Achieving The Goals of QbD and PAT

Bridging the Gap Between Process Development and Manufacturing

October 28, 2008, Heidelberg, DE

Overview

- The best way to achieve the goals of Quality by Design and reduce business risks is to begin the QbD collaboration during Process Development
- Today's manual data access and disconnected analytics (aka spreadsheet madness) are inconsistent with achieving the goals of QbD
- On-demand data access and collaborative investigational analytics are required for successful collaboration between Process Development (PD) and Manufacturing (MFG)
- Significant business and quality compliance benefits are achieved from this collaboration by using today's technology

Quality by Design (QbD)

- **The Goals of QbD:**
  - Product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from the performance of test batches
  - QbD is derived from:
    - ⇨ **A combination of prior knowledge and experimental assessment**
    - ⇨ **A cause-and-effect model that links CPPs and CQAs**

Janet Woodcock, FDA, 2004

Business Benefits of QbD

- **Reduced batch failures, final product testing and batch release costs**
- **Lower operating costs from fewer failures and deviation investigations**
- **Increased predictability of manufacturing output and quality**
- **Reduced inventory costs from raw material, WIP and finished product**
- **Faster technology transfer between development and manufacturing**
- **Faster regulatory approval of new product applications and process changes**
- **Fewer, shorter, less costly regulatory inspections**

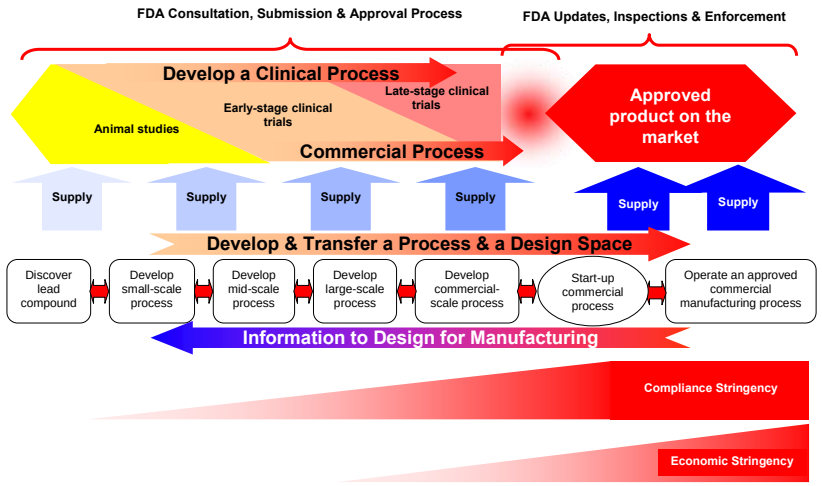
Process Understanding

- Process understanding is required in order to achieve QbD
- A process is well understood when:
  - all critical sources of variability are identified and explained
  - quality is designed into the process so that variability is managed by the process
  - product quality attributes can be accurately and reliably predicted
- Accurate and reliable predictions reflect process understanding
- Process understanding is inversely proportional to risk

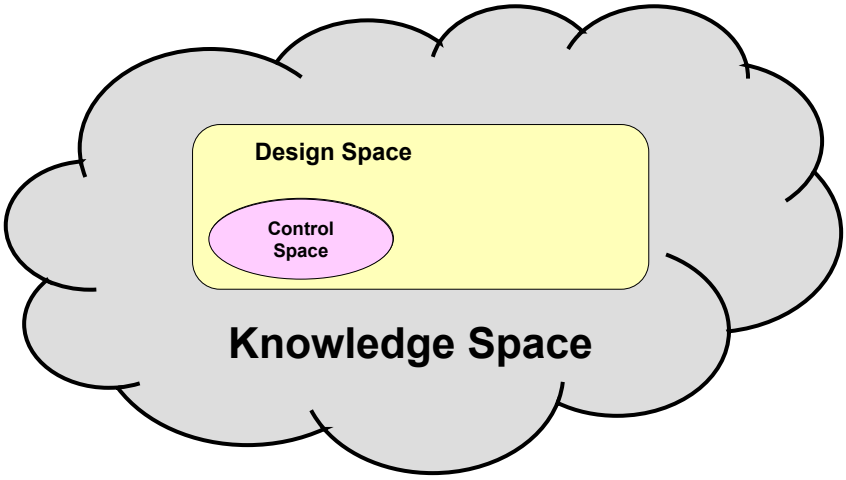
To Quote the FDAs SRP Document

- "It is expected that sites with effective quality systems and superior process understanding will be less likely to have a history of significant violations or have multiple product recalls, and such sites would, generally, be expected to have less frequent or intense inspectional coverage than would otherwise be the case."

Where Does QbD Come From?



The Idea Behind The Design Space



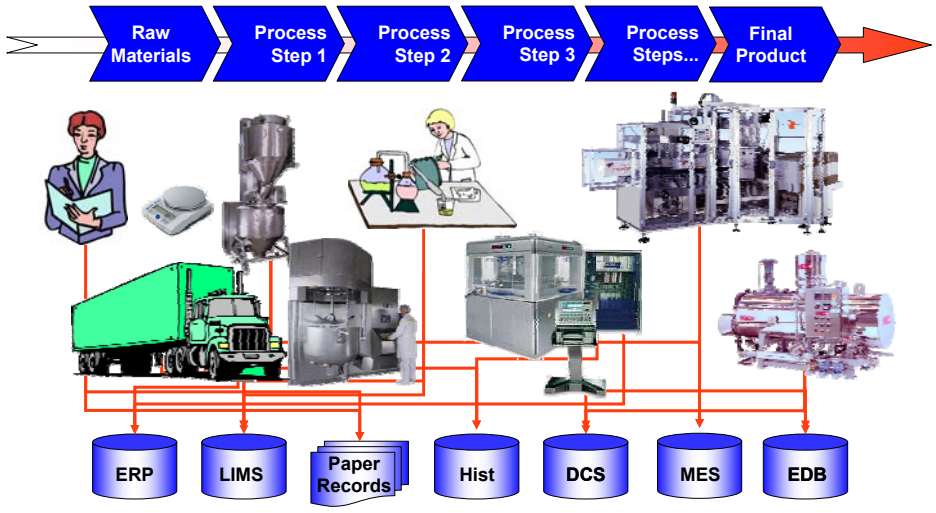
To Quote the FDA's PAT Guidance Doc

"Continuous learning through data collection and analysis over the life cycle of a product is important. These data can contribute to justifying proposals for post-approval changes. Approaches and information technology systems that support knowledge acquisition from such databases are valuable for the manufacturers and can also facilitate scientific communication with the Agency."

