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TRANSFORM YOUR WORLD

Sanofi Genzyme's Operational Improvement: Batch Record Review-By-Exception (RBE) Implementation using OSIsoft PI System, PAS-X & DeltaV

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David Maglaya

SANOFI GENZYME

Outline

- Background
- Program Drivers
- Program Goals
- Program Overview
- System Integration Strategy
  - ISA S95
  - Architecture
- System Integration Examples
- Benefits
- Project Recap
- Future

Sanofi Genzyme Background

- Sanofi Genzyme was one of the industry's earliest innovators in large-scale commercial production of therapeutic enzymes using recombinant DNA technology
- Many of Sanofi Genzyme's products are biologics
  - Manufacturing is a lengthy process involving delicate living cells that are highly sensitive to their environment and even the smallest of changes in the production process.
- Areas
  - Rare Diseases
  - Multiple Sclerosis
  - Oncology
  - Immunology

Yuua Matsui, Fabry disease
Nagoya, Japan

Fabrazyme Manufacturing Facility

- Fabrazyme ERT (Enzyme Replacement Therapy) manufacturing facility in Framingham, MA
- 4 x 2000L bioreactor cell culture, upstream purification
  - FDA approved in 2012
- 4th bioreactor commissioned in 2013

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What is RBE?

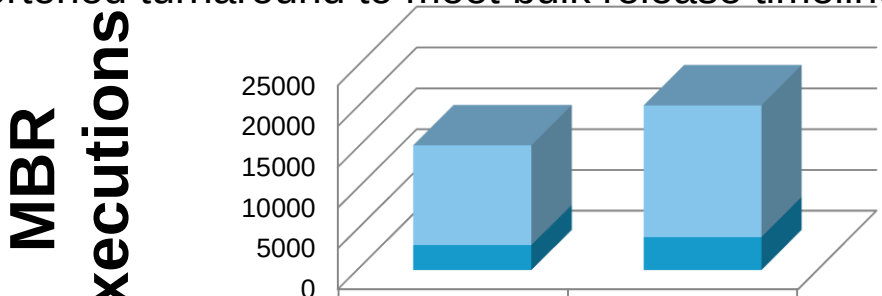
- Traditional Batch Record Review
  - Involves reviewing all data in batch record
  - Manual data entry from various systems
  - Time consuming
  - Focus is not on critical aspects of batch record
- RBE stands for Review-By-Exception
  - The **right level of review** (by the System, Manufacturing, QA) of the **right aspects** by **record type** (Criticality / risk-based**)**
  - Flag variances from normal execution
  - Review only those variances
- RBE includes Integration of Systems
  - Automatic data transfer between shop floor systems
  - Automated workflows in electronic batch records

RBE Program Drivers

2000L Fabrazyme upstream production in 74 NYA, Framingham Biologics utilizes Electronic Batch Records in the Manufacturing Execution System (MES)

Drivers for RBE program:

1. 33% increase in capacity; from 3 bioreactor trains to 4
2. Shortened turnaround to meet bulk release timelines



	2013 # Executed MBRs	2014 # Forcasted MBRs
High Frequency Records	12262	16165
Normal Records	3066	4041

Primary objective of RBE: To reduce manual reviews of batch records

- ❑ Without RBE: Full manual review of batch records by MFG and QA
- ❑ With RBE: **Automatic review** by MES **OR simplified** manual review

RBE Goal – Automated System Review

- In a scenario where the batch record executes without events, the batch record is **automatically** reviewed by MES
- The only entries that require manual review are:
  - Event Log entries
  - Verifiable manual data entry for critical parameters
    - ✓ System Integration **eliminated** most of these touch points
- Guidelines for simplified review were established by a cross-functional management team consisting of MFG, QA, and MES
- Change in culture
  - No need to review the entire batch record
  - Trust the systems and MBR configurations

RBE Program Overview

Phased Approach – risk/savings based

- **Phase I** targeted the high frequency Master Batch Records(MBRs)
  - Equipment Prep and Cleaning (CIP, COP)
  - 79% of executed records in 2013
  - Total MBRs: 33
  - Completion: Q3 2014
- **Phase II** consisted of Solution Prep and Equipment Use Records (EURs)
  - Buffer and Media MBRs, and Filter Integrity Test EURs, etc.
  - Total MBRs: 22
  - Completion: Q1 2016
- **Phase III** will consist of all other process MBRs
  - Bioreactor, phenyl chromatography, etc.

