

Discoverant Extracts More Value from BMS Electronic Data Sources

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Agenda

- ▶ **BMS Large Scale Cell Culture (LSCC) Facility**
- ▶ **Overview of LSCC Paperless Plant Systems**
- ▶ **Quality Control Hierarchies**
- ▶ **Process Hierarchies Leveraging Electronic Data Sources**



Project Overview – Facility Scope



BMS has invested \$750 million in the construction of a Large-Scale Cell Culture (LSCC) manufacturing facility for the commercial production of biopharmaceuticals in Devens, MA.

This facility has 120,000 liters of bioreactor capacity. Designed for multi-product campaign manufacturing.



Inoculum
Prep



Cell Culture



Separation





Project Overview – Site Layout





Paperless Plant Business Requirements

- **Reduce Deviations**

- Recipe Driven Operations*
 - Automated Equipment*
 - Electronic Work Instructions*
 - Equipment Tracking*

- **Expedite Batch Review & Release**

- Recipe Driven Operations*
 - Electronic Data Capture*
 - Exception Reporting*

- **Improve Data Analytics Capabilities**

- Efficient Data Analysis*
 - Data Sharing Across Biologics Network*

- **Improve Inventory Management**

- Recipe Driven Operations*
 - Material Tracking*
 - Weigh and Dispense*

- **Drive Standardization**

- Recipe Driven Operations*
 - Utilize Industry and Corporate Standards*

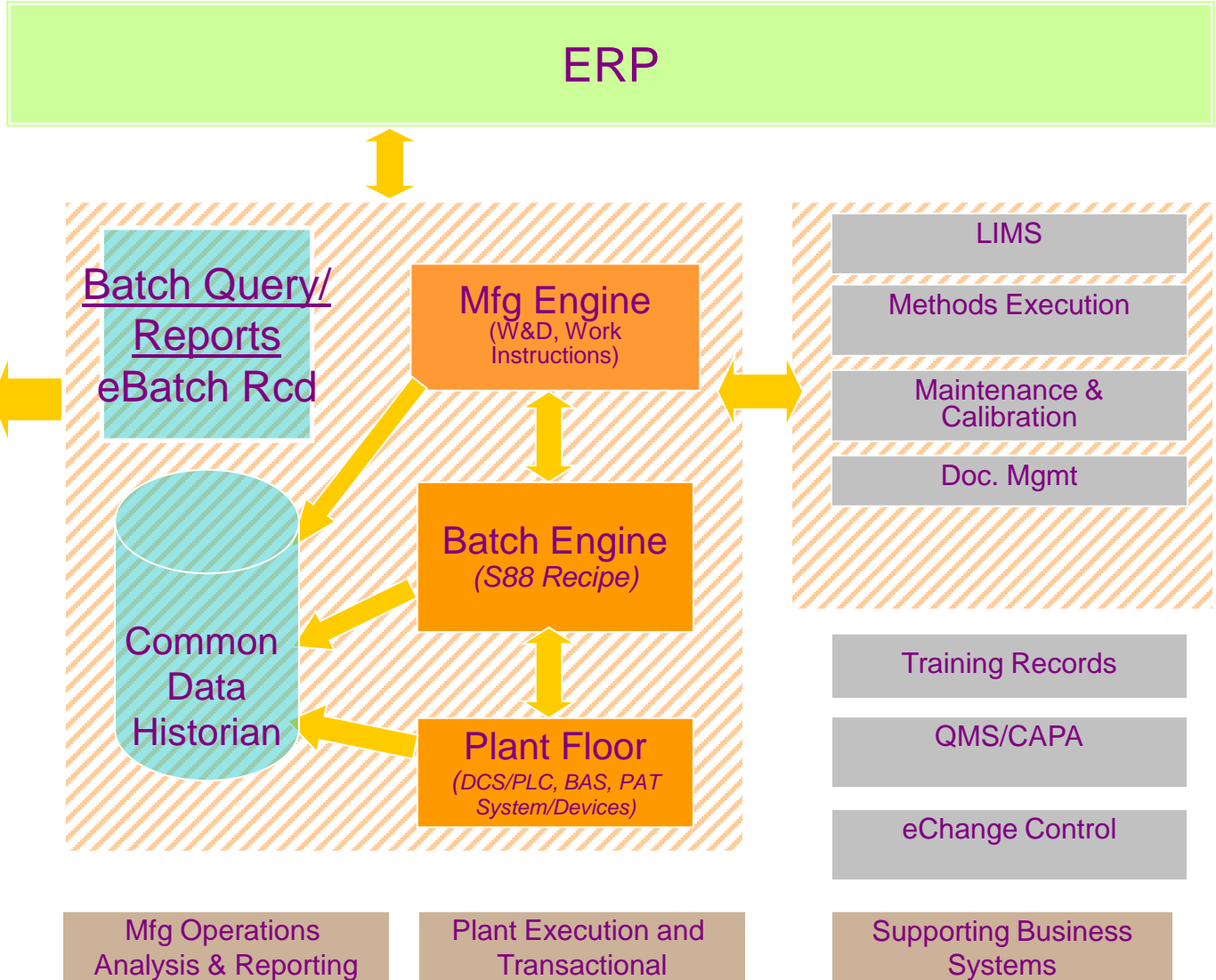




Paperless Plant Components

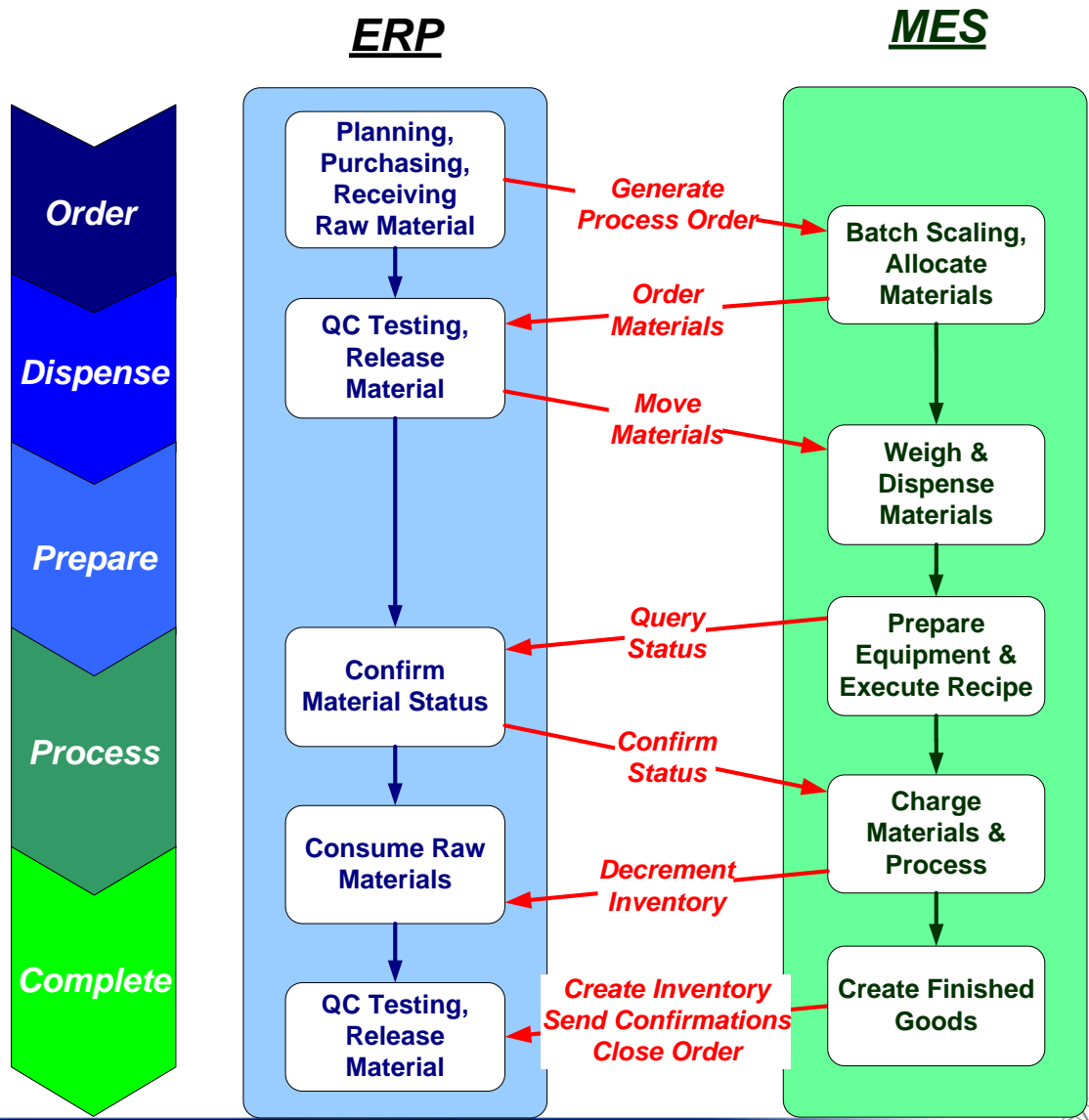
Enterprise Manufacturing Intelligence Portal