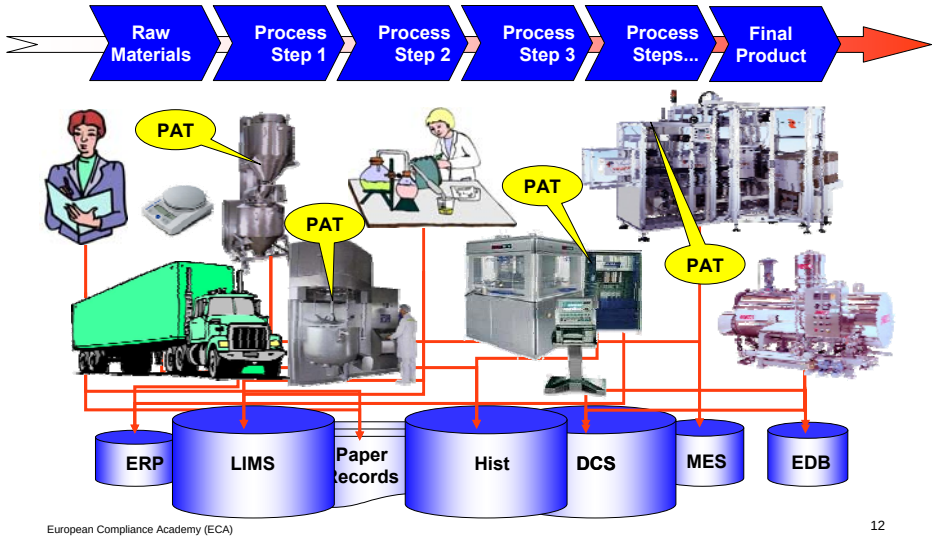
Requirements for QbD Data Collaboration

- Provide interactive, on-demand access for end users to all the data in a combined form, to complete investigations in minutes not months
- Deliver analytics that include descriptive (what happened?) as well as investigational (why did it happen?)
- Enable productivity and compliance improvements that go beyond logistical and organizational issues
- Include all types of data, as well as paper-based data, to make meaningful analysis possible
- Allow non-programmers and non-statisticians to complete tasks quickly and effectively as a collaborative team

Today's Manufacturing Data Landscape



Adding PAT to the Mfg. Data Landscape



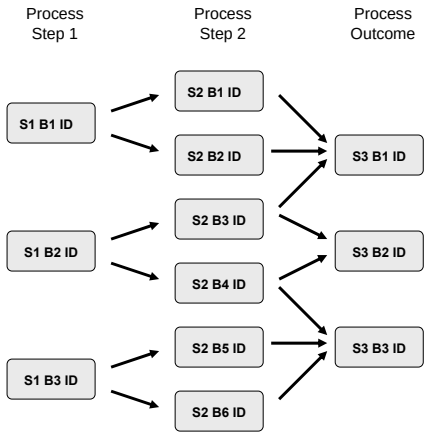
All Types of Data Must be Accessible

- **Discrete data**
  - Measured once per batch
  - MES, EBR, LIMS, ERP, Paper, Others
- **Continuous data**
  - Strip charts – time series profiles
  - SCADA, Historians, DCS, PLC, Instruments
- **Replicate data**
  - Several measurements, same sample/time
  - MES, EBR, LIMS, Paper, Others
- **Event data**
  - Batch, equipment records, SCADA, etc.
- **Keyword and free text data**
  - Enables records to be retrieved and understood

Data Access Must be On-demand / Interactive

1. Test Hypothesis or Explore for Understanding
2. Gather Data - Organize, Constrain and Filter
3. Preliminary Analysis
4. Gather More Data – Organize, Constrain and Filter
5. Conduct Analysis
6. Share Results
7. Gather More Data – Organize, Constrain and Filter
8. Extend the Analysis
9. Publish Results

Genealogy: Lot Traceability



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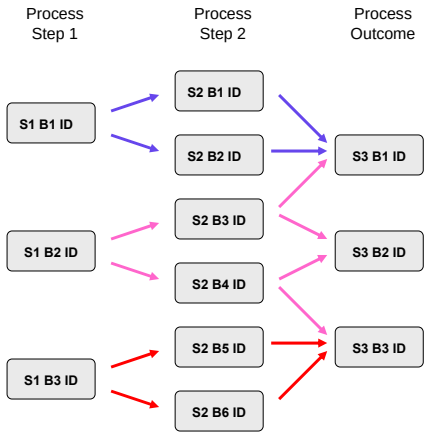
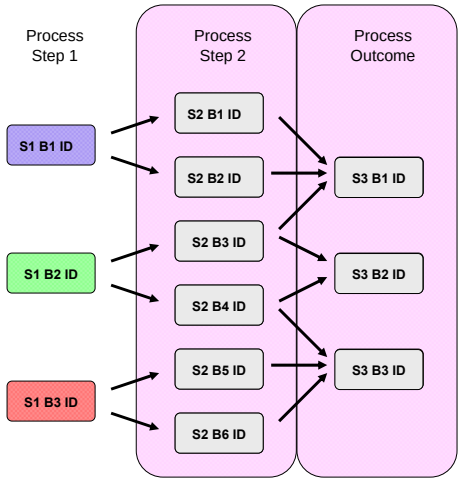


