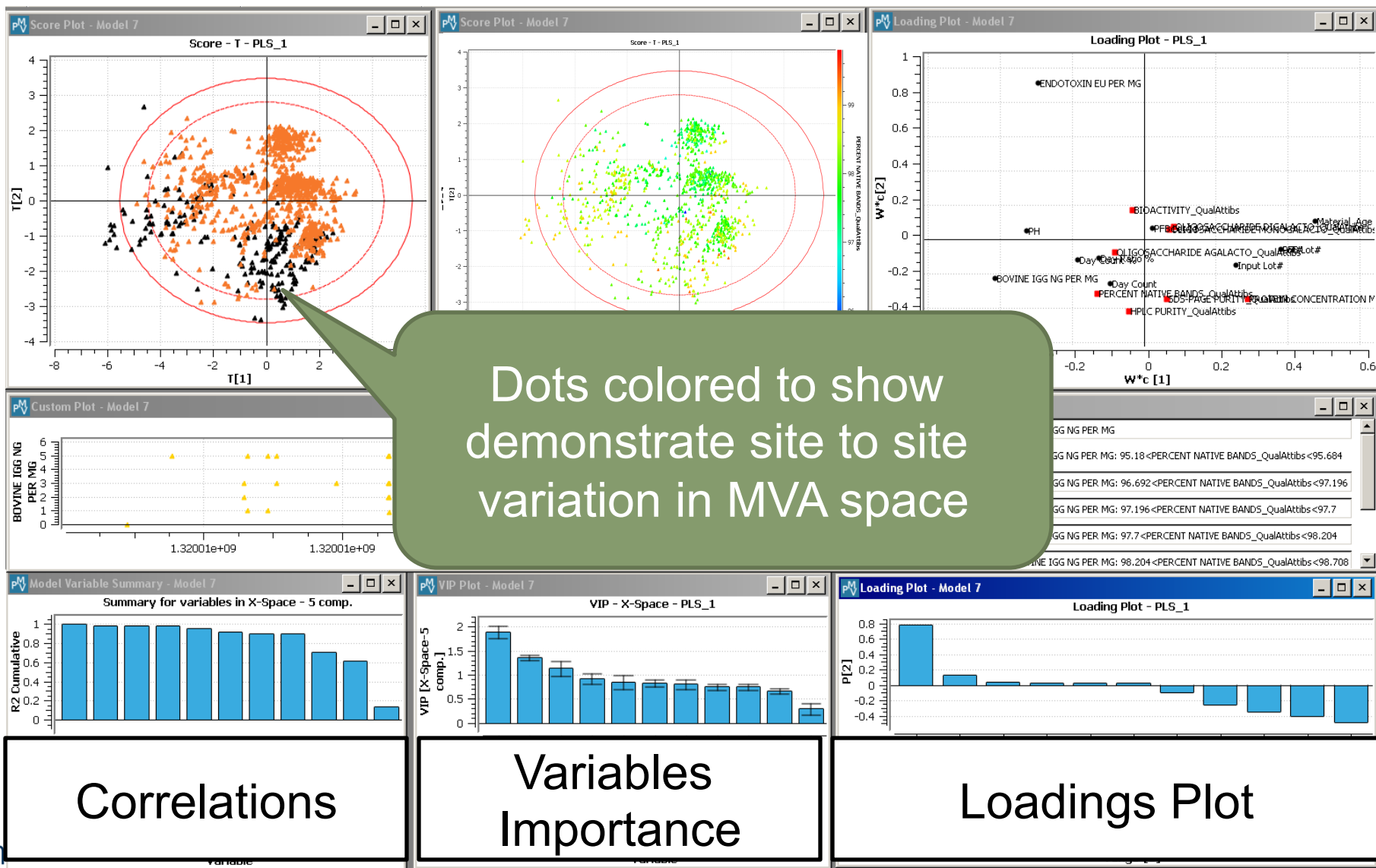
Enabling Multivariate Analysis

Figure depicts Biologic aggregated upstream data (VCD) and downstream quality



- Get the scientists/engineers focused on analyzing the data ... not finding and aggregating
- Lot's to learn ... multivariate analysis is easy to say, it is harder to REALLY comprehend.

MVA Dashboard for the brave!