- KPI Dashboards
- Enterprise Data Historian
- Enterprise Reporting
- Advanced Analytics



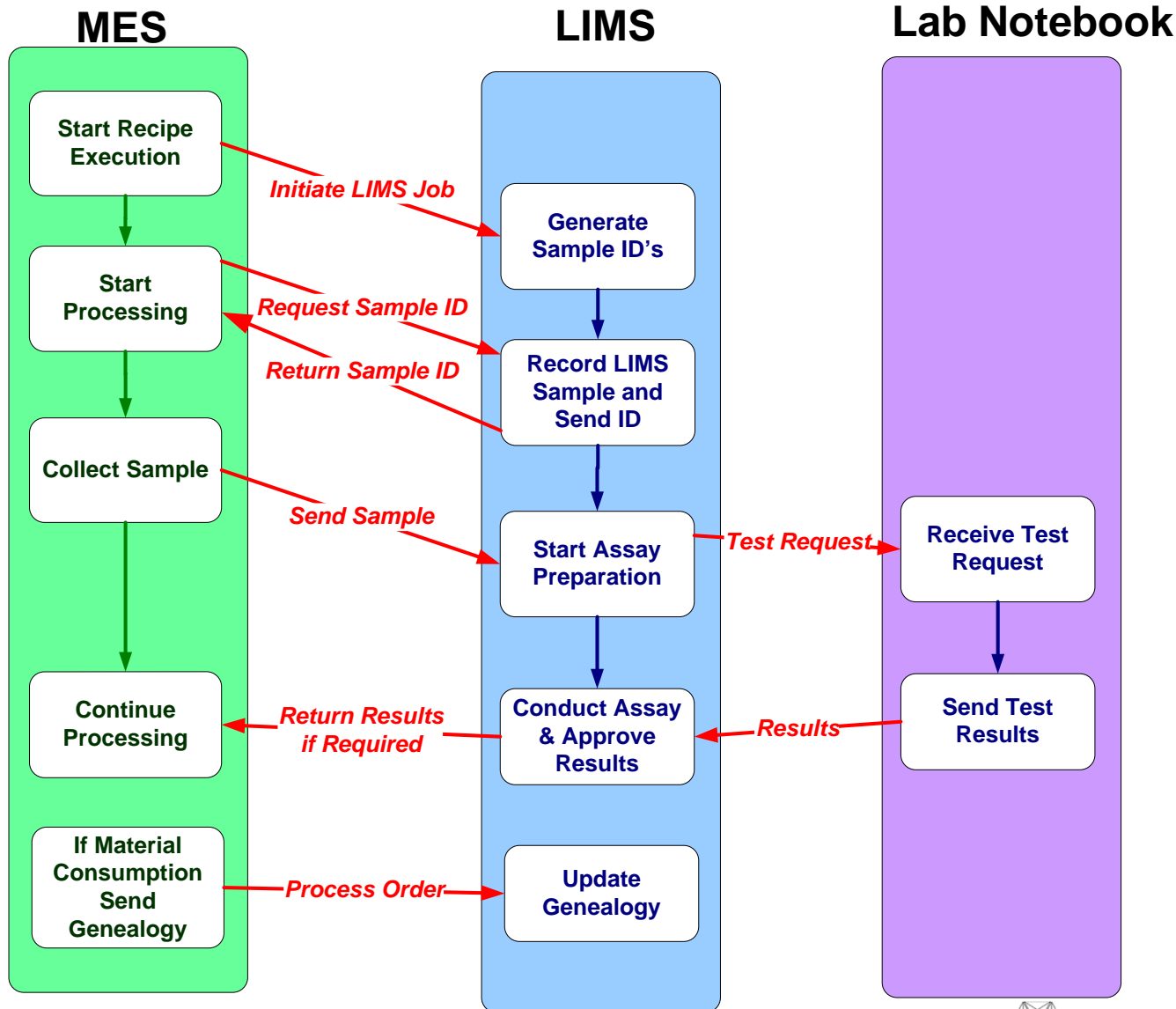


Interface - MES/SAP





Interface – MES/LIMS/Lab Notebook

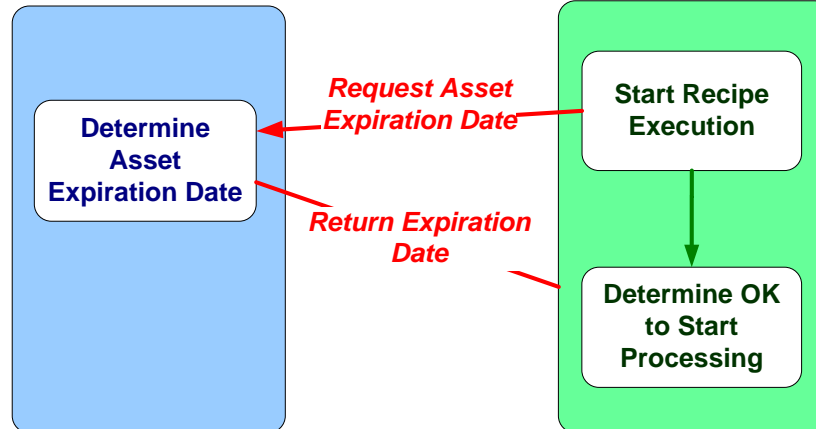
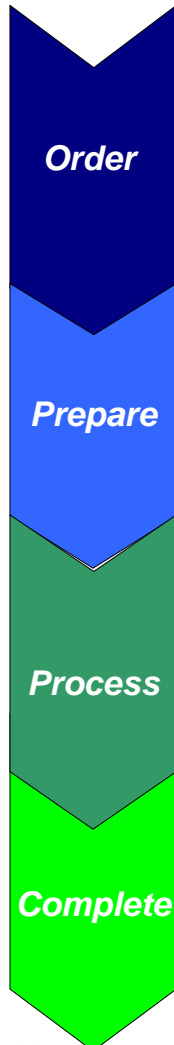




Interface –MES/Asset Management

Asset Management

MES



Asset expiry is earliest of 3 dates:

Calibration due date

PM due date

Corrective

Maintenance due date





What can we do with all of this data?