Genealogy: Correlating Downstream with Upstream



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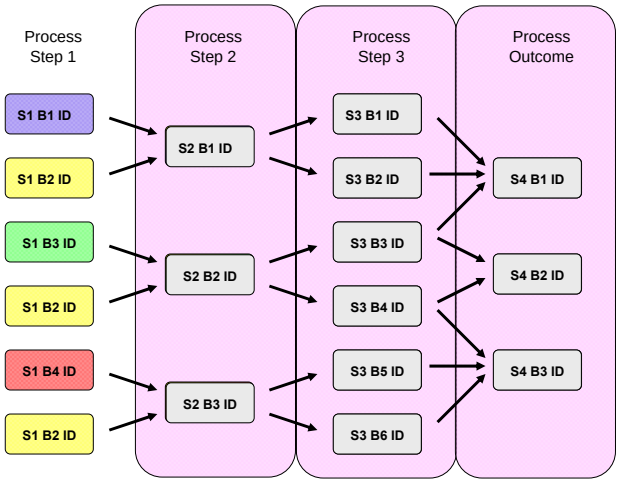
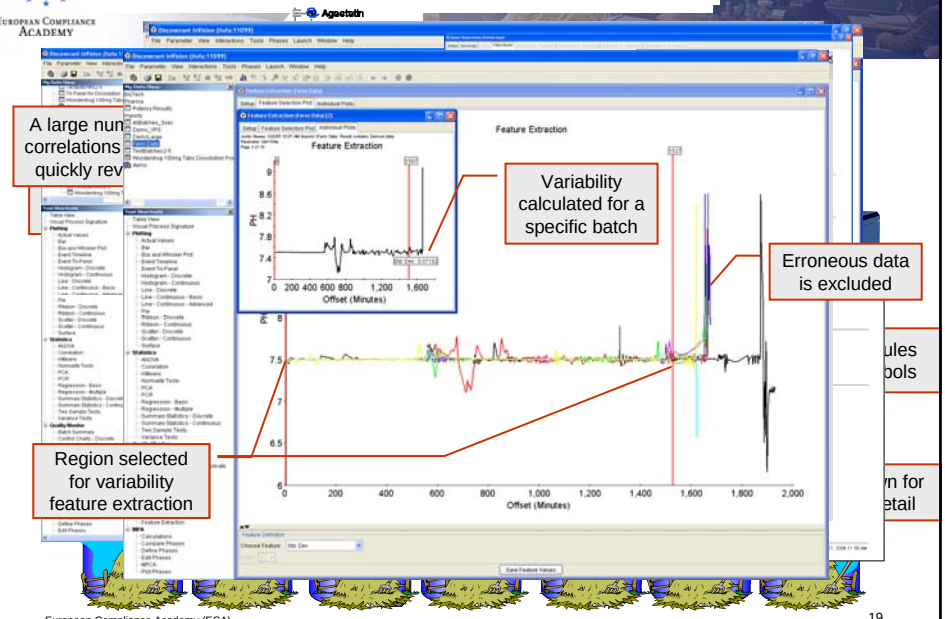
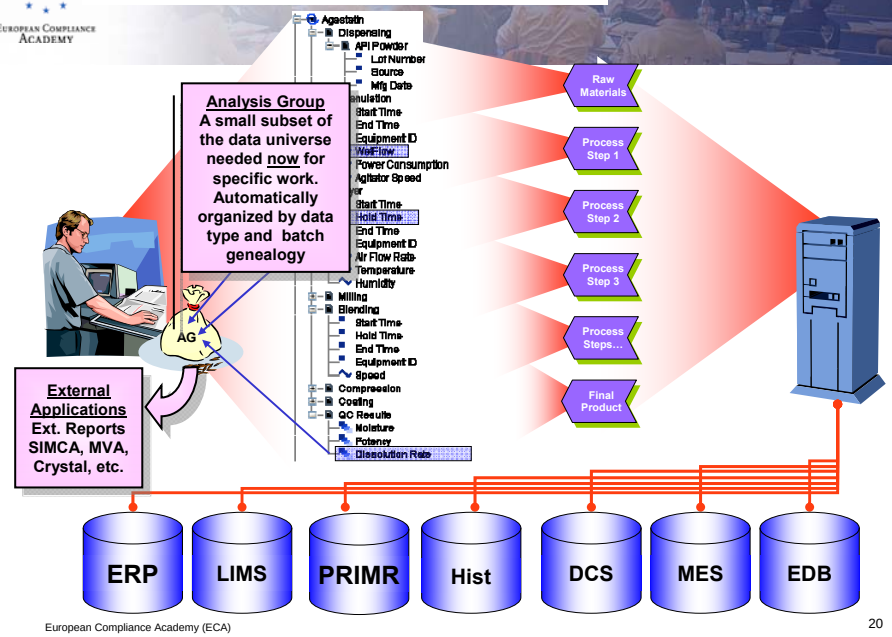


Deep Dive Analytics for
Actionable Information in Relevant-time



On-demand Data Access



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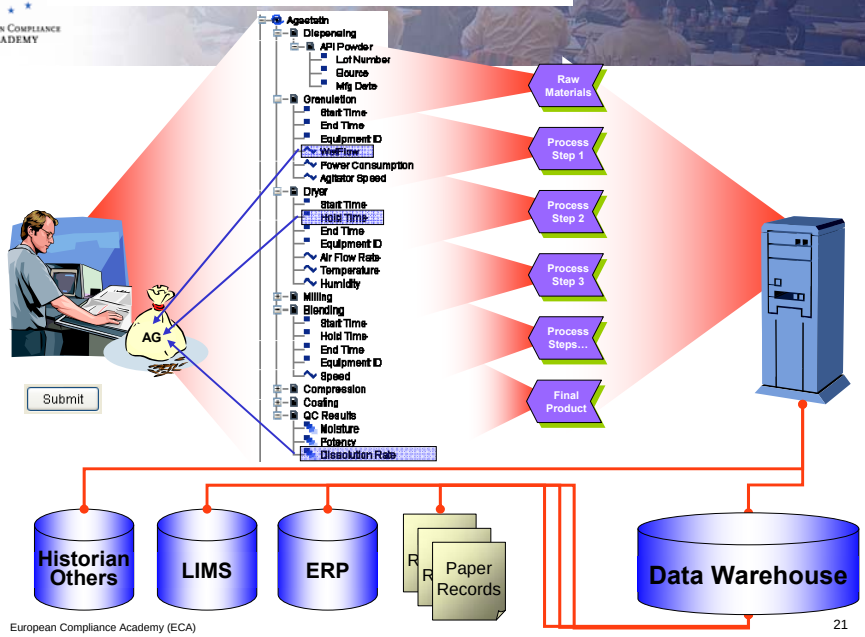
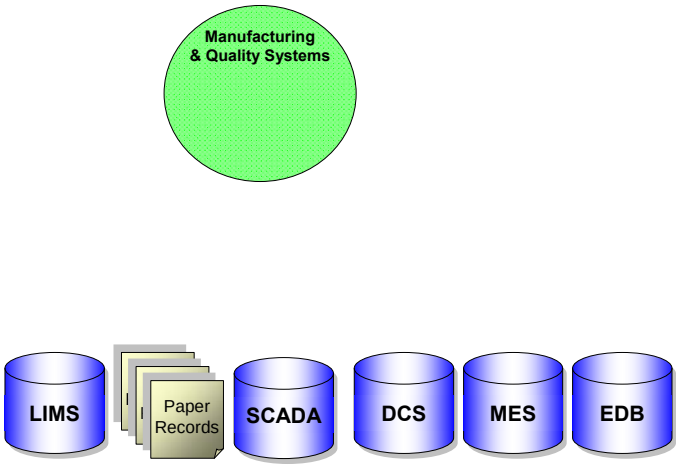