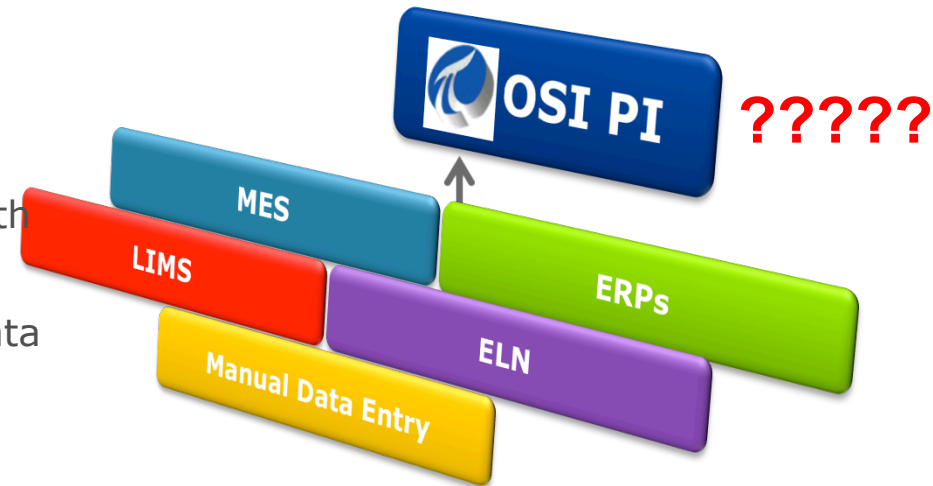
Looks Simple Enough !! What's Missing ?

- Content
 - No Product and Process Libraries
- Execution
 - Disparate systems, non standards based
- Visualization
 - Data to feed Tools, skillsets to digest, etc
- Ability to do C/E/V across multiple sites both internal and external to the company

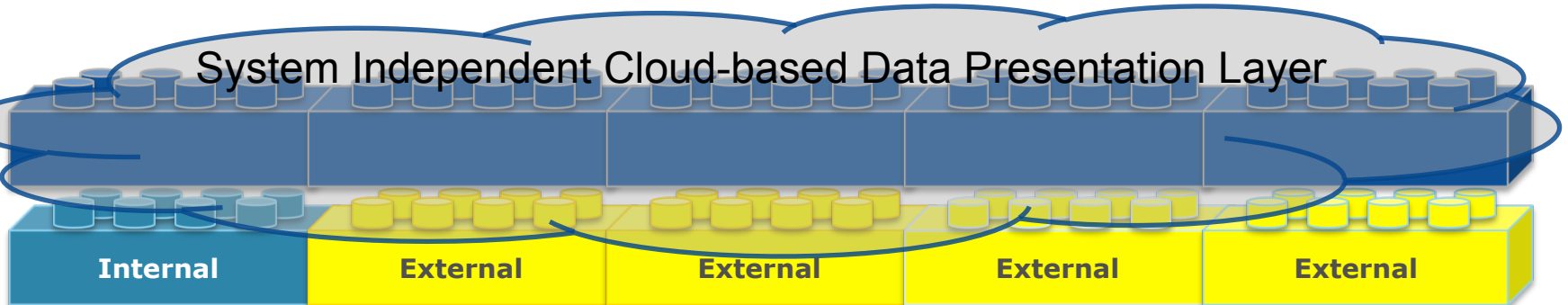
How can OSI Help Change the Game ?

Data Aggregation Across Products, Process Segments, Companies and Industries !

- Very disparate systems landscape – now including MES, ELN, Manual Data Entry...
- Ability to share contextualized process data with internal and external partners is critical
- Require capability to capture and aggregate data for visualisation, reporting & analysis



System Independent Cloud-based Data Presentation Layer



Answering any and all questions of interest !!!

Conclusions:

