“DOES PHARMA Lag Far Behind POTATO CHIP Makers ? “

Wall Street Journal - 9/3/2003

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Overview

- Regulatory Directions
- Corporate vs. Process Systems
- Overview of BMS Systems
- Harmonization
- Plug-n-Play
- The Missing Links
  - Process Analytics
  - Modeling

FDA Observations About the Regulatory System

- Regulatory burden: high and costly, but not viewed as contributing to better science.
- High burden on FDA resources.
- Antithesis of continuous improvement.
- Empirical methods are probably approaching their theoretical maximum effectiveness.
- Janet Woodcock, M.D., Director, CDER.

Pharmaceutical Quality for the 21st Century

- GMP Final Report (September 29, 2004)
  - http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm
- New Quality Assessment System (Recent ODNC White paper)

Specific Objectives

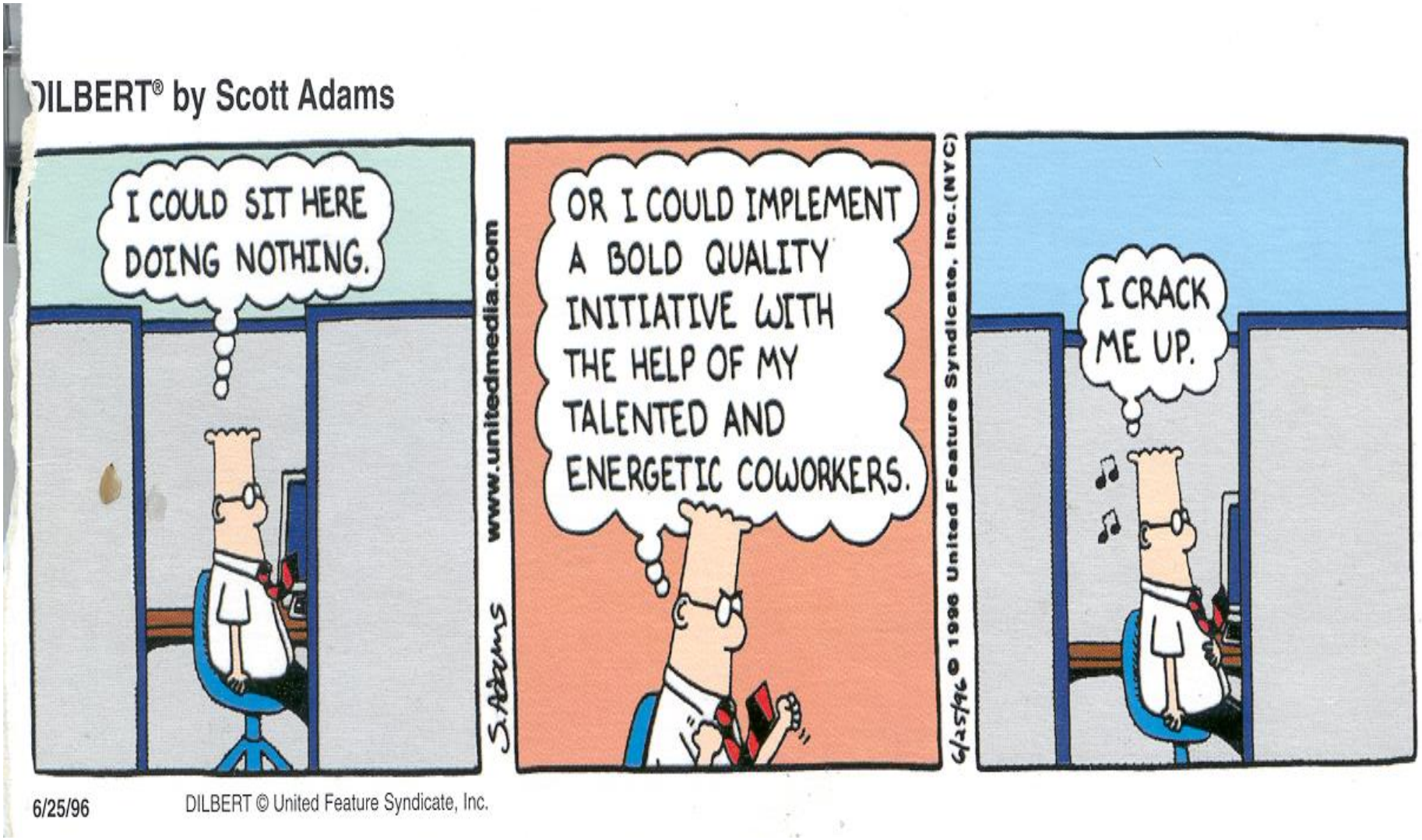
- To encourage the early adoption of new technological advances by the pharmaceutical industry
- To facilitate industry application of modern quality management techniques
- To encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- To ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science