Investigational Analytics in the System Environment



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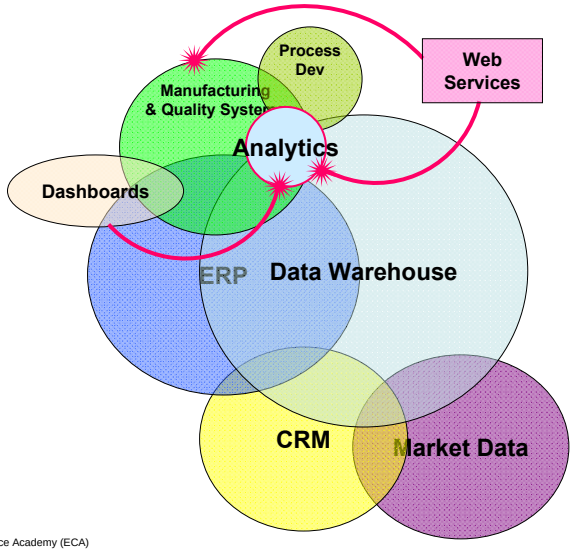
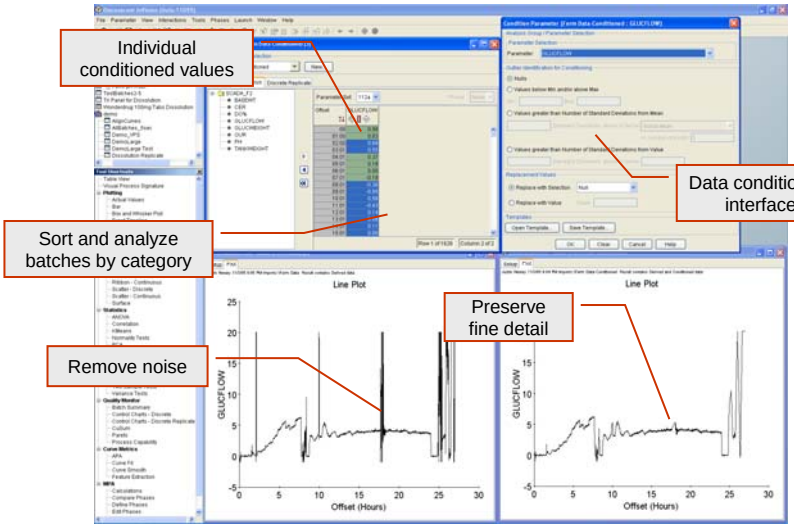


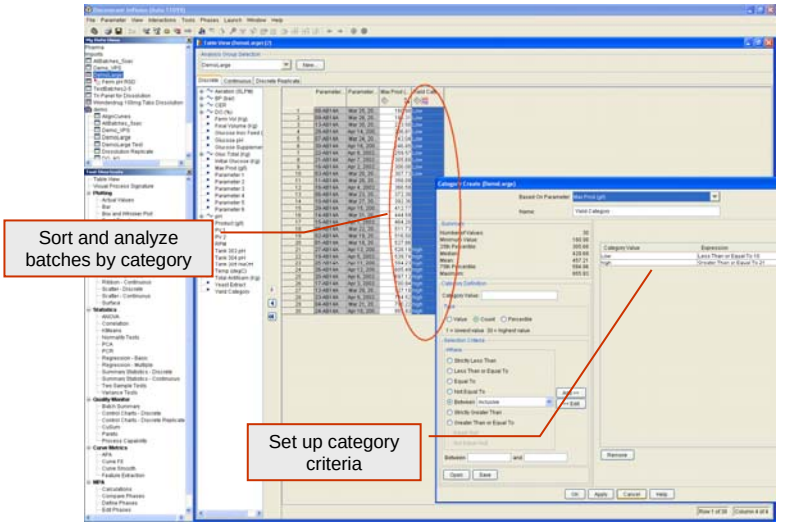
Capabilities for QbD in Bioprocesses

- **Condition continuous data and plot in real time**
- **Extract and Quantify Features of Continuous Data On-screen**
  - Trend and monitor fermentation feeds, rates, etc
  - Identify and correlate features that drive desired outcomes
- **Analyze Continuous Data Profiles for Interactions**
  - Understand combinations of features that drive fermentation outcomes
- **Characterize and Compare Chromatography Profiles**
  - Determine column resin lifetimes and set specifications
  - Compare chromatograms quantitatively

