MES/Batch Integration in Life Science Applications
GEN INT-11 B

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Presentation Agenda

- Vacaville CCP1 System Architecture
- MES/Batch Integration Strategies
- Relative Benefits & Drawbacks
- Recommended Design Elements
- Questions…
Vacaville CCP1 Facility

- Vacaville Technical Operations is one of six major drug substance production sites in the Roche/Genentech manufacturing network and plays an important role as a high-volume Active Pharmaceutical Ingredient (API) manufacturer.

- CCP1, in GMP operation since 2000, is licensed for 7 products at a production fermentation capacity of 144,000L (12 x 12kL).

- The maximum recovery throughput in CCP1 is 6 runs per week (rpw) or 72,000L of cell culture fluid (6 x 12kL). It currently operates at a sustained throughput of 5.2 rpw, utilizing 87% of its maximum capacity.

- Through 2013, CCP1 has successfully completed over 50 GMP campaigns (>2000 runs) to produce over 22,600 kg of bulk API for 7 products to treat patients with critical medical conditions.

  Vacaville production of +66.7M patient dosages are estimated to have prolonged oncology patient lifespans by almost 4.7M years.
Manufacturing Operations and Control Domain

“... includes all the activities and information flows in Level 3, 2, and 1 and information flows to and from Level 4.”
CCP1 System Architecture (original)

- Corporate SAP Enterprise Resource Planning (ERP) system
- Beckman LIMS Laboratory Information Management System
- Batch Assay History Record (BAHR) Genentech custom Review By Exception system
  - Collects & organizes GMP status and data
  - Tracks manufacturing & material status
  - Collects & archives critical release reports
  - Provides QA lot review & release functionality
- OSIsoft PI Process Historian
- CCP1 employs a custom gPOMS MES solution built with the POMS Production Operations Management System programming toolkit.
- A custom BHDS Batch Historian and OLRT Batch Review system performs integration of batch data, creation of enhanced batch reports, and facilitates QA & Manufacturing batch review.
In 2013, a major software project upgraded the CCP1 system with new:
- InBatch Batch Management application
- ArchestrA SCADA & InTouch HMI
- Wonderware Process Historian

All Batch recipe, equipment and material databases were programmatically migrated from Direktor to InBatch at a significant savings in engineering and revalidation efforts and costs.
- System cutover from old to new was completed in 8 hours.
- The facility returned to GMP operation after 10 days of engineering testing and successfully ramped back up to full production within a month.

The legacy Siemens APACS DCS control layer is still in use, but planning to also be replaced in a subsequent project.
Alternate MES/Batch System Architectures

- Functional capabilities inherent in other vendors’ MES and Batch Management products have driven an alternate, but common MES/Batch system architecture. The diagram below focuses on just the elements in the S95 Manufacturing Operations & Controls Domain.

- Note how the two architectures span the Level 3/2 boundary differently. This important distinction can have a major impact on the resulting capability, reliability, supportability, and overall quality of an integrated automation solution.

- In the CCP1 architecture, InBatch extends upwards into Level 3 with functionality to perform equipment arbitration and manage WIP materials.

- In the alternate architecture, the MES has responsibility for equipment and material management, and also extends downward into Level 2 to handle user interaction and deliver operator instructions.

- In this scenario, the Batch Manager is used just to start automated procedures and coordinate phase logic execution in the DCS.
Software Quality Metrics: Coupling & Cohesion

• **Coupling** is the degree to which a program module relies on other modules. Low or ‘loose’ coupling is a sign of a well-structured computer system and good design.

• High or ‘tight’ coupling means that: a) related modules have to know internal details of each other, b) changes ripple through the system, and c) the system is potentially harder to understand and troubleshoot.

• **Cohesion** refers to the degree to which the elements of a module belong together and is usually described as either ‘high’ or ‘low’ cohesion. The metric is a measure of how strongly related to each other the pieces of functionality performed by a software module are.

• Modules with high cohesion tend to be preferable because it is associated with several desirable software traits including: robustness, reliability, reusability, and understandability, whereas low cohesion is associated with undesirable traits such as being difficult to maintain, test, reuse, and even understand.

• Coupling is usually contrasted with cohesion. Loose coupling often correlates with high cohesion, and vice versa. Loose coupling combined with high cohesion typically supports the general goals of high software reliability and maintainability.

*The software quality metrics of coupling and cohesion were invented by Larry Constantine in the late 1960s as part of “Structured Design” published in the article (Stevens, Myers & Constantine, 1974) and book (Yourdon & Constantine, 1979). They subsequently became standard terms used in software engineering.*
High vs. Low Cohesiveness of Procedural Execution

- In CCP1’s architecture, all procedural execution is managed by the InBatch application. ERP Shop Orders and/or MES Work Orders automatically initiate S88 unit procedures in the Batch Manager. InBatch is responsible for performing asset management and hygienic status tracking, delivering operator instructions, tracking WIP materials, and reporting completion status and final material consumption/production to the MES.