The Simple View

Present State	Desired State
Documentation Focus	***Data Focus***
Have SOPs	Understand Critical Process Parameters-Quality Attributes
Follow SOPs	Measure Process Capability
Meet Specifications Validate Process	Perform Continuous Quality Verification
Don't Change	***Undertake Continuous Improvement***

(Migliaccio 2003)

MCKENZIE CUBICLE -1999



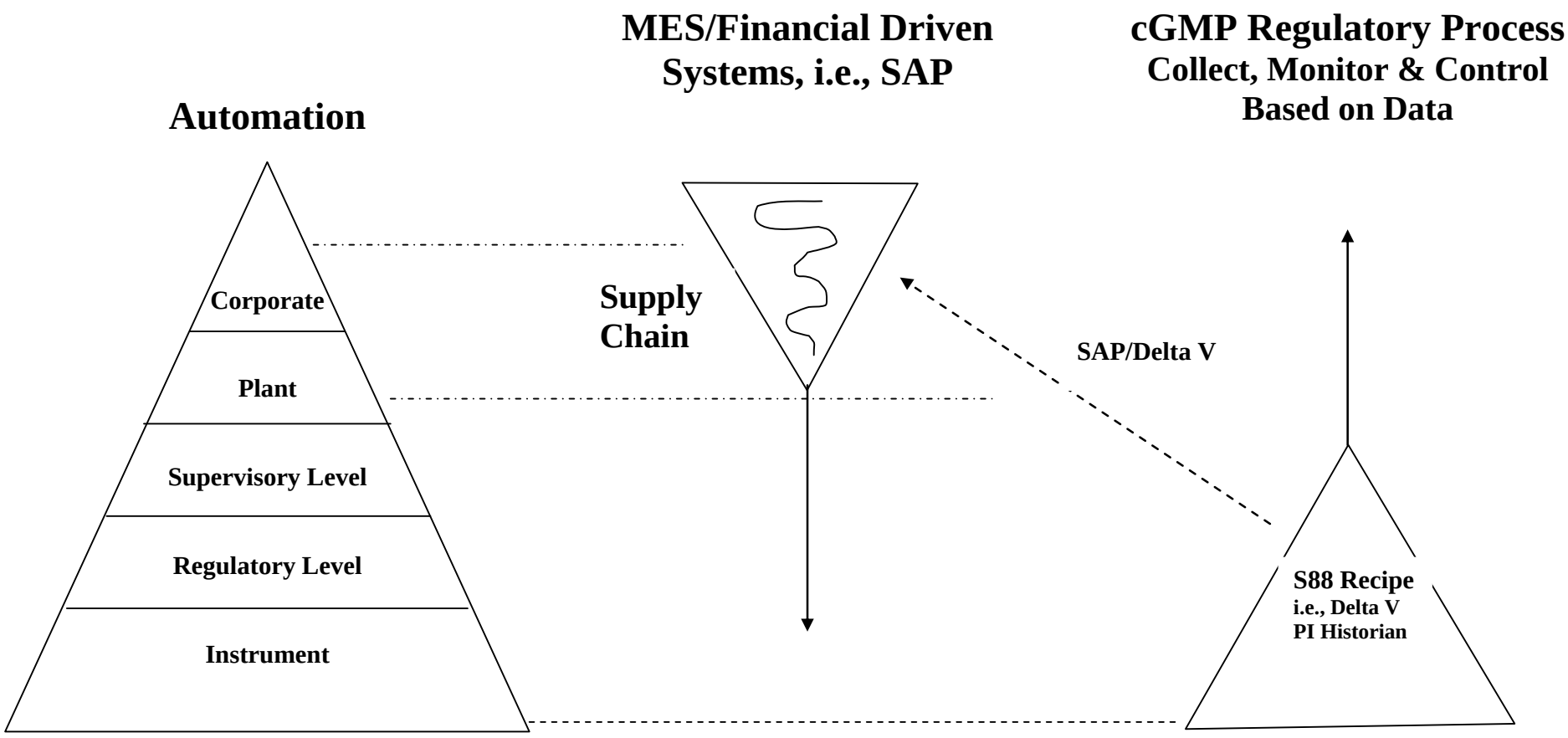
BMS Approach

Meet the Challenges by executing fundamental changes to the development and manufacturing approach

Integration	→	**Integrated scientific, manufacturing, & commercial objectives**
Science	→	**Development of the best route with full intrinsic process knowledge**
Manufacturing	→	**Apply new technologies for effective utilization of process knowledge**

Bottom Line : How to Achieve these ?

Corporate versus Process Systems



Which is right approach?
To truly allow "Window into Process" and to incorporate PAT, we have to look more at getting the Foundation built for automation and less at driving corporate systems down into plant level.