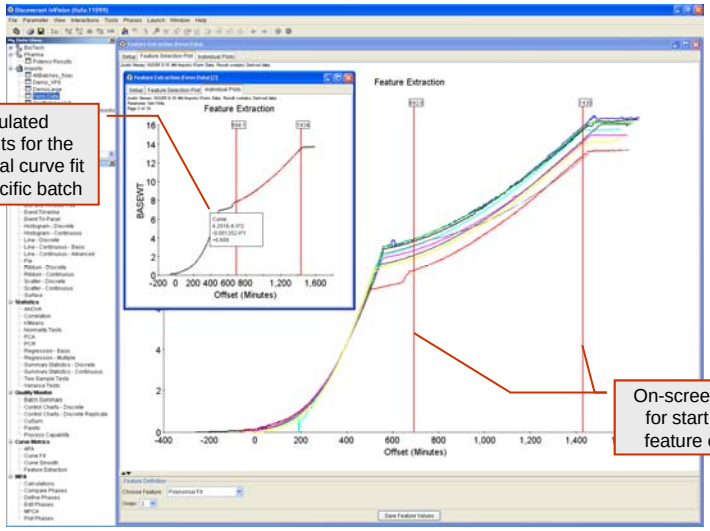
Data Conditioning



Category Creation



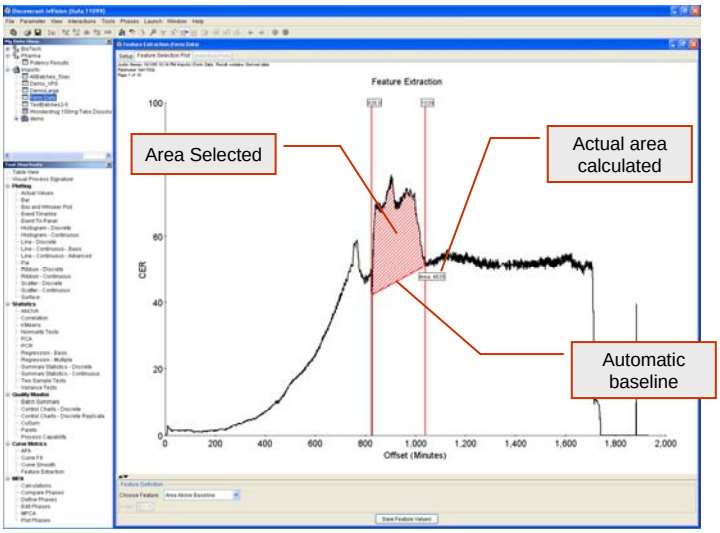
Feature Extraction – Curve Fitting



Calculated constants for the polynomial curve fit for a specific batch

On-screen selection for start & stop of feature extraction

Feature Extraction - Area

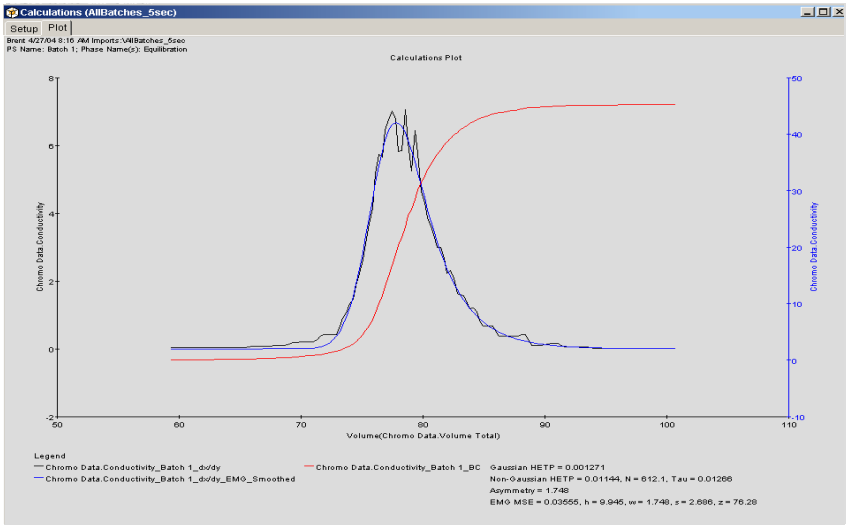


Area Selected

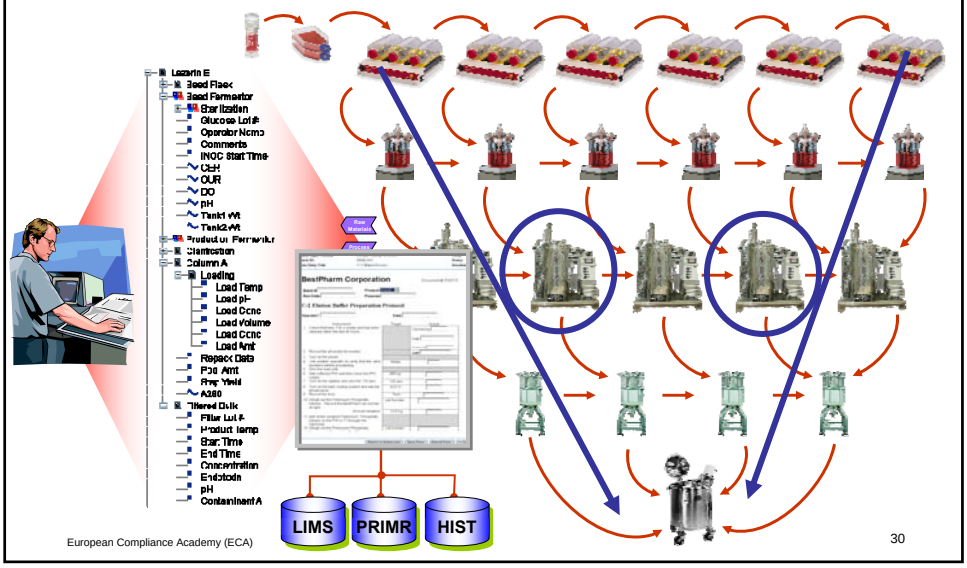