Data Analytics Vision

- ▶ **KPI Dashboards**
 - Facility and Process Overviews
 - Drill Down Capabilities
 - Transparent Data Access

- ▶ **Enterprise Reporting**
 - Standardized Process Trending Capabilities
 - Biologics Network Data Sharing
 - Efficient Tech Transfer of Future Processes

- ▶ **Advanced Analytics**
 - Implementation of Statistical Process Control Programs
 - Increased Understanding of Process
 - Predictive Multivariate Modeling
 - Support of Investigations, Optimization and Troubleshooting





Quality Control Systems

- ▶ **Electronic Laboratory Notebook**
 - All data used in the analysis of a sample is captured in the electronic laboratory notebook
 - Analyst
 - System Suitability
 - Raw Materials
 - Equipment
 - Final Result Forwarded to LIMS

- ▶ **LIMS System**
 - Sample ID linked to electronic laboratory notebook sessions
 - Only the final result is captured in LIMS
 - There is some supporting sample context data





Leveraging Data from Both Systems

- ▶ **Discoverant allows data from the electronic systems to be pulled together under a specific context**
- ▶ **All of the supporting information contained in the electronic laboratory notebook system can be leveraged and used to understand the variability observed in laboratory analysis results**
- ▶ **Unique views of data can be constructed to answer questions on analytical method systems, results analysts, equipment and materials**





First of Kind QC Data Hierarchies

- ▶ **System Suitability - Allows the user to trend the controls and standards within a method to help determine how the QC system and method is performing.**
- ▶ **Sample Suitability – Allows the user to trend sample results to navigate through the Smartlab data and to help identify the sources of variability that can impact the sample result.**
- ▶ **Environmental Monitoring - allows the user to be able to trend environmental monitoring and water testing data by Area, by Room, by Site, by Test, by Date Range and by Person Tested**





Overview of QC Data Hierarchies

- Hierarchy: System Suit
- + @ Daudi - Jurkat
 - + @ Free Thiols
 - + @ Peptide Map
 - + @ SEC
 - + @ PCR
 - + @ A280 - DS
 - + @ NANA/NGNA System Suit
 - + @ Info
 - + @ Equip
 - + @ Reagents
 - + @ Sys Suit
 - + @ NANA/NGNA Cal Curve
 - + @ IEF
 - + @ Triton X-100
 - + @ Bind Pro A System Suit
 - + @ Bind Pro A Cal Curve
 - + @ ELISA - Pro A
 - + @ ELISA - CHOP
 - + @ ELISA - MCP-1
 - + @ TOC
 - + @ Biacore
 - + @ Oligo
 - + @ A280

- Hierarchy: Sample Suit
- + @ Bioassay
 - + @ Free Thiols
 - + @ Methotrexate
 - + @ Peptide Map
 - + @ Endotoxin
 - + @ SEC
 - + @ SDS Page
 - + @ PCR
 - + @ A280 - DS
 - + @ pH
 - + @ Heavy Metals
 - + @ Biacore
 - + @ Clarity Deg of Opal
 - + @ Oligo
 - + @ A280
 - + @ NANA/NGNA
 - + @ Info
 - + @ Reagents
 - + @ Reference Material
 - + @ Equipment
 - + @ Sample Purification
 - + @ Hydrolysis
 - + @ System Suitability
 - + @ Sample
 - + @ Triton X-100
 - + @ Bindable Pro A
 - + @ ELISA - Pro A
 - + @ ELISA - CHOP
 - + @ ELISA - MCP-1
 - + @ Visible Particles
 - + @ TOC
 - + @ Specific Gravity
 - + @ Nitrates
 - + @ IEF
 - + @ Degree of Coloration
 - + @ Conductivity

- Hierarchy: Env Monitor
- + @ Bio
 - + @ Cond
 - + @ Endo
 - + @ Col
 - + @ TOC
 - + @ Nitrates
 - + @ Viable Air
 - + @ NonViable Air
 - + @ Surface
 - + @ Personnel





Statistical Process Control of Methods

- ▶ **Increase Understanding of QC Methods**
- ▶ **Reduce QC Method Variability**
- ▶ **Support Manufacturing Investigations**
- ▶ **Provide Early Warning of QC Method Issues**