BMS Needed Some Muscle

BMS Road Map

- Laboratory
  - Process Intensification/DOE (High Thruput, Symyx)
  - Electronic Notebook (Intellichem)
  - Spectroscopic Techniques

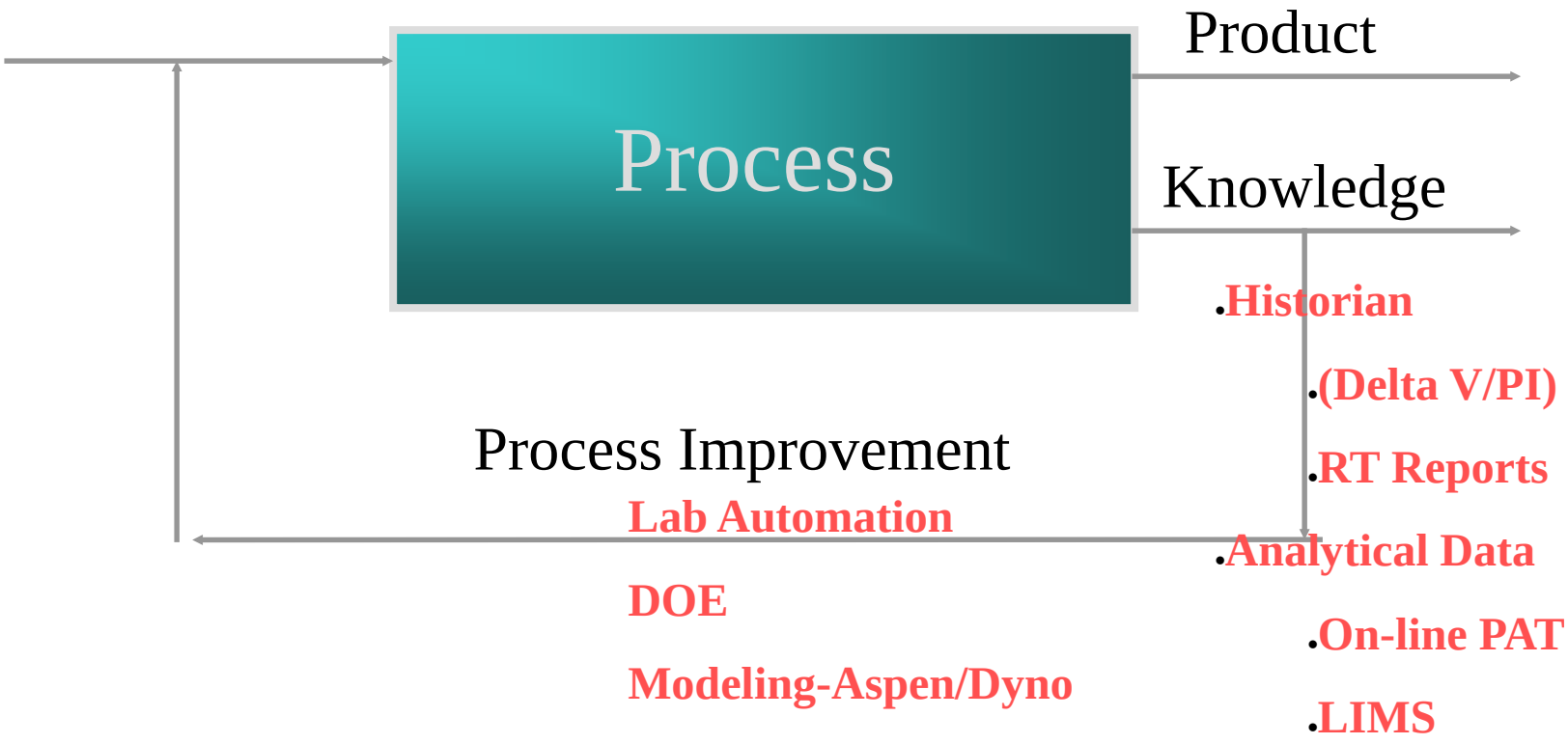
- Quality Systems
  - Materials
  - Equipment
  - Facilities
  - Procedures (ICH Q7A) i.e.-Batch Execution

- Process Control
  - Plant Web (S88, *AMS*)
  - OSI PI Historian
  - Plug-n-Play
  - *Process Assurance Technology (PAT)*
  - *Modeling -Aspen/Dyno Chem*

"Let's run a batch…."