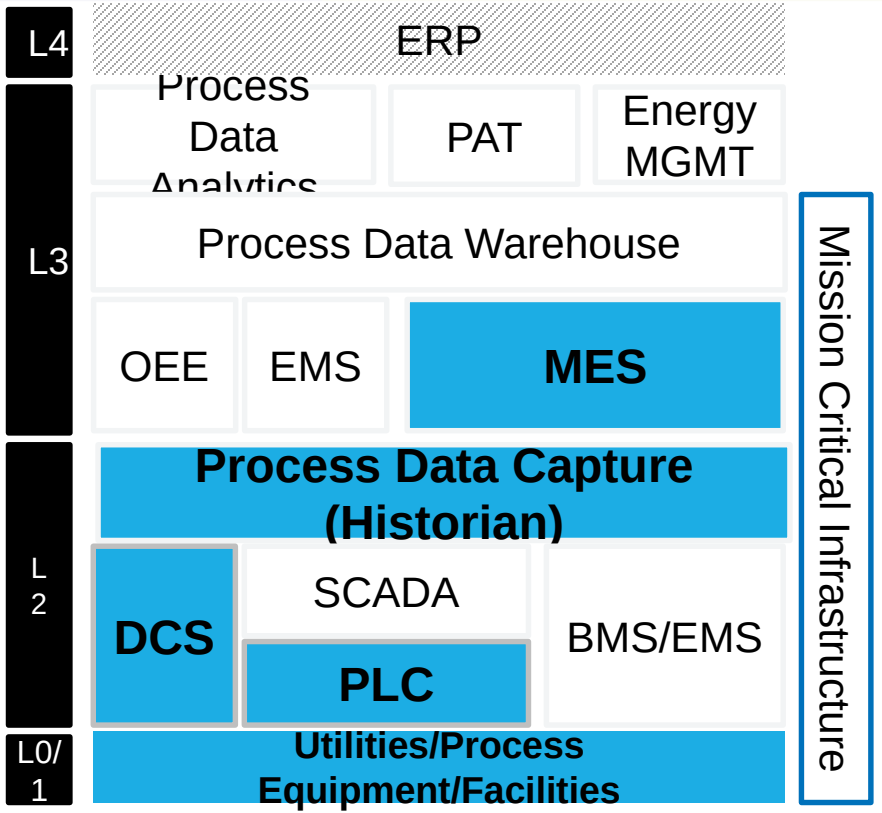
Phase I complete

Phase II complete

Phase III not yet started

ISA S95 Structure → Enables for RBE

- Industry accepted standard for integration
- Includes system roles and responsibilities
- Light integration approach adopted
- Changes made to Levels 0-3 to enable RBE
- Unidirectional data flow from Level 2-3