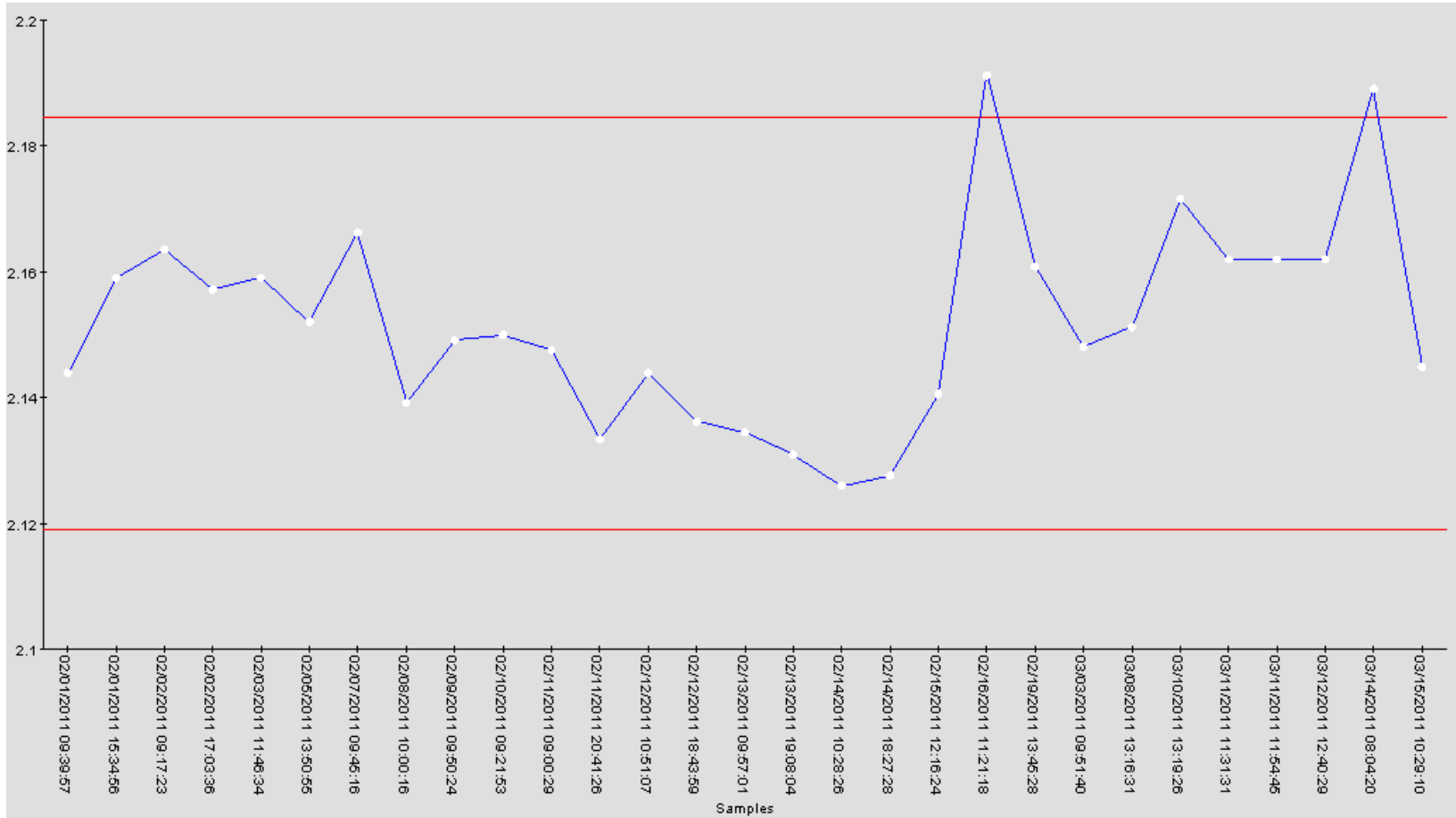
Statistical Process Control of Methods

- ▶ **Procedures are being developed to standardize SPC strategy**
- ▶ **Procedures involve leveraging data compilation capabilities to analyze data and develop statistical control limits.**
- ▶ **Limits are then applied and used to identify special cause variability of method system suitability data.**
- ▶ **Outliers are documented and investigated by SMEs**
- ▶ **Data hierarchies are used to support the investigation**





Example Output from System Suitability Trending





Ability to Navigate through Data

Category Values

Category: NANA/NGNA System Suit.Info.Analyst

<input type="checkbox"/>	almeid	<None>
<input type="checkbox"/>	boinok	NANA/NGNA System Suit.Equip.HPLC ID
<input type="checkbox"/>	colonn	NANA/NGNA System Suit.Equip.Lot No Col
<input type="checkbox"/>	denno	NANA/NGNA System Suit.Equip.Lot No Guard Col
<input type="checkbox"/>	dignar	NANA/NGNA System Suit.Equip.Supp Col
<input type="checkbox"/>		NANA/NGNA System Suit.Equip.Supp Guard Col
<input type="checkbox"/>		NANA/NGNA System Suit.Info.Analyst
<input checked="" type="checkbox"/>	Plot	NANA/NGNA System Suit.Info.Cal Curve Proc ID

Output Op Value





Ability to Navigate through Data – EM Example

Discrete Control Charts (Water Testing Demo)

Setup | Plot | Report

Analysis Group Selection
Water Testing Demo [New...]

Y Axis Parameters

Available Parameters:

- Bio.Micro IDs
- Bio.Mold
- Bio.Mold Micro Morph
- Bio.Pipet EIN #
- Bio.Sample Source
- Bio.Total CFU
- Bio.Total CFU_100ML
- Bio.Total CFU_ML

Selected Parameters:
Bio.Total CFU_ML

Chart Options
Chart Type: Individuals [Rules...]

Axis Values

X Axis: Parameter Set Groups

Subgroup Size: 2

Grouping Parameter: <Select Value>

Sort X-axis by: Parameter Set Date

Segmented Charts

Use Segmented Charts

Segment by Parameter: <Select Value>

Segment by a change in control target values

Segment by category value

Category Values

Category: Bio.Room

- D_131_2176
- D_131_3030
- D_140_1500
- D_490-69
- D_696-24

Parameter Set Restrictions

Range: All

Output Options

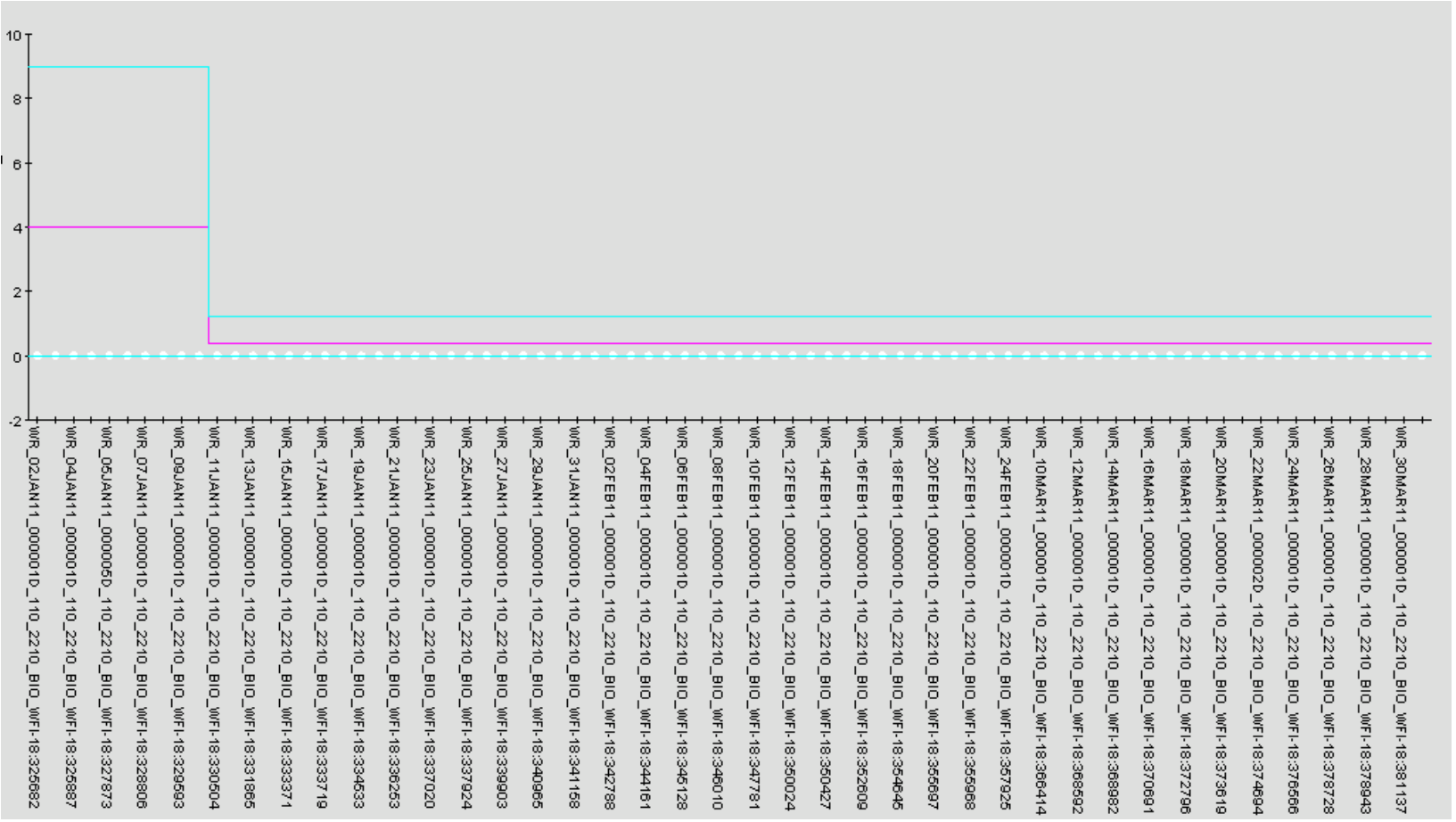
Plot Report Automatically Update Outliers in Report Page per Category Value