Materials
Facilities/Equipment
Process Parameters

- SAP
- AMS, Maximo & Documentum
- S88 Recipe, On-line Process Analytics

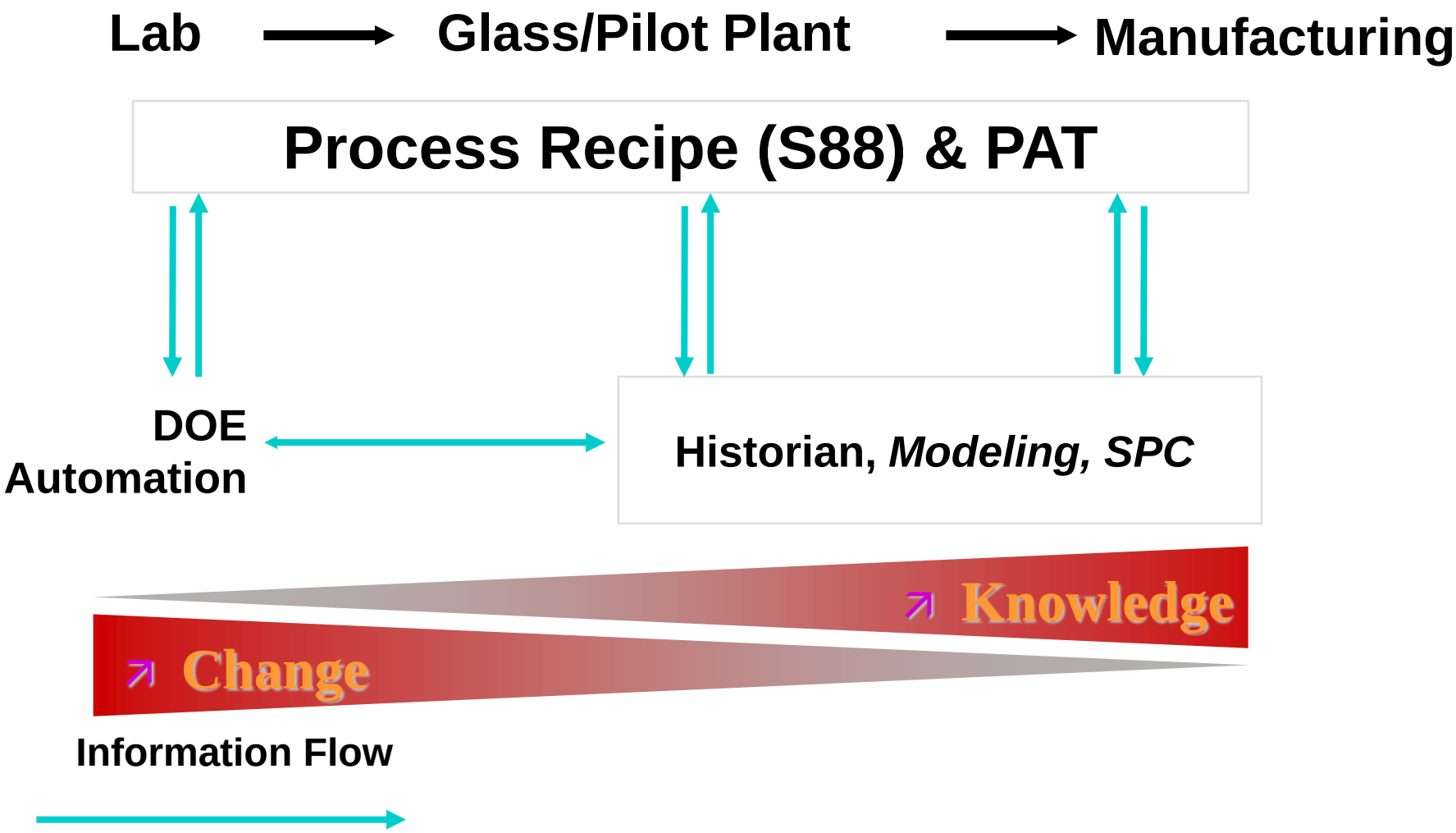


*This applies to Organic, Pharmaceutical Formulation, and Fermentation Processes

Goal: Leverage recipe approach & systems from Laboratory to Manufacturing

S88.01 Batch Standard-Learnings

ISA S88 defines separation of product information from production equipment capability to provide productivity improvements.



Harmonization- Manufacturing & Pilot Plants

Consistent Capabilities & Procedures (Laboratory to Pilot Plant to Manufacturing**)**

- Equipment PIDs
- Organic Areas from glass plant (50 l) to plant (2000 gallon)
  - Inert, Charge, Distill, Extract, Filter, etc.
  - ~125 plus standard phases, validated
- Electronic Execution
  - Recipe on Delta V
  - Seamless link with SAP for management of materials (charges, etc.)
  - Common historian (PI) & Quality Review (RT reports) at desktop
- TOTAL SAVINGS = 7.5 man years, 1,300 Documents, 7,800 Signatures

Harmonization on many levels

- Operator Interface
- Control Modules
- Phases
- Recipes
- Data Historian/Reporting

Operator Interface

- Successes
  - 90% of all graphics re-used on new projects.
  - Standard Faceplates & Dynamos
  - Operator Messaging & Prompts
- Challenges
  - Avoiding customization
  - No Version Control on graphics
  - Integration of Portable Equipment
  - Alarm Interfacing not Optimal
  - Security not Area Model Driven

Control Modules

- Successes
  - ~80% of all modules used on new projects are based on validated modules from previous projects.
  - Standard equipment layouts are key

- Challenges
  - Use of bus technologies, Portable Equipment
    - Plug-n-Play – Difficult to manage !!!
    - System Architecture not aligned for flexible facilities
  - Standard BMS modules developed for traditional I/O required modification and retesting for Buses

Phases

Successes

- Two thirds of the phases used in New Brunswick are common (activity not code) across buildings & Ireland
- Computer handles routine tasks
- Critical batch information reported thru phase

Challenges

- Subtle differences due to equipment/engineer
- Phase harmonization on OEM equipment (centrifuge, dryers, etc.)- Cost & Schedule
- Harmonization will either make the phases overly complicated for less automated applications or inadequate for more automated applications.