System Versions

WERUM
KÖRBER SOLUTIONS

PAS-X

PAS-X Version 2.3/04

EMERSON

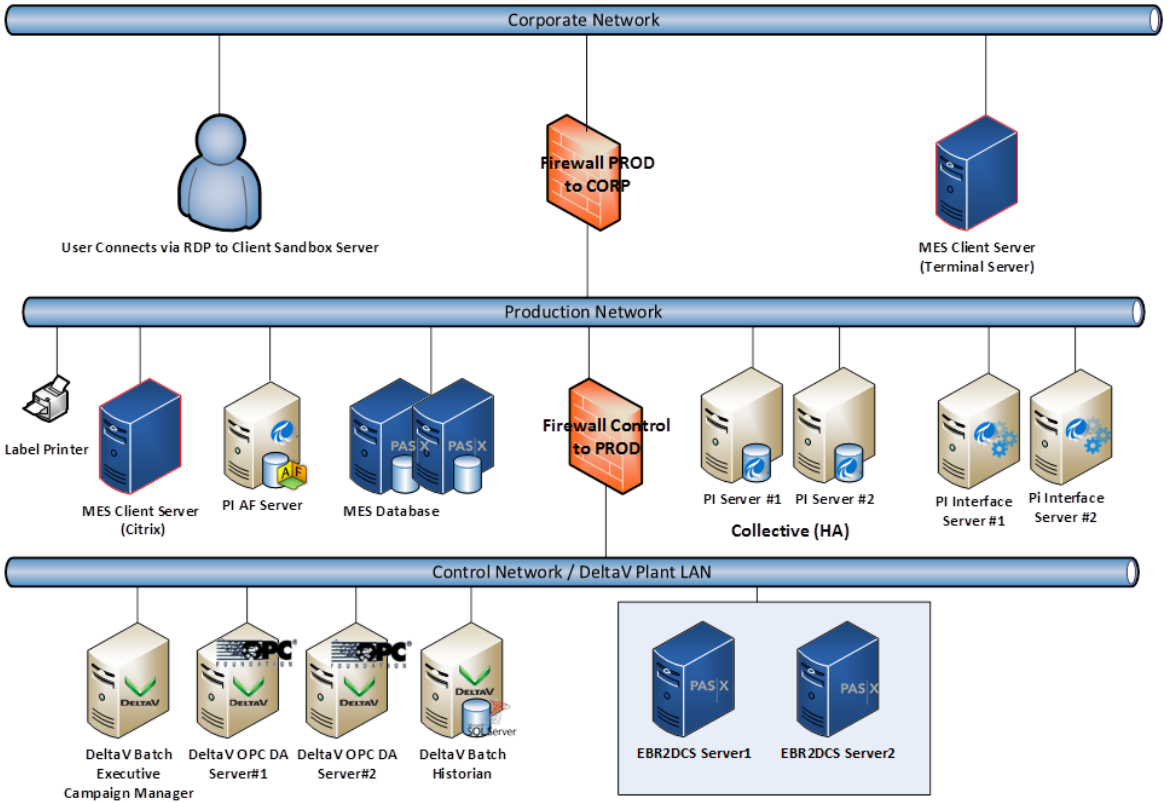
DELTAV

DeltaV Version 11.3.1

OSIsoft

PI Server 2012

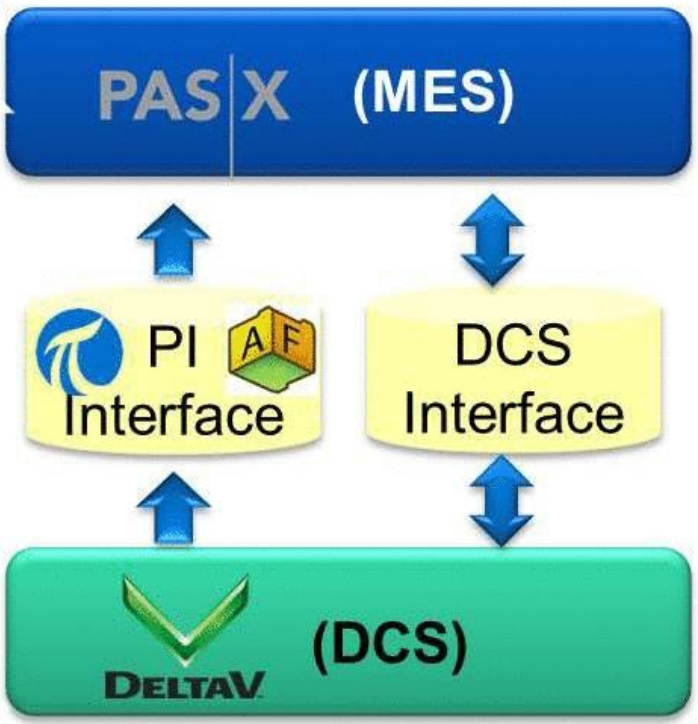
IS/Automation System Architecture



System Integration

- **PAS-X (MES)**
  - Bi-directional Interface with DeltaV Campaign Manager
  - Uni-directional Interface with OSIsoft PI Server
  - Uni-directional Interface with OSIsoft PI Asset Framework
  - Electronic Batch Record sends commands to DCS (Campaign Manager) to automatically start recipe
  - Reads process / batch data in near-real time via OSIsoft PI Server

TIM01003 Wash Cycle End Time	-----	10/22/2015 05:46:08	10/22/2015 05:47	PI	
ATT01004 PI Interface End	Complete	Complete	10/22/2015 05:47	PI	