Actual area calculated

Automatic baseline

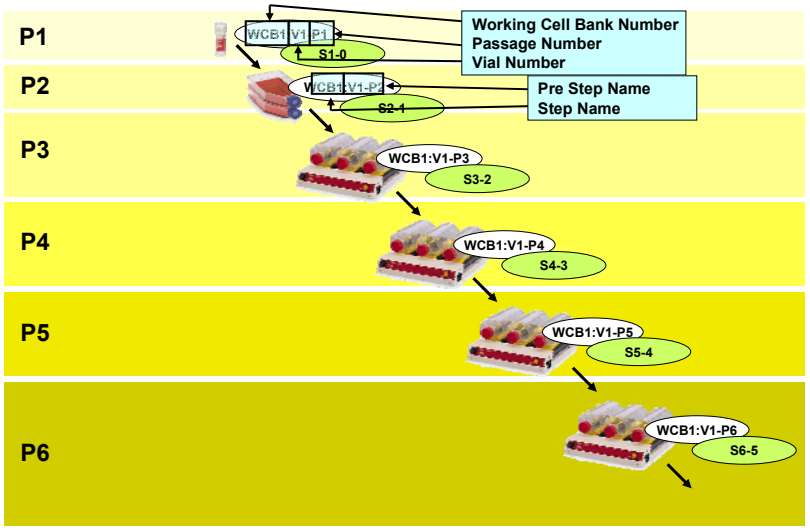
Chromatography Analysis - I



Practical Aspects of Data Access in PD



Configuring the Matrix for Data Analysis



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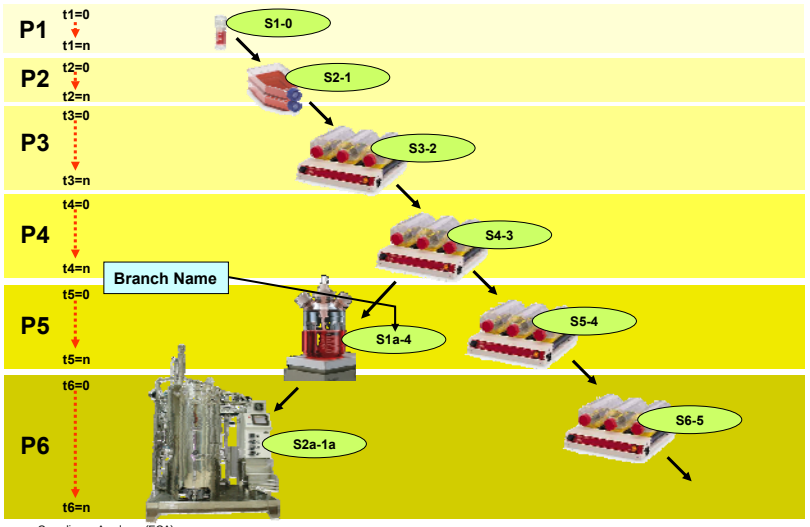
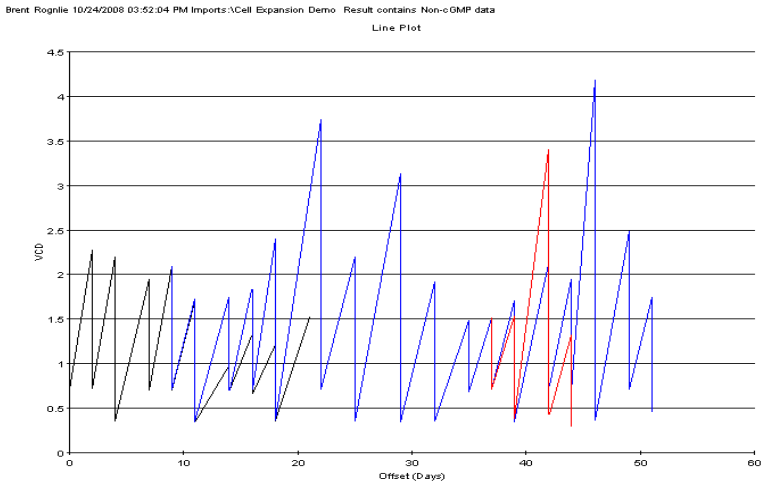
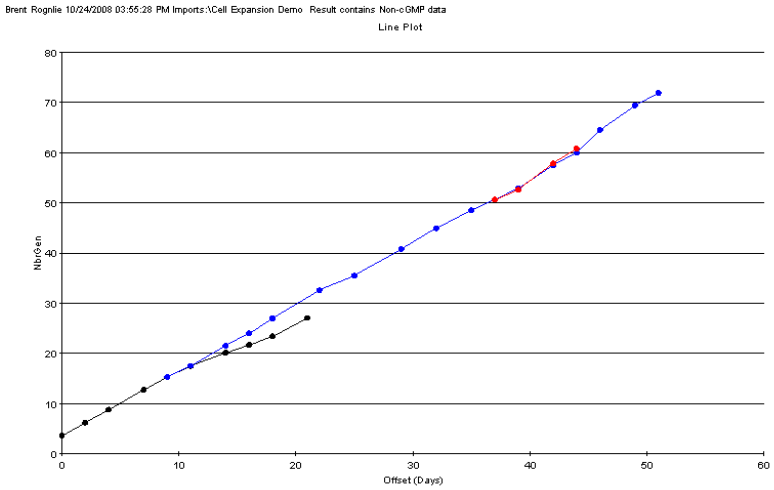