Recipes

- Successes
  - Operations are utilizing common vocabulary, parameters
  - Forces better pre-batch planning
  - Running by recipe, all electronic execution provides consistency
  - Compliance Oversight on materials, operations
  - Concurrent operations
  - Recipes have replaced 100 plus page logsheets, documentation errors eliminated
  - Historian captures discrete and continuous information uploaded to desktop

- Challenges
  - Recipe harmonization and transportability has been an unrealized goal at BMS.
  - Training curve for understanding how to write a recipe (not recipe studio but fundamental knowledge)
  - Standardized unit procedures based on varied start-up of facilities
  - Multiple systems for batch intensive, small I/O plants due to batch executive limitations and reliability concerns
  - Unable to use archived recipes due to configuration changes
  - Still some areas holding onto paper

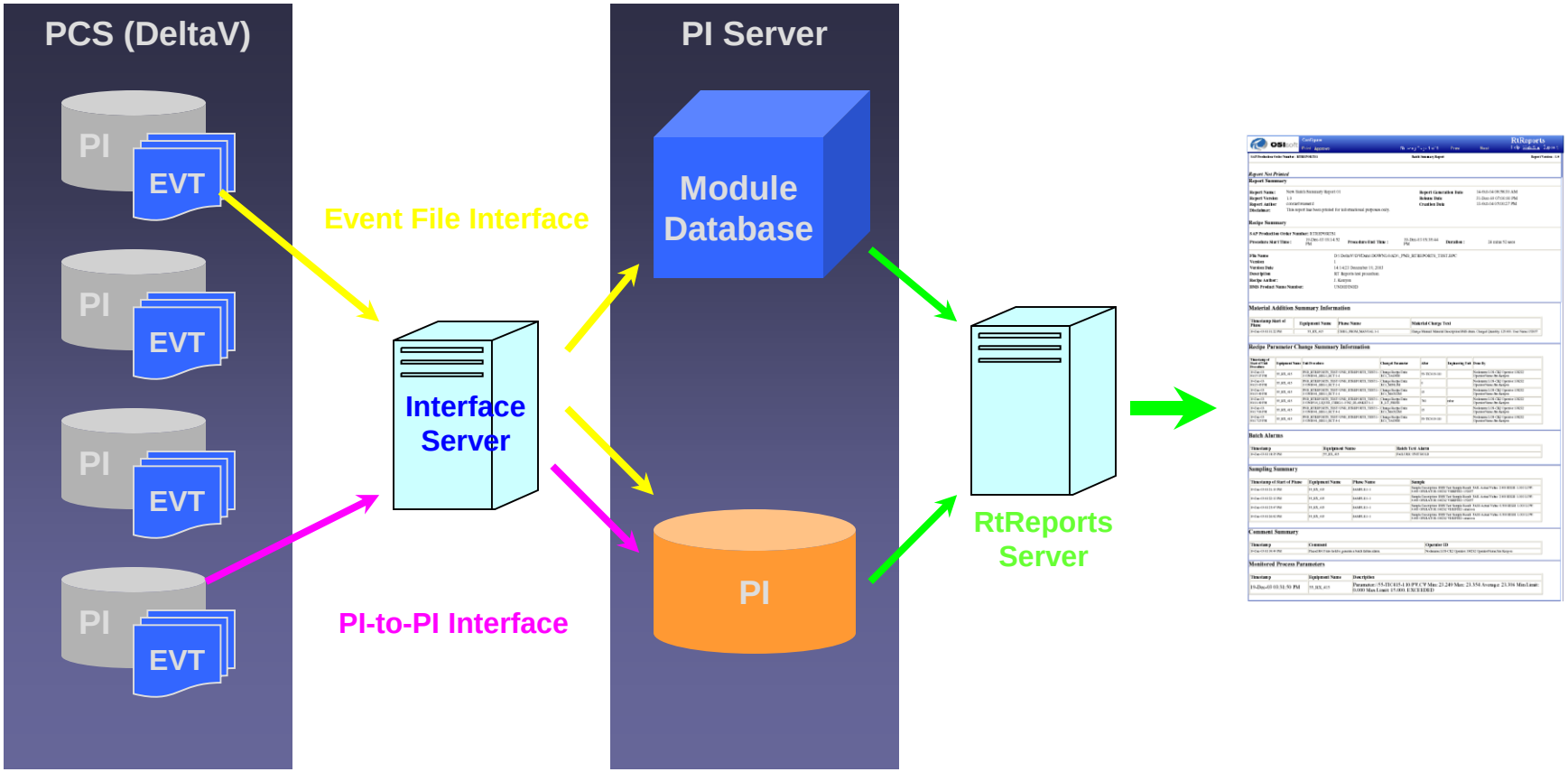
Historian/Reporting

- Successes
  - Quality group releasing batches based on Delta V review
  - Used for equipment qualification and troubleshooting
  - Continuous data on desktop (PI)-scientists love it !!!