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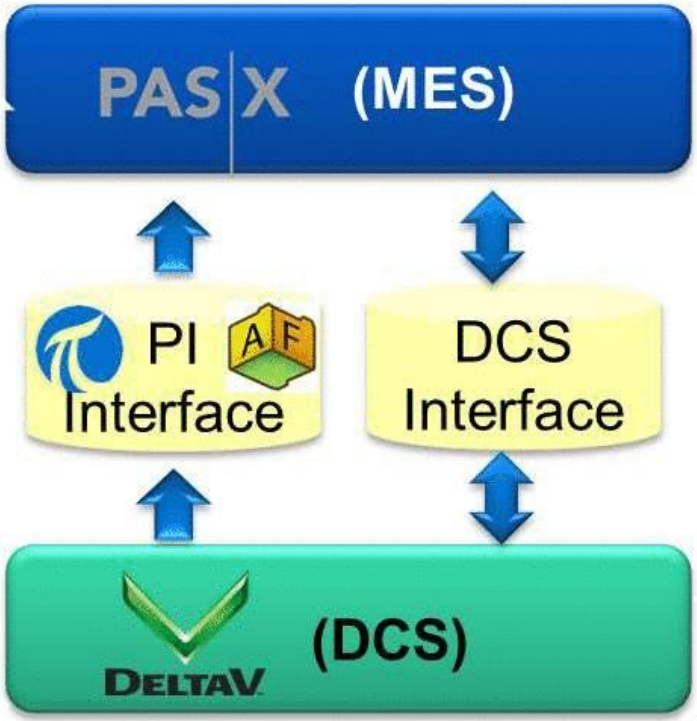
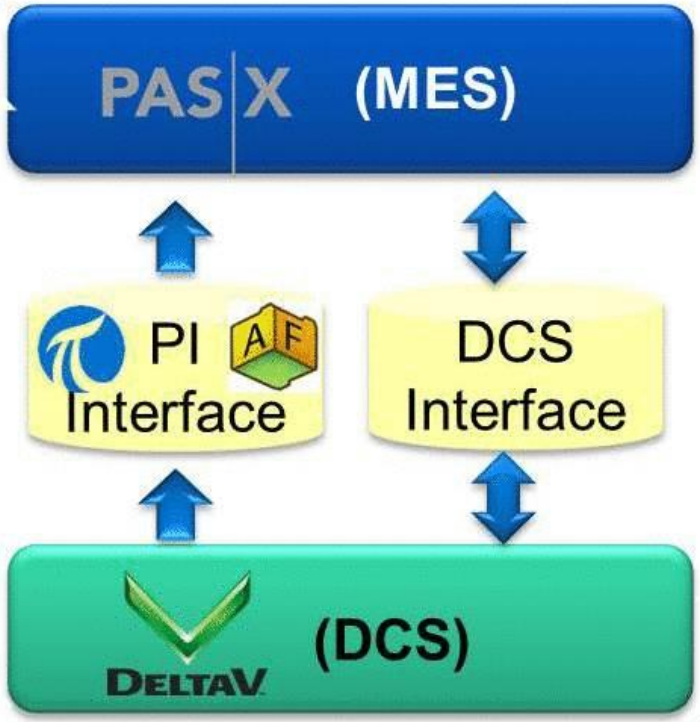
System Integration

- **DeltaV (DCS)**
  - Executes selected automated sequence
  - Provides real-time process control
  - Process data / Batch data sent to the PI Server



System Integration

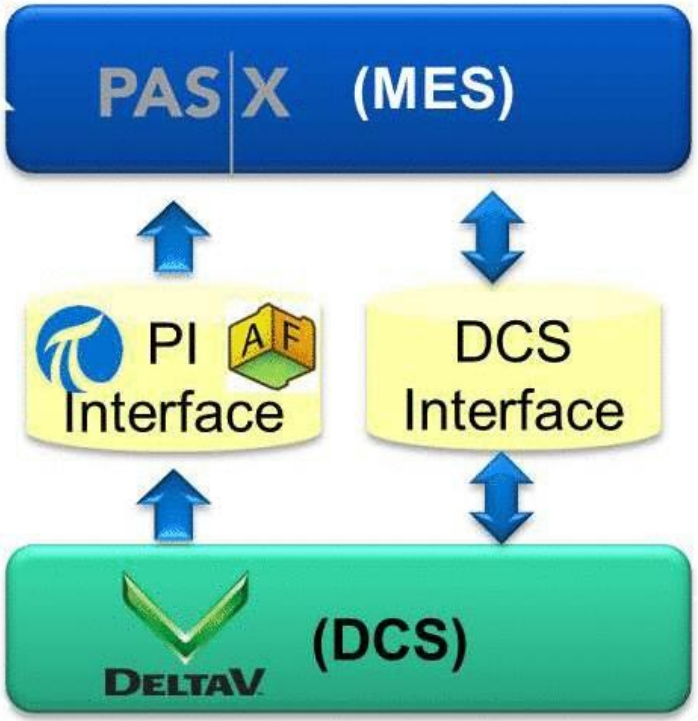
- **OSIsoft PI (Historian)**
  - Stores process and batch data via standard PI Interface
    - ✓ PI Interface for OPC DA
    - ✓ PI Interface for RDBMS
  - Create templates in PI Asset Framework (PI AF) that is used in MES