Display





Automated Limits





Micro IDs

	Par...	FIELD_IN...	Bio.Micro IDs
					◇
1	WR_...	1	Gram positive beaded rod
2	WR_...	1	Gram positive beaded rod
3	WR_...	1	Gram positive beaded rod
4	WR_...	1	Gram positive beaded rod
5	WR_...	1	Gram positive beaded rod
6	WR_...	1	Gram positive beaded rod
7	WR_...	1	Gram positive beaded rod
8	WR_...	1	Gram positive beaded rod
9	WR_...	1	Gram positive beaded rod
10	WR_...	1	Gram positive beaded rod
11	WR_...	1	Gram positive beaded rod
12	WR_...	1	Gram positive beaded rod
13	WR_...	1	Gram positive beaded rod
14	WR_...	1	Gram positive beaded rod
15	WR_...	1	Gram negative rod, minimal growth
16	WR_...	1	Gram negative rod, minimal growth
17	WR_...	1	Gram positive beaded rod
18	WR_...	1	Gram positive beaded rod
19	WR_...	1	Bacillus lentus
20	WR_...	1	Gram negative rod, pleomorphic - minimal growth
21	WR_...	1	Gram positive beaded rod
22	WR_...	1	Gram positive beaded rod
23	WR_...	1	Gram negative rod, pleomorphic - minimal growth
24	WR_...	1	Gram positive beaded rod
25	WR_...	1	Gram positive beaded rod
26	WR_...	1	Gram positive beaded rod
27	WR_...	1	Gram positive beaded rod
28	WR_...	1	Gram positive beaded rod
29	WR_...	1	Gram positive beaded rod





Configuration Challenges

- ▶ **Prior to configuration develop a detailed understanding of the underlying data structure in each source system**
 - Text vs. Numeric Fields
 - Approval of data within each data source
 - Organization of data

- ▶ **Focus on Developing Analytical Goals**

- ▶ **Begin Developing Procedures to Assess Changes in Source System Data**





Validation/Qualification

- ▶ **Separate Discoverant System Validation from Hierarchy Qualification**
- ▶ **Leverage the Hierarchy Verification Utility (HVV)**
 - HVV is a COTS tool that allows data to be input in the Discoverant system and compare the entered data to source system data using the system configuration
- ▶ **Develop a Hierarchy Qualification Procedures that is flexible but still meets cGMP requirements**
 - How will the current hierarchies be maintained?
 - How will additional hierarchies be added to the system?





Electronic Batch Record Design

- **Bill of Materials**
 - Material ID's
 - Material Quantities

- **Processing Requirements**
 - Instructions
 - Parameters
 - Order of Execution

- **Analytical Requirements**
 - *Samples*
 - *Link to Lab Execution System for Assays*

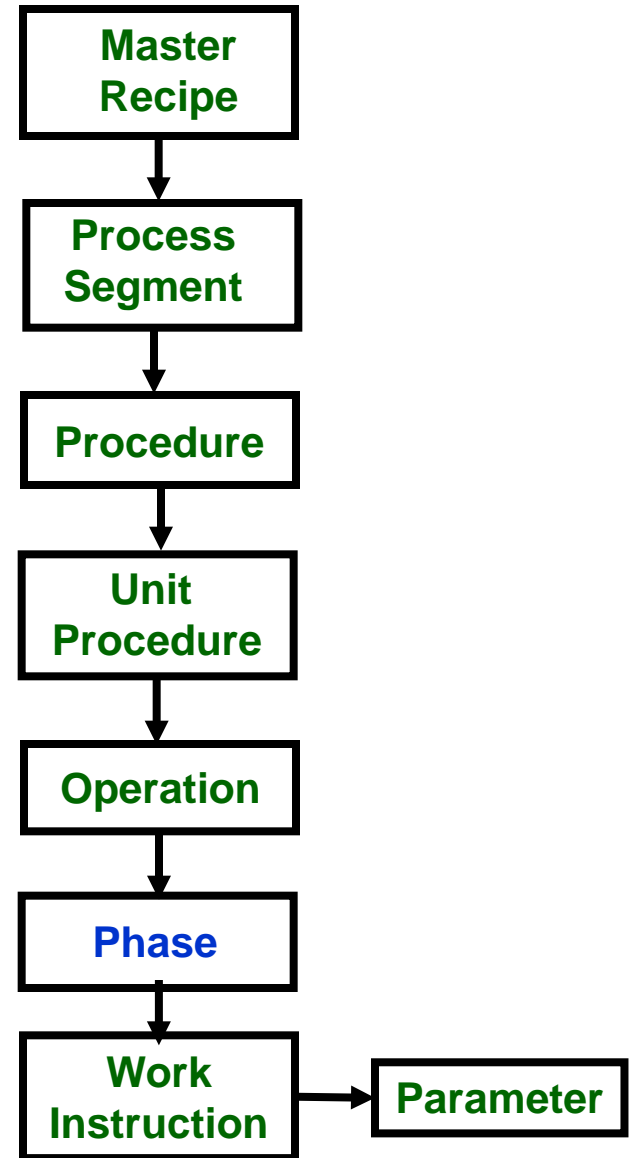
- **Exception Definition & Recognition**
 - *Control*
 - *Limits*
 - *Notification*
 - *Documentation*