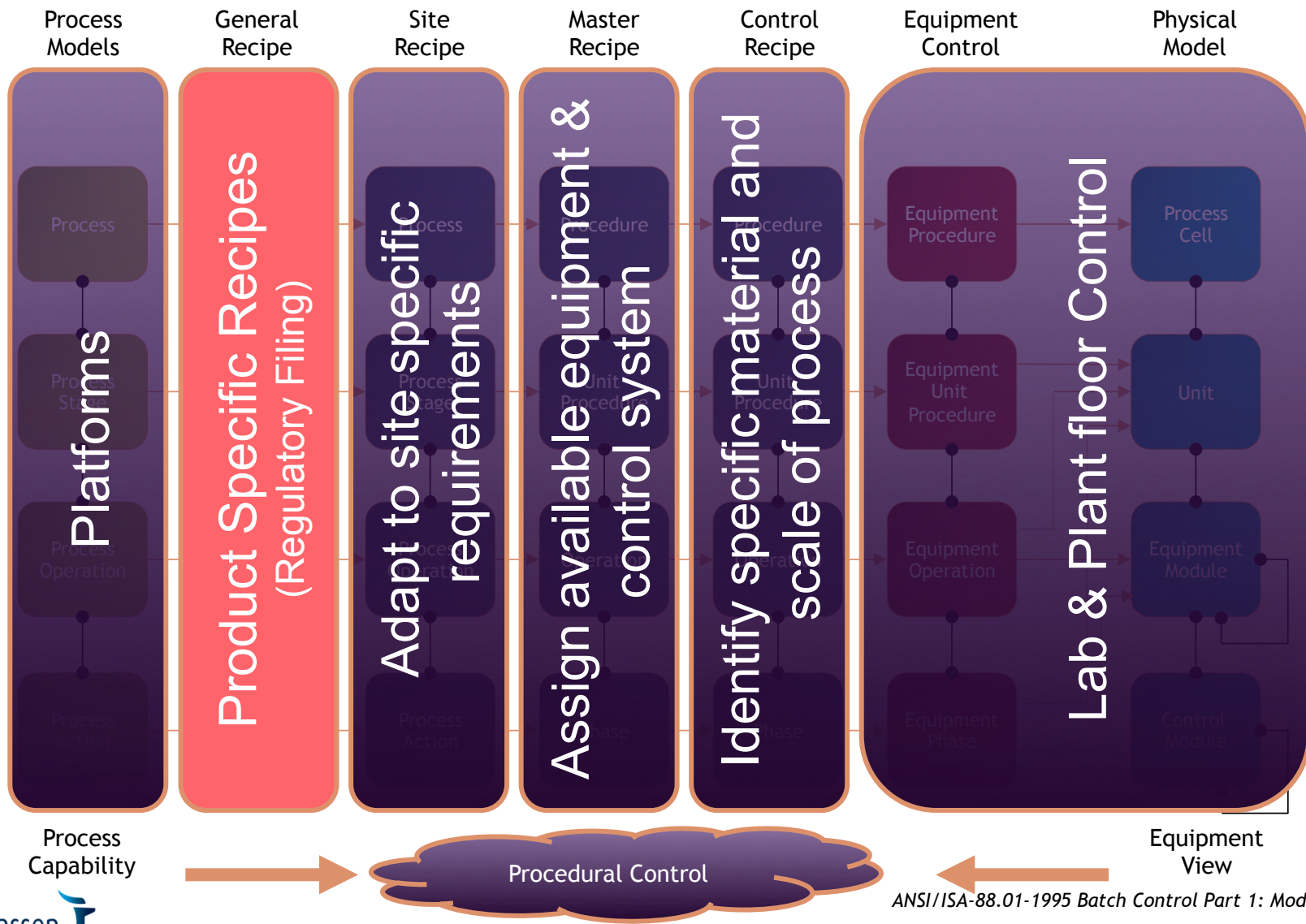
- To establish a sustainable approach to quality by design a long term strategy has to be designed and implemented for CONTENT/EXECUTION/Visualization
 - Data centric = data based versus document based
- Leveraging the S88/S95 standards has proven applicable to all process and lab segments
 - Helps overcome complications in modeling the data itself – it's been done for you!
- **We have a long way to go !**
- **We need help from our Partners !**

Acknowledgements

- All those throughout the past years that have continued to support and drive the end to end recipe framework to enable lifecycle management of our products
- Dimitris Agrafiotis, Victor Lobanov, Peter Gates, Walter Cedeno, John Stong, Andrew Skalkin – Informatics COE
- Susan Chandy, Danielle Higgins, Morten Kristensen, Ted Joachimowski – Project Management Leads: Phase 1

Back up

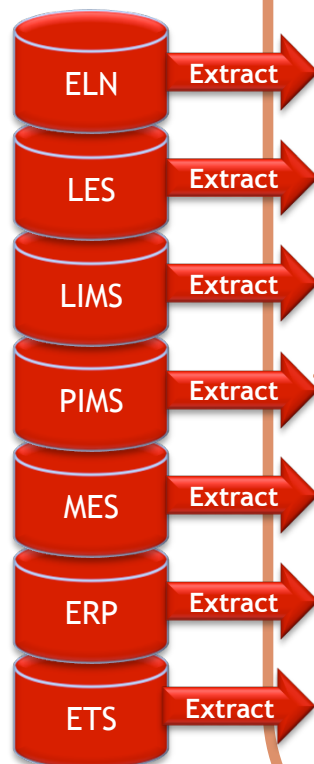
Recipe Framework



ANSI/ISA-88.01-1995 Batch Control Part 1: Models & terminology

S88/S95 Model

Operational
Source
Systems



Extract

Extract

Extract

Extract

Extract

Extract

Extract

Data
Staging
Area

Services:

Clean, combine,
and standardize
Conform
dim
M

Process

Sorting
sequential
processing

Load

Data
Presentation

Data Mart #1
DIMENSIONAL
Atomic and
Summary data
Based on single
Business process

Access

Recipe Framework

Load

Data Mart #2 ...
(Similarly designed)

Access

Data
Access
Tools

Ad Hoc Query
Tools

Report Writers

Analytic
Applications

Modelling:
Forecasting
Scoring
Data mining

Figure 1. Basic elements of the data warehouse (Kimball & Ross, 2002, p. 7).