System Integration – PLC Example

Flow of Commands / Information:

- DeltaV batch recipe starts PLC cycle
  - Autoclaves and Parts Washers
- PLC cycle runs process and monitors for alarms
- DeltaV waits for PLC completion status
- If PLC alarms occur, DeltaV records as report parameters

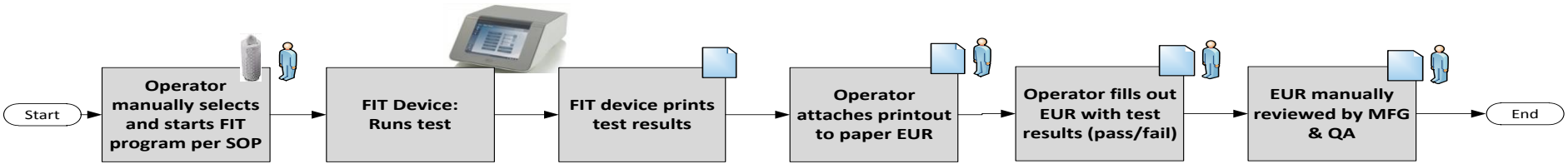


System Integration – FIT Example

- Filter Integrity Tests (FIT) are used to confirm the filter performance and claimed filtrate quality

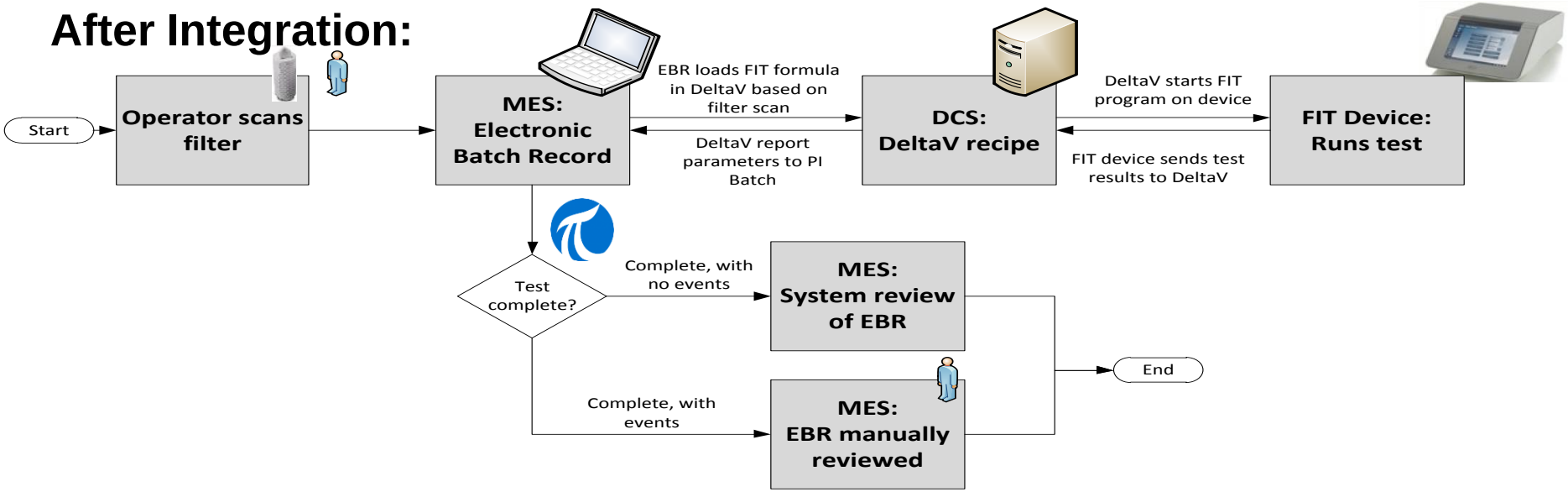
- Filters are pre-tested before the filter is used for processing and post-tested after the filter has completed its process use

Before Integration:



System Integration – FIT Example