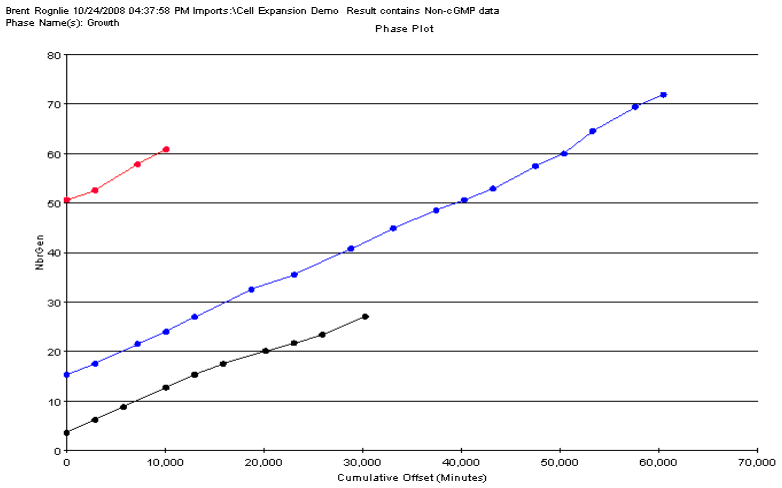
Growth Rate Analysis Example - 1



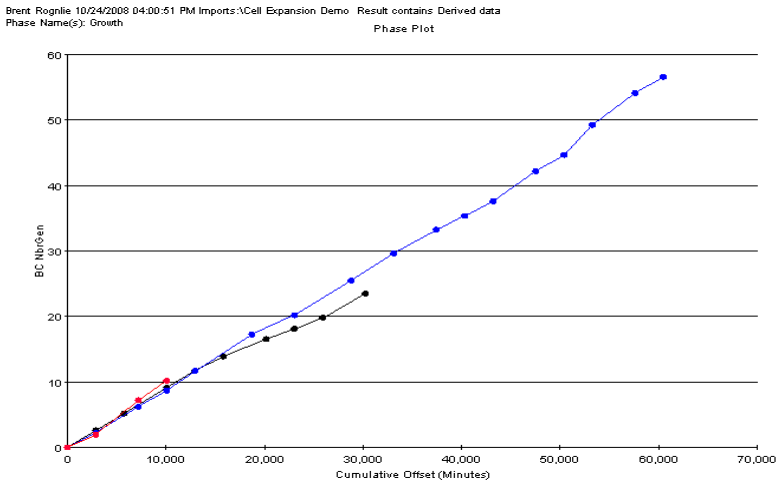
Growth Rate Analysis Example - 2



Growth Rate Analysis Example - 3



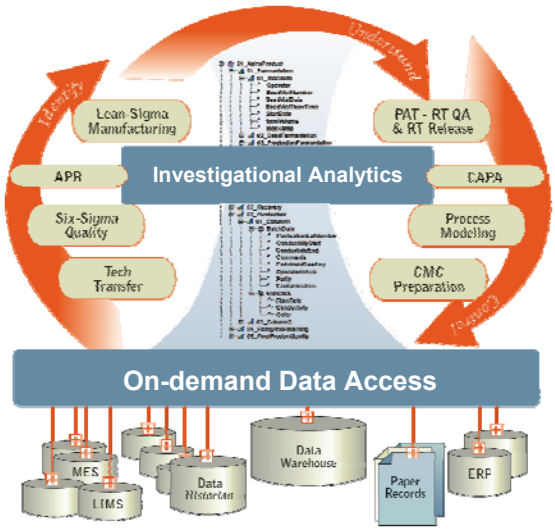
Growth Rate Analysis Example - 4



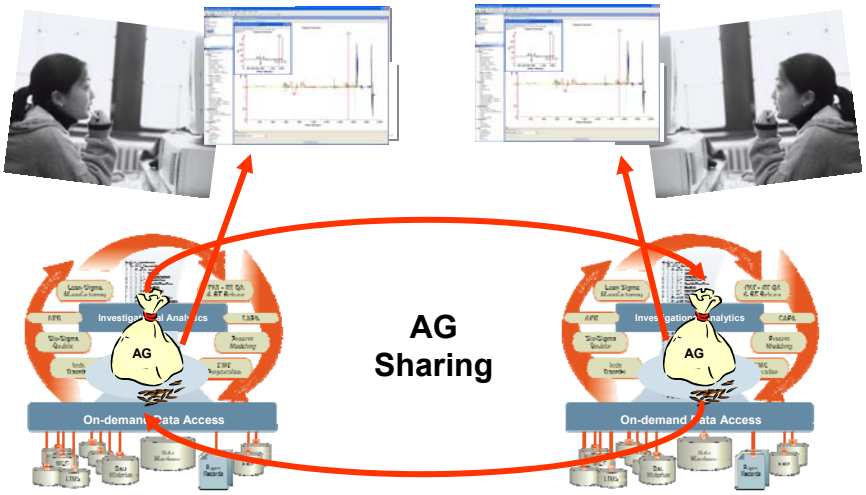
Trends Driving Collaboration

- **Globalization and scarcity make geography an important factor in collaboration**
  - Centers of excellence/Communities of Practice
    - ⇨ Rationalization, right sizing
  - Concentrated and dispersed talent
    - ⇨ Local “feet-on-the-ground”
  - Dispersed projects
    - ⇨ Time zones, geographic and political barriers
  - CMOs/TPMs
    - ⇨ Business barriers
  - Requires appropriate enabling technologies