- In the alternate architecture, MES procedures, operations and phases drive execution of subordinate Batch unit procedures. The Batch Manager only starts and coordinates DCS-based phase logic, while the MES assumes responsibility for procedural control, asset management, presenting operator instructions and material use tracking.
CCP1 Recipe Structure

- CCP1 MES automatically schedules InBatch unit procedure on behalf of an ERP Shop Order or manually entered MES Work Order.
- InBatch phases start and control CCP1 DCS-based or ArchestrA-based ‘virtual’ (i.e. non-equipment) phase logic per standard S88 phase state machine model.
- Both DCS and ArchestrA phases can utilize CCP1 MES functionality via a web service interface. Infrequent service interruptions are handled with a supervisor’s approval to proceed via electronic signature.

*Example: performing material status verification just prior to consumption at the point of use.*
In the alternate architecture, MES phases, which usually do not follow a standard phase state machine model, are used to start a subordinate Batch procedure consisting of one or more unit procedures.

Most DCS phase logic has MES transactions embedded in the equipment control logic (e.g. for operator prompts) and some DCS phases only send transactions to the MES.
Loose vs. Tight Coupling of MES, Batch and DCS Systems

- High functional cohesion with InBatch providing all procedural control, equipment arbitration of units and connections, and WIP material tracking capability also results in loose coupling with minimal Batch/MES interaction during procedure execution (while greatly simplifying integration).
  - The CCP1 MES can be offline for hours or even days without stopping shop floor execution.

- In a tightly coupled architecture where MES retains responsibility for user interaction and material management, DCS phase logic must invoke MES functions to record use of all materials and instruct operators to perform manual steps.
  - MES Bill of Instruction, Bill of Material, and Bill of Equipment references must be synchronized between MES and DCS phases in order to trigger proper equipment usage, user instructions, and material consumptions in the MES.
  - MES interaction within DCS phase execution requires setting and resetting individual flags and transaction data fields that are passed between MES functions and DCS phase logic, usually via an OPC interface, which must be kept running.

- With a tightly coupled design, care must be taken to avoid the risk of MES/DCS deadlocks.
  - DCS phase logic or MES functions can require system administrator intervention if DCS/MES interactions gets out of sync in stateful transactions.
CCP1 vs. Alternate Strategy - Benefits & Drawbacks

- **Plant Equipment Utilization**

  - CCP1 InBatch procedures acquire and release equipment assets as needed, allowing for high equipment turnover and timely readiness for subsequent operations.

  - In the alternate architecture, equipment assets used by Batch procedures must first be allocated in the MES and will typically remain allocated for the entire duration of the procedure.

  - The MES and Batch equipment models may differ as many Batch products do not manage connections and segments between process units. When equipment not defined in the Batch model needs to be allocated in mid-procedure, DCS phase logic must ask the MES to verify equipment status and, if acceptable, allocate the equipment.

  - In some situations, DCS phase logic can flood the MES with repeated allocation requests until the equipment is finally ready and available for use – generating potentially hundreds of thousands of meaningless batch history records.
• **Reliability & Supportability**
  
  - In a tightly coupled architecture, there are many parameters that must be manually synchronized between MES recipes, Batch procedures, and DCS phase logic as part of configuring the various integration points. Configuration errors will typically cause undesirable results.
  
  - OPC is a technology frequently used to integrate MES with Batch and control systems, but OPC functionality may not be sufficiently reliable or deterministic for the communication demands of a tightly coupled integration.

- Distributing and closely linking procedural functionality among MES, Batch and DCS systems makes troubleshooting difficult and time consuming (even with extensive vendor support).
CCP1 vs. Alternate Strategy - Benefits & Drawbacks

- **Batch History Data Collection & Integration**
  - CCP1 equipment usage and material data is already combined in the InBatch batch history. Custom BHDS logic to query for alarm information from Wonderware Alarm database to incorporate into batch record is fairly straightforward.
  - InBatch makes it easy to consume and store batch data in whatever form needed (if not using the standard InBatch batch history database).
  - In the alternate architecture, custom programming may be required to retrieve and merge procedural execution data from the MES and Batch Manager and then integrate with MES material and equipment data before finally incorporating DCS alarm data to create the batch record.
  - MES/Batch/DCS data integration may require investment in complex and expensive custom ETL* software that is very challenging to develop, validate, support and enhance.

* Extract, Transfer, and Load
MES/Batch Integration - Recommended Approaches

• Favor ‘High Cohesion’ and ‘Loose Coupling’ for MES/Batch integration
  ✓ Ensure the Batch Management application includes all functionality required to meet Manufacturing and Quality Assurance requirements.
  ✓ Minimize having many detailed interactions between major systems. Where warranted, include provisions to accommodate for potential system downtime.

• Leverage API Function Libraries to augment Batch system capabilities
  ✓ Facilitate Batch system integration with ERP, MES and LIMS functionality.
  ✓ Utilize equipment hygienic status as part of Equipment Asset Allocation logic.
  ✓ Integrate multiple Batch Managers with shared equipment and material transfers.

• Integrate major system functions to increase overall plant productivity
  ✓ MES/DCS: recipe initiation and completion status, material point of use verification, material consumption & production reporting, operational status reporting.
  ✓ MES/ERP: genealogy & inventory updates, shop order progress, finite scheduling.
  ✓ DCS/LIMS: advanced sampling notification, sample label printing and sample registration, assay test result retrieval back into DCS phase logic and batch report.
  ✓ Ensure that documented work-arounds are in place to continue manufacturing operations in the event of a MES, ERP and/or LIMS interface failure.
Questions?