- Challenges
  - Event data to desktop
  - Too many individual, batch intensive, low IO systems
    - Batch events occur across multiple facilities
    - Supply Chain not easily viewed (API & Drug Product)
    - Comments post batch (lost)
    - Need Web-based view to multi facilities
  - OSI-Emerson relationship problematic
  - Trying to reproduce paper versus query approach

Architecture

PI & RT Reports



Continuous Data

- Successes
  - Wide use of DataLink to view historical data in Excel
  - Process book used to monitor current operations
- Challenges
  - Educating users on capabilities of client tools
  - Lack of integration between client tools
  - Integrating data from other sources (e.g. PAT) without custom interfaces
  - Use of Historian data to support modeling

Batch Data

- A Long AWAITED Almost Success- RtReports
  - View batch events and associated parameters at desktop
  - Single report template works across all buildings and units
  - Enabled by consistent use of phases and report parameters
  - Detailed reports provide continuous data trends in context of batch events
  - EVT interface used to move historical batch data into PI

- Challenges
  - Batch view client tools only in limited use
  - Ongoing challenge to update batch event data in real-time
  - What is retained for compliance: the ability to regenerate report results or the results themselves? (*paper versus query approach*)
  - Integration of batch data with data from other sources
    - Inventory, Analytical tools, Supply Chain

Report Not Printed

Report Summary

Report Name:	New Batch Summary Report	**Report Generation Date**	19-Nov-04 11:30:02 AM
Report Version	1.0	**Release Date**	31-Dec-69 07:00:00 PM
Report Author	DEVELOPMENT\cnelson	**Creation Date**	17-Sep-04 02:03:35 PM
Disclaimer:	This report has been printed for informational purposes only.		

Recipe Summary

SAP Production Order Number:
100983731D07282004

Procedure Start Time : 28-Jul-04 04:54:12 PM **Procedure End Time :** 26-Aug-04 05:28:44 PM **Duration :** 2mons 29 days 34 mins 32 secs

File Name	D:\\DeltaV\\DVData\\DOWNLOAD_PNB_561389-01_REV2.BPC
Version	3
Version Date	10:01:15 July 27, 2004
Description	bms 561389-01
Recipe Author:	139044
BMS Product Name Number:	UNDEFINED

Material Addition Summary Information

Timestamp Start of Phase	Equipment Name	Phase Name	Material Charge Text
29-Jul-04 06:58:18 AM	55_RX_335	CHRG_FROM_MANUAL:1-1	Charge Manual: Material Description:BMS-561389-06. SAP Number:1166869. Charged Quantity 41.400. User Name:152664
29-Jul-04 07:34:19 AM	55_RX_335	CHRG_FROM_MANUAL:1-1	Charge Manual: Material Description:SDA 3C. SAP Number:1179624. Charged Quantity: 656.10 User Name:152664
29-Jul-04 10:56:00 PM	55_RX_305	CHRG_FROM_MANUAL:1-1	Charge Manual: Material Description:SDA 3C. SAP Number:1179624. Charged Quantity: 41.900 User Name:151676
30-Jul-04 08:51:22 AM	55_RX_335	CHRG_FROM_MANUAL:1-1	Charge Manual: Material Description:WFO. Charged Quantity: 400.000. User Name:151951
30-Jul-04 10:12:05 AM	55_RX_335	CHRG_FROM_MANUAL:2-1	Charge Manual: Material Description:SDA 3C. SAP Number:1179624. Charged Quantity: 448.00 User Name:151951

"Plug-n-Play"

- Fieldbus Devices "quick-connect" to junction brick
- Auto-sensing:
  - device, tag, configuration, etc.
- Ability to integrate & track portable equipment
- This is a Key Element of Flexibility for Design of a Pilot Plant and long-term continuous operations
- Reality-very difficult to manage
  - Configuration
  - Segment Loading (25 Virtual Communication Limit)
  - Downloading on segment effects equipment on it
  - System Architecture not aligned for flexible facilities
  - Wheel less Portable Equipment – an oxymoron

“Plug & Play” cont’d

Plug-n-Play for Unit Operations

Activity	**Without**	**With**
Extraction	Flashlight/Site glass	Portable skid with mass meter, control valve and pump
Controlled Addition	Operator with scientist looking over shoulder	Portable skid with mass meter, control valve and pump and feedback
Cake Wash	Grab samples taken to lab.	Plug in-line pH & Conductivity detectors

On-line Analytics Operational in NB

A) **Raman**
- → **Real-time identity for materials**
- → **Real-time polymorph determination**

B) NIR
- → **Solvent switch determination**
- → **Drying endpoint**

C) Lasentec
- → **Real time particle analysis**

D) FTIR
- → **Reaction progress and completion**

E) Mass Meter*
- → **Real time density for extractions**

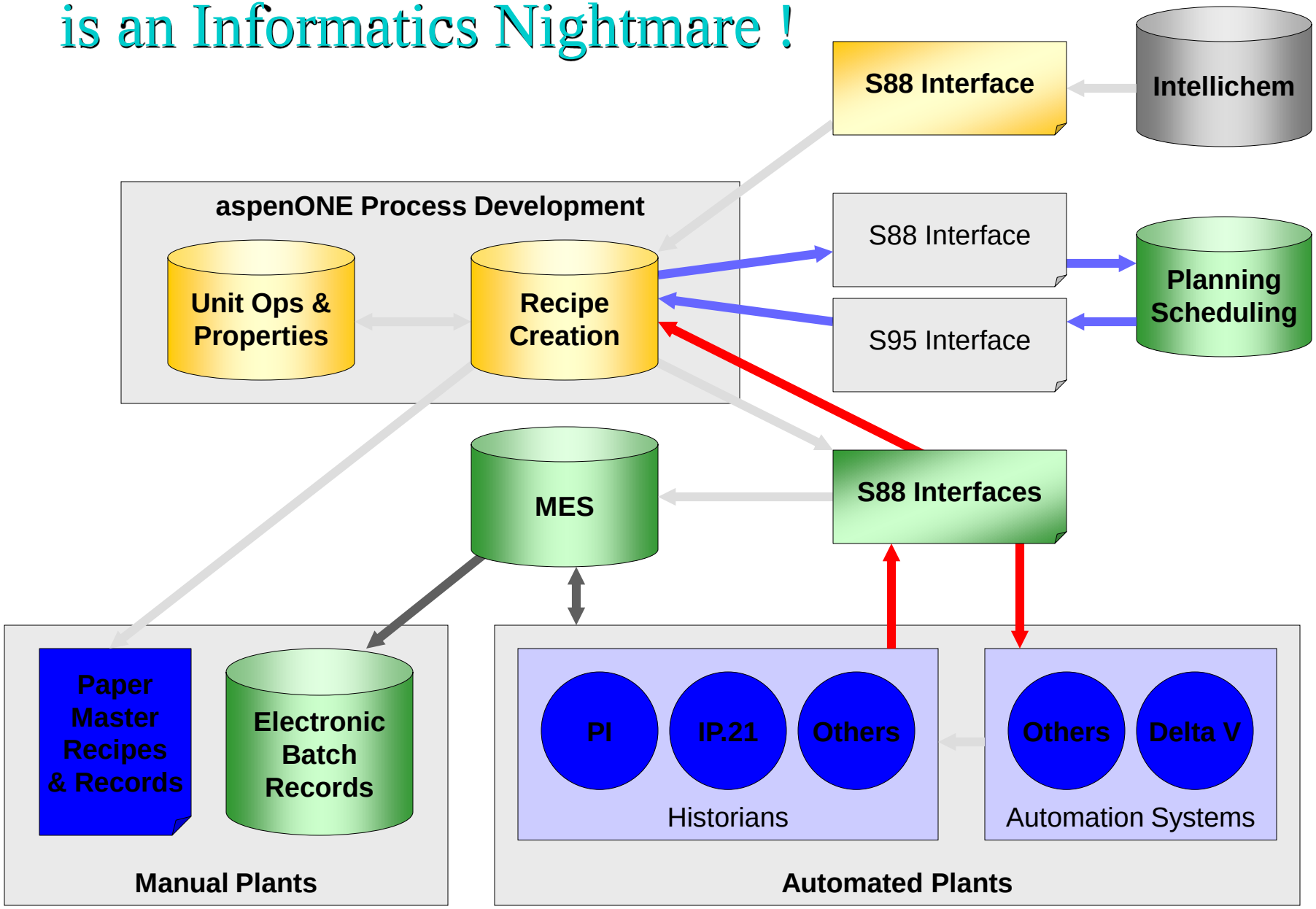
F) Conductivity*
- → **Real time confirmation for cake washing**

***Plug n Play**

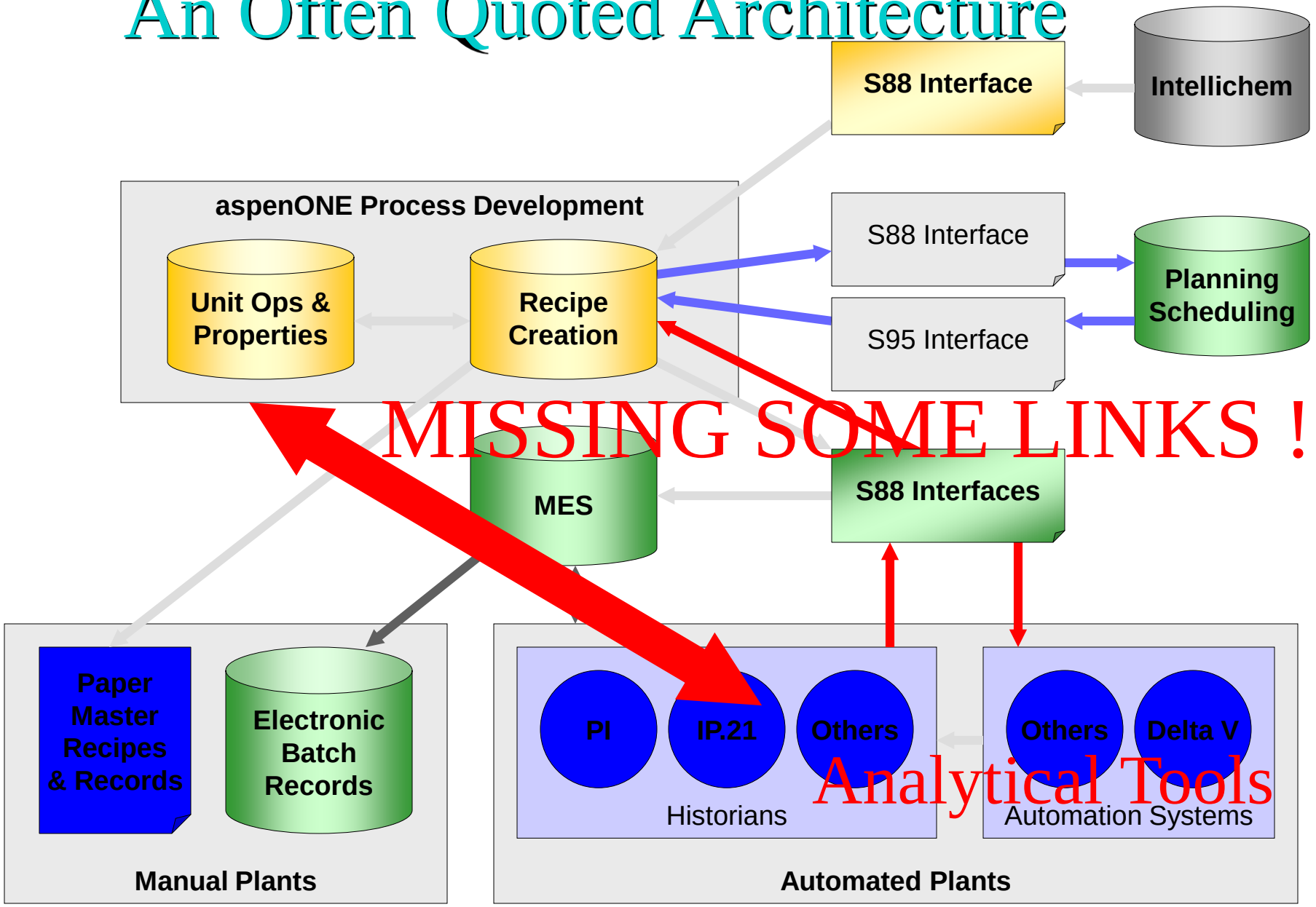
Issues – Portability, Connectivity to Process Control & what/how for data storage

Link to Spectroscopic Techniques is a Must for Continuous Verification !

An Often Quoted Architecture is an Informatics Nightmare !



An Often Quoted Architecture



Bottom Line

- **Heat is on**
  - **Generate process knowledge and share in depth with agency**
  - **Drive continuous improvement in Pharma**
- **OSI – Great for Continuous data, Event data/RT Reports – Soon To be realized !**
- **Plant Web has done great job with S88 and recipe**
- **Emerson & OSI NEED to IMPROVE:**
  - **Connectivity between process data, analytical tools, modeling tools (Unit ops and SPC) and other batch data.**
  - **Ability to handle flexible equipment/analytical instrumentation better. Common architectures and standards with OEMs.**
  - **Working relationship to leverage our investments**

Acknowledgements

- BMS –Reinhardt, Ramsey, Clarke, Ferrari, Rubito, Bartells, Heit, Rossi, Ian Bruce and many many more
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- OMICRON – Mike Purcell, Dave Soll, Greg Sorin and Kevin Farras
- Emerson- Mr. Dean, Raoul Mercer, Josh Davies, CJ Lu, James Nielson, Steve Rigby, Neil Hammill, Bryan Jones, Dave Dietz, Ferrill Ford, Dr. Tune (Mark Coughran), Norm Ito, Simon Capewell