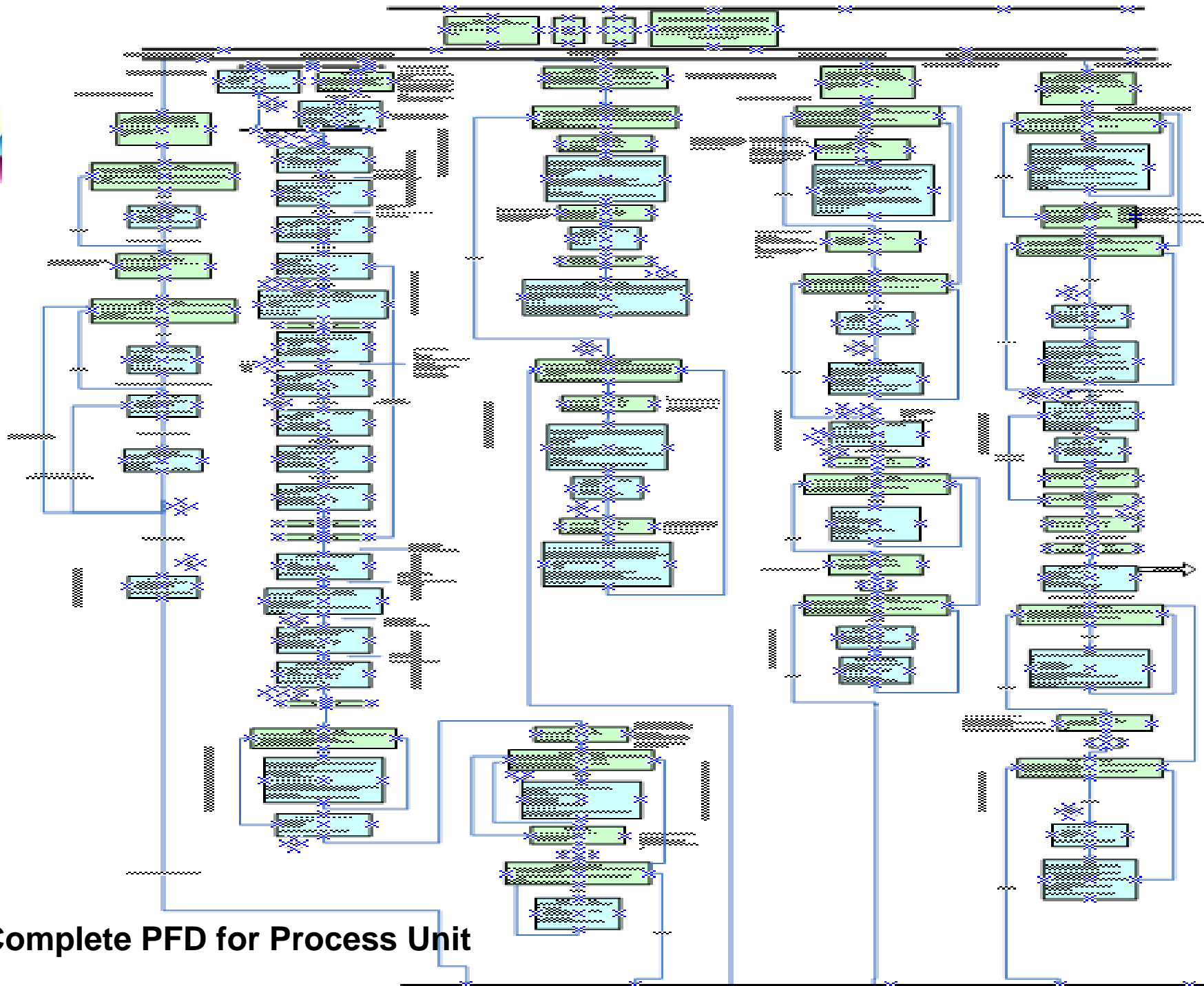




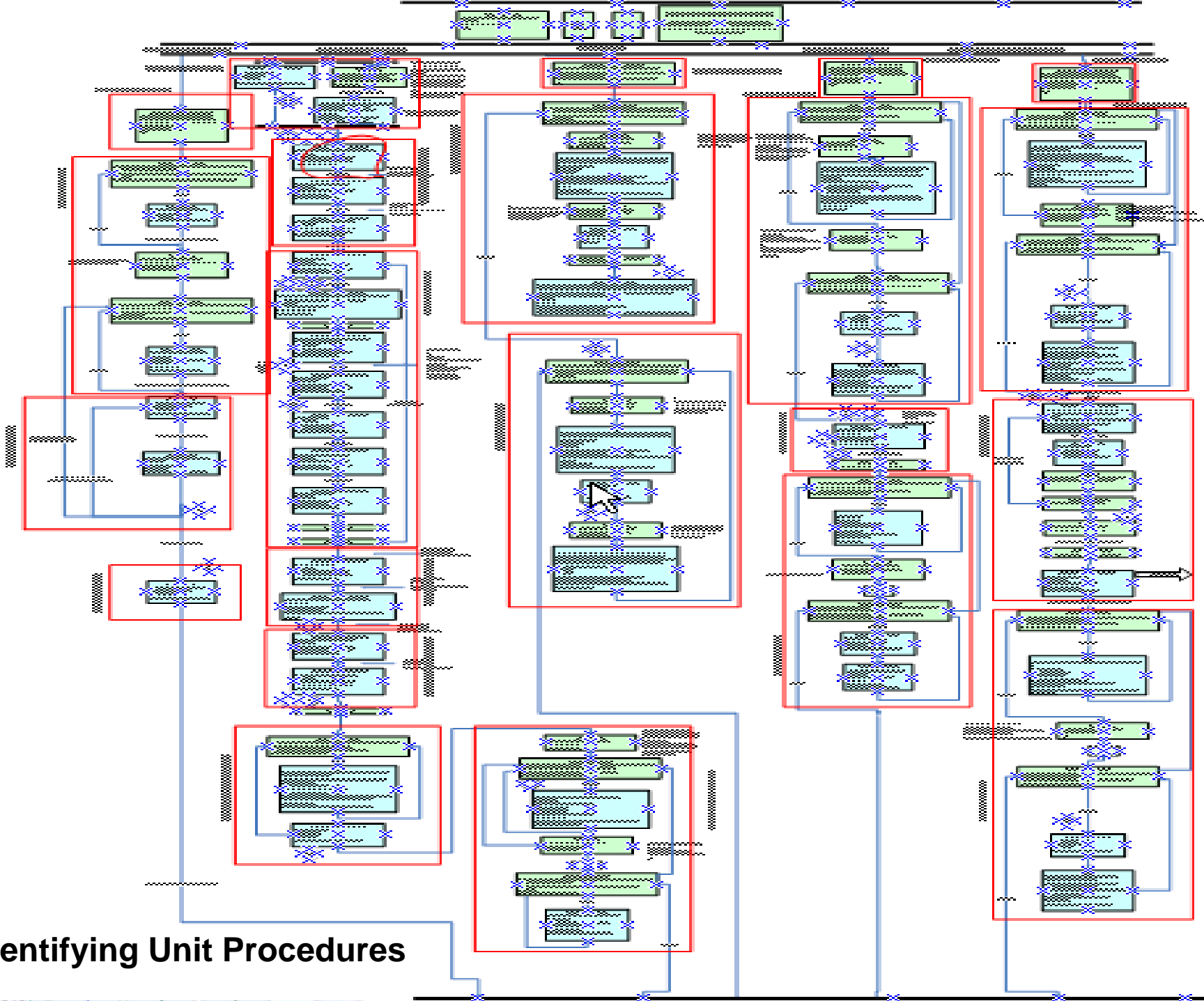
Electronic Batch Record Design – S88

- All recipes have been configured using S88 structure
- Recipes interface with LIMS, ERP, MAXIMO, Data Historian and DCS

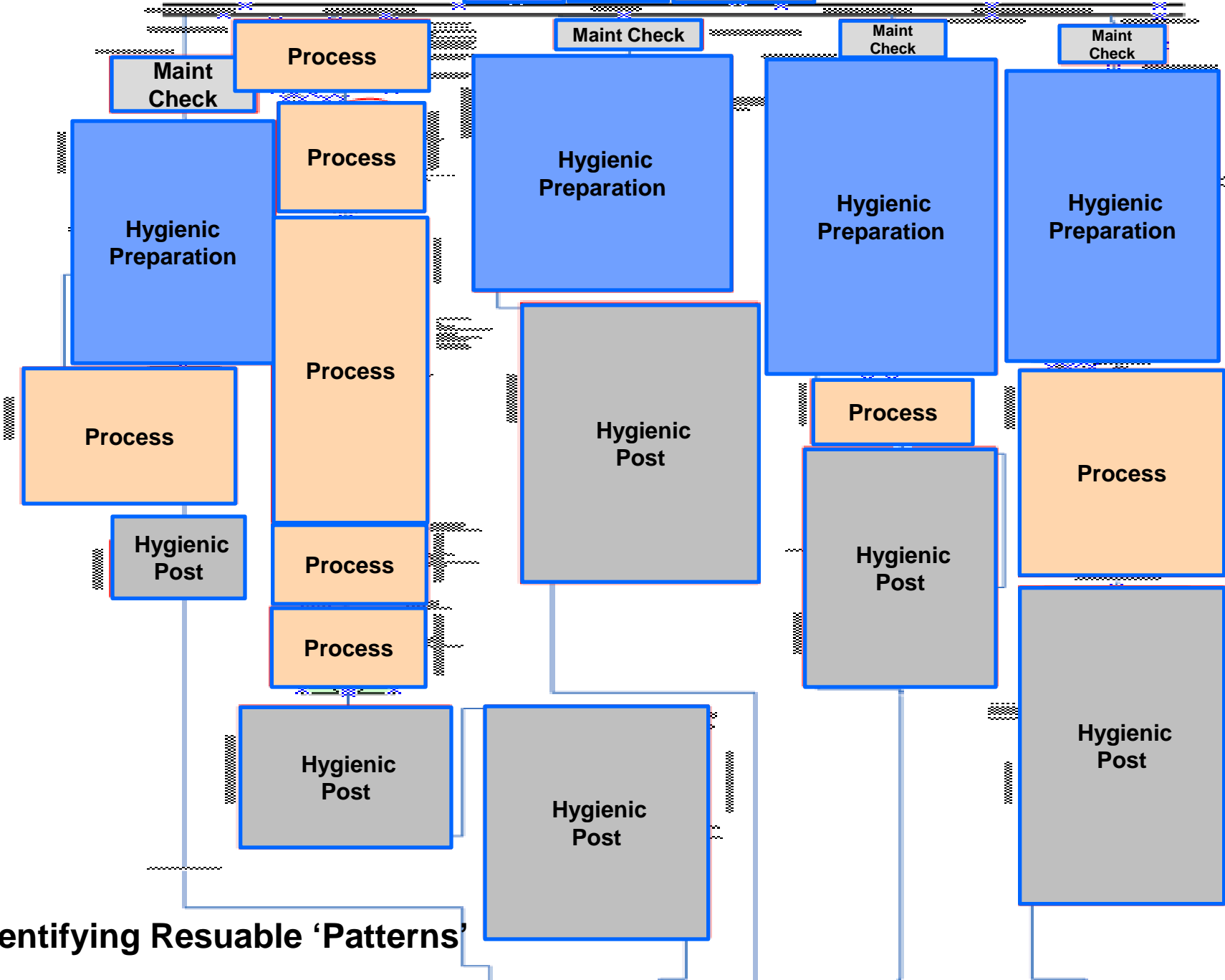




Complete PFD for Process Unit



Identifying Unit Procedures



Identifying Resuable 'Patterns'



An enormous amount of data is now available for data analytics.

The challenge is to create context around the data and organize the data from each source system.



Process Hierarchy Configuration

- ▶ **The hierarchy is configured to the MES system to pull all discrete batch data (except LIMS data)**
 - Universes within the hierarchies have been designed to be generic i.e bioreactor, chromatography
- ▶ **Contextual information from the MES system is used to pull data from other systems**
 - MES data is used to pull data historian data and LIMS data
- ▶ **Genealogy is tracked in the MES system. Database views have been created so that the hierarchy configuration can derive the genealogy from the MES data**



Challenges Encountered during Process Hierarchy Configuration

- ▶ **The electronic batch record recipes are dynamic. Context needs to be created leveraging objects within the recipe structure.**
 - Chromatography Cycles
 - Reprocessing
 - Cell Culture Growth Data
 - Equipment Status

- ▶ **Data must be structured to meet analytical goals**

- ▶ **Data Overload**
 - So much data is available it has been a challenge to stay within scope.
 - Analytical goals must be established and adhered to.

- ▶ **Changes in MES recipe structure can break hierarchy configuration**





Benefits of Hierarchy Configuration to Electronic Systems

- ▶ **The hierarchies are being configured based on S88 structure of the recipes. This allows for efficient changeover to a new process**
- ▶ **All batch data is available for configuration**
- ▶ **The hierarchies can take advantage of any data available from the MES, LIMS or Data Historian systems**
- ▶ **Data is available near real time**





Process Hierarchy to Support Business Processes

- ▶ **Annual Product Review (APR)**
 - Data analysis can be automated reducing the time required for the APR

- ▶ **Quality Investigations**
 - Provides a validated source of data to utilize in manufacturing investigations

- ▶ **Process Improvements**
 - Improvements to process robustness and productivity through trending and multivariate analysis will be straightforward and done with validated data

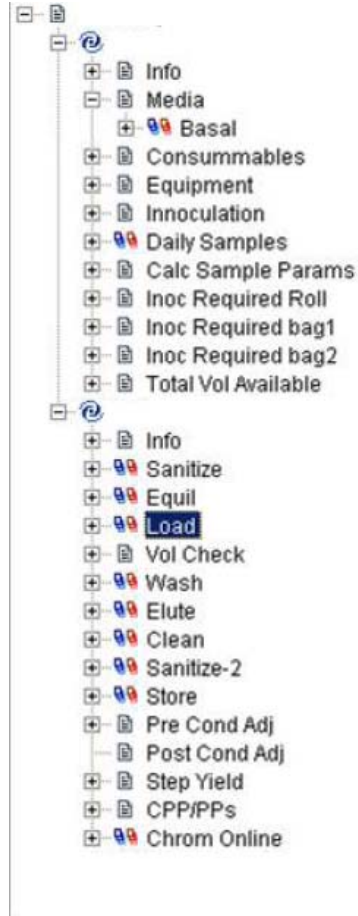
- ▶ **Statistical Process Monitoring**
 - Allows for the implementation of statistical rules to be automated
 - Real-time alerts of trends and limit violations
 - Ad-hoc and standardized reports and graphs can be generated

- ▶ **Technology Transfer**
 - Standardize the platform to view and perform statistical analysis on data from biologics network



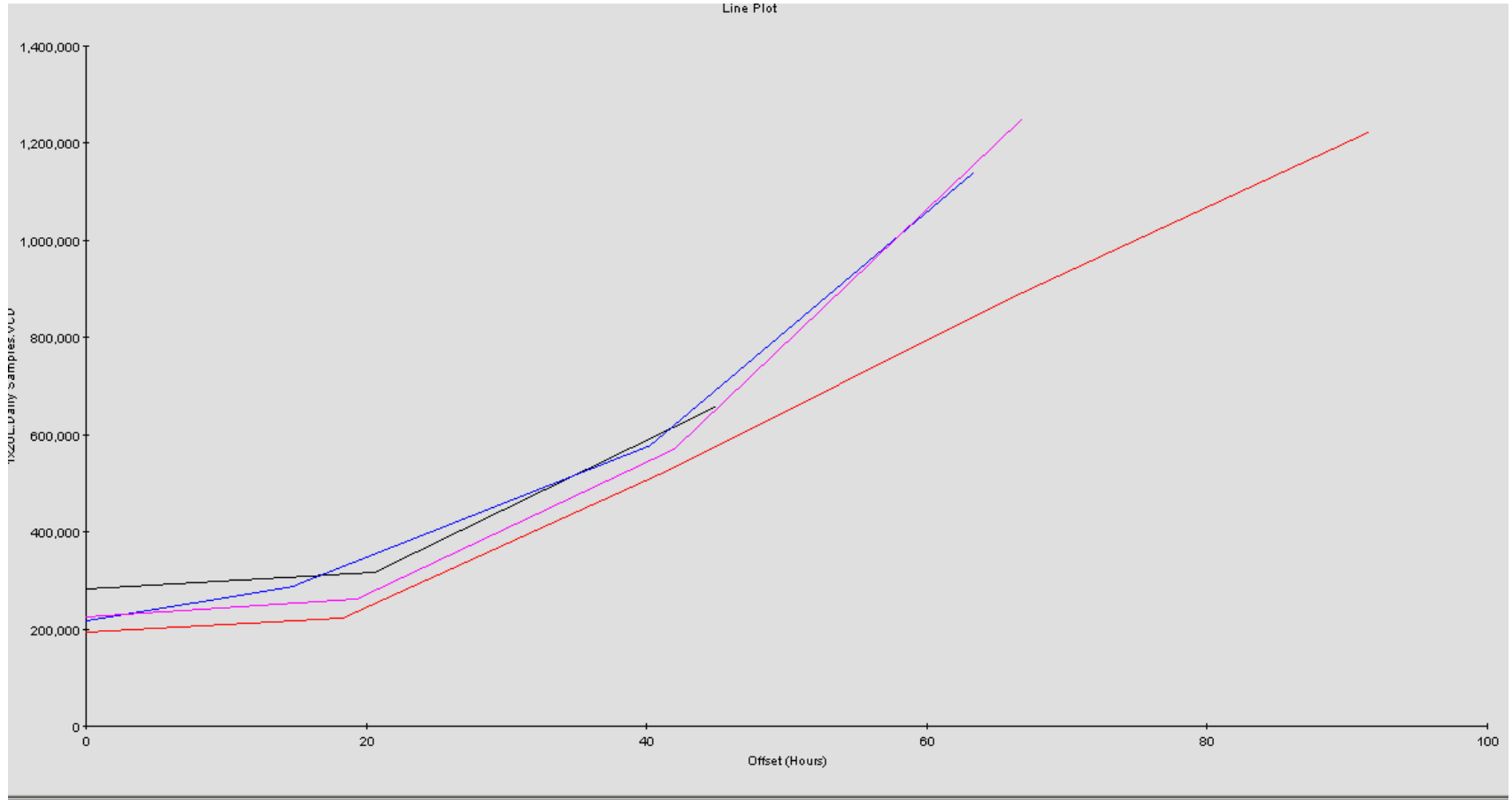


Current Status of Process Hierarchy Configuration



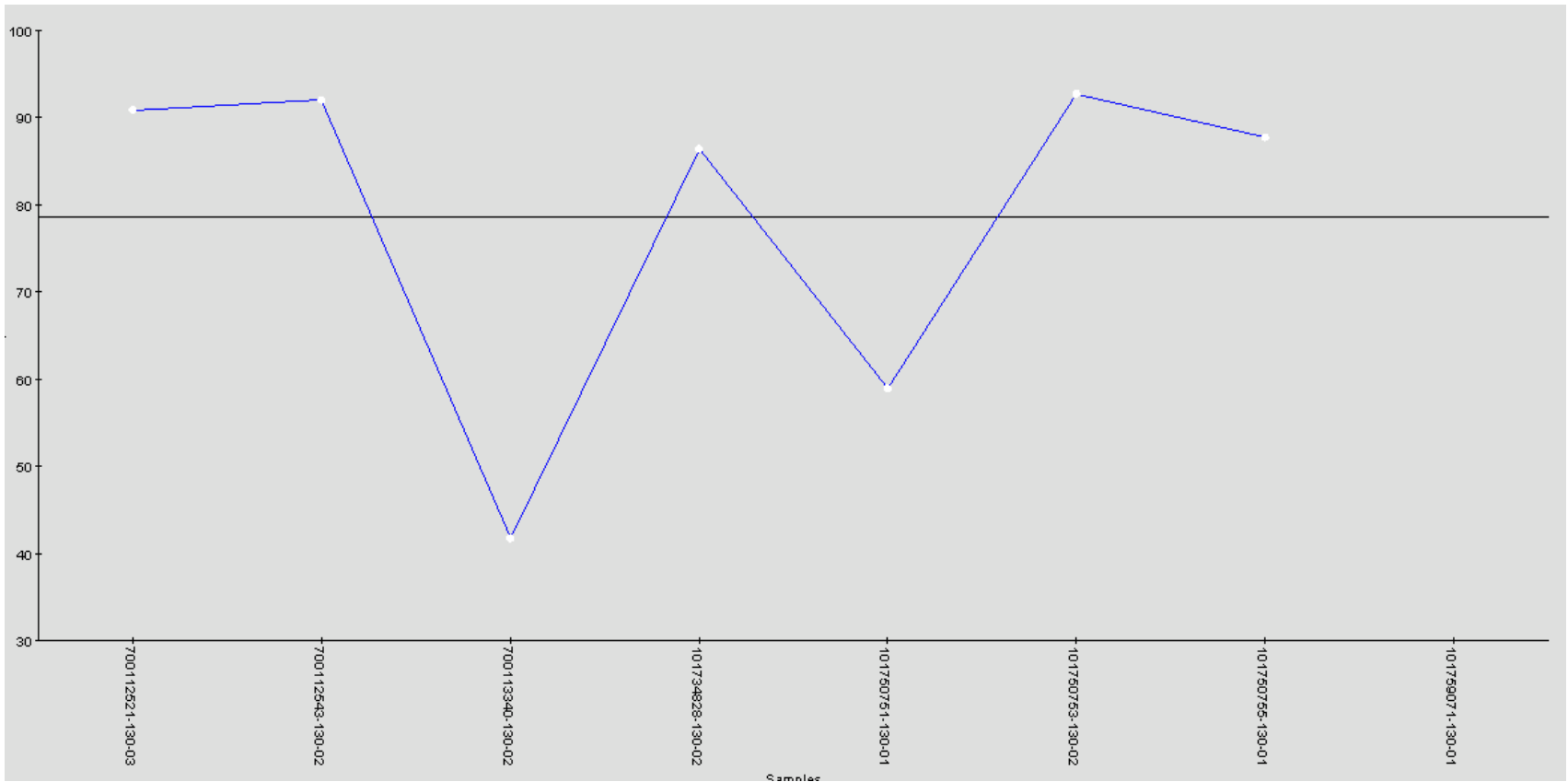


Example of Cell Culture Growth Data





Example of Chromatography Yield Data





Future Hierarchies

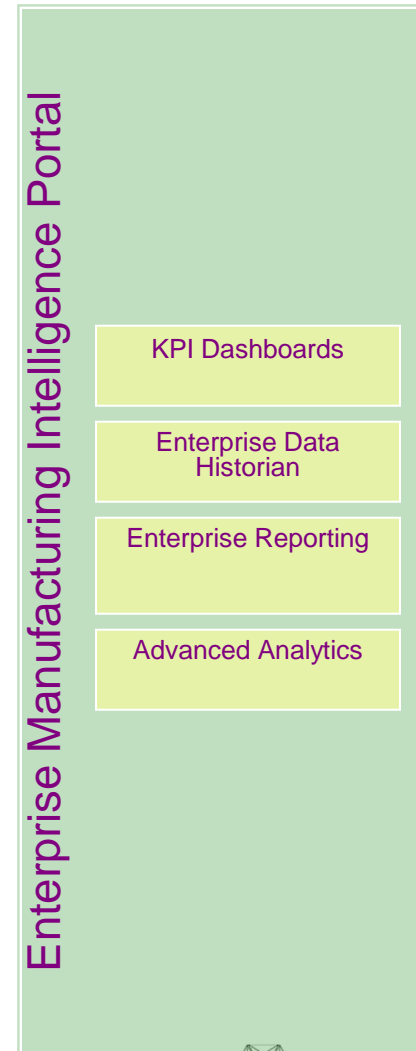
- ▶ **Buffer Prep Centric Hierarchies**
- ▶ **SIP Centric Hierarchies**
- ▶ **CIP Centric Hierarchies**
- ▶ **Cross Facility Product Specific Hierarchies**





Data Analytics Vision

- **Complete First of Kind Hierarchies**
- **Develop Standardized Reports**
- **Design KPI Dashboards**





Questions?