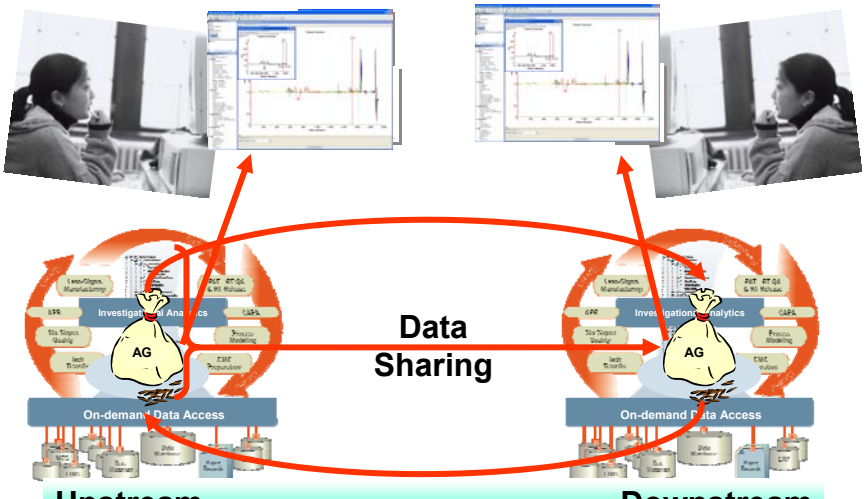
The Enabling Platform for Collaboration



Multi-site Collaboration - 1

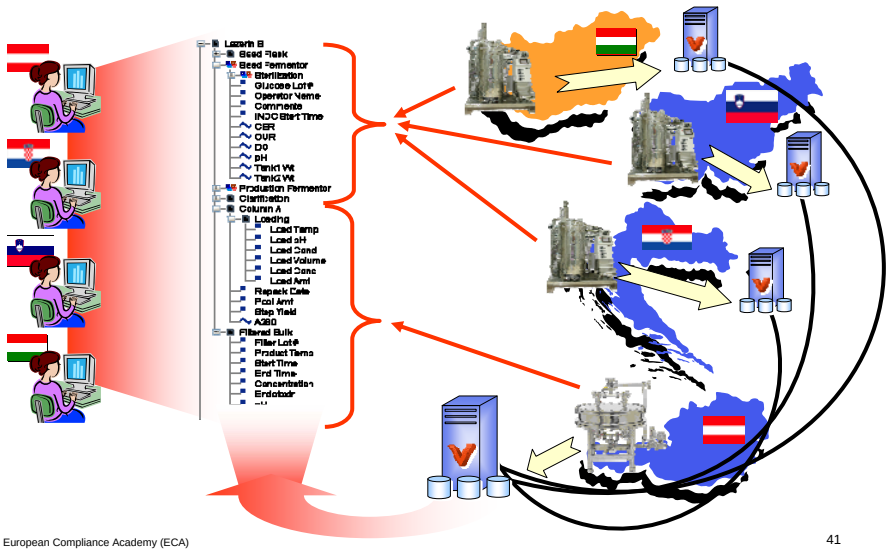


Multi-site Collaboration - 2

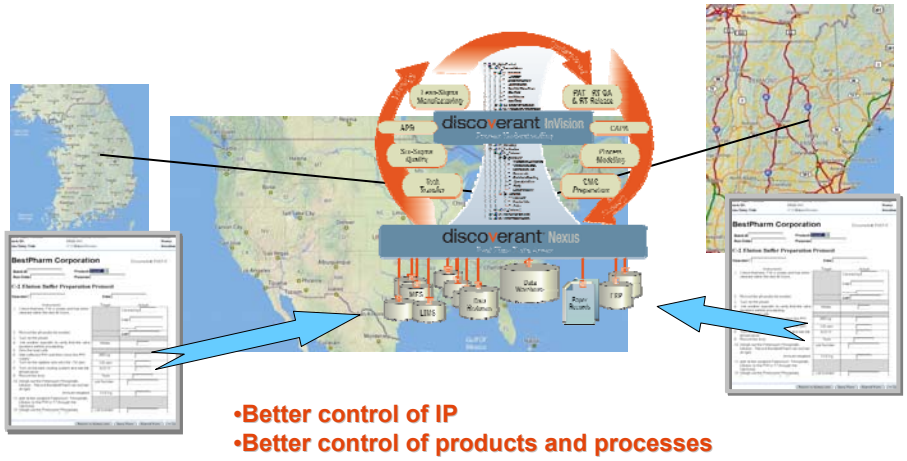


Upstream → → → → → → → → → → Downstream

A Single View of Dispersed Operations

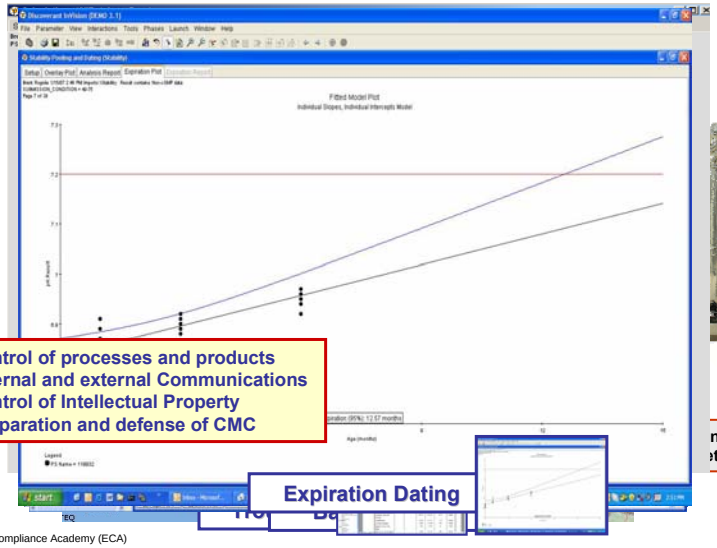


CMO Collaboration – Sponsor Perspective



- Better control of IP
- Better control of products and processes
- Better internal and/or external tech transfer
- Better preparation and defense of CMC

CMO Collaboration – CMO Perspective



- Better control of processes and products
- Better internal and external Communications
- Better control of Intellectual Property
- Better preparation and defense of CMC

Expiration Dating

Removing Geographic Barriers

Summary

Today's data management technology readily enables:

- Real time access to data from multiple disparate sources
- Collaboration across different disciplines scales & sites
- Retrieval of data from current and previous runs at any scale
- Reduction in the time required to understand causes
- Investigations using continuous and discrete data together
- Automatically accounting for process splits and recombinations
- Sharing of data analysis results and reports in widespread teams
- Simplifying periodic reporting (e.g. Batch Reports, APRs, PQRs)

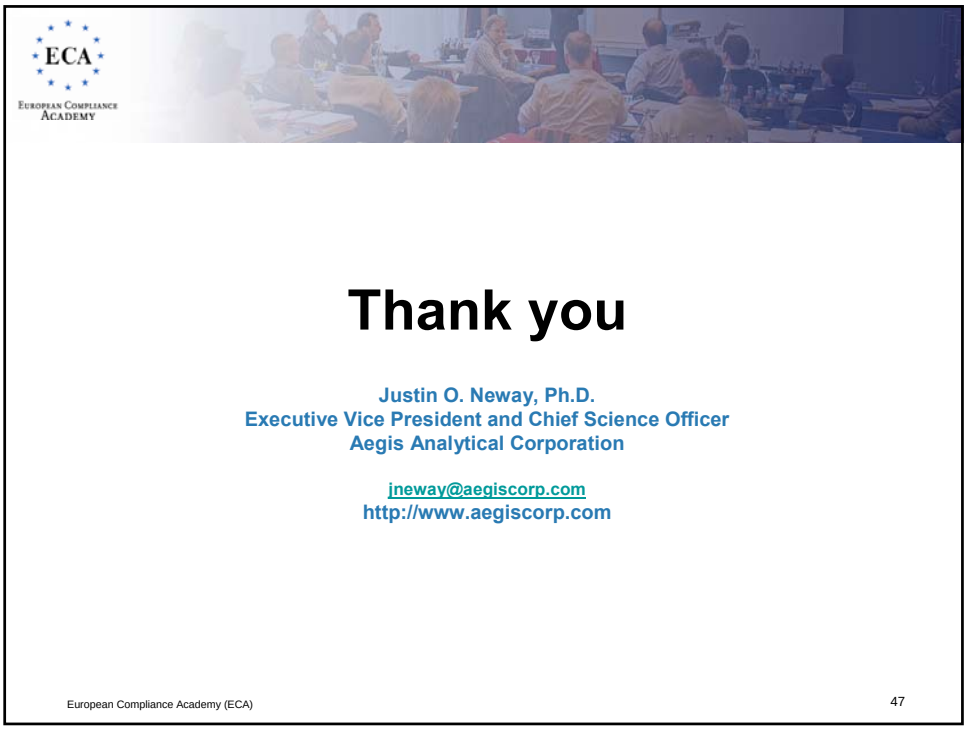
Additional Practical Information

7th Annual Biological Production Forum, Munich, Germany, June 3-4, 2008

Workshop Title: Achieving Manufacturing Excellence across the Global Manufacturing Network Using an On-demand Process Data Access and Analytics Platform

⇨ **Practical experience from a 24-site rollout**

Randall A. Tatlock, Eli Lilly



Thank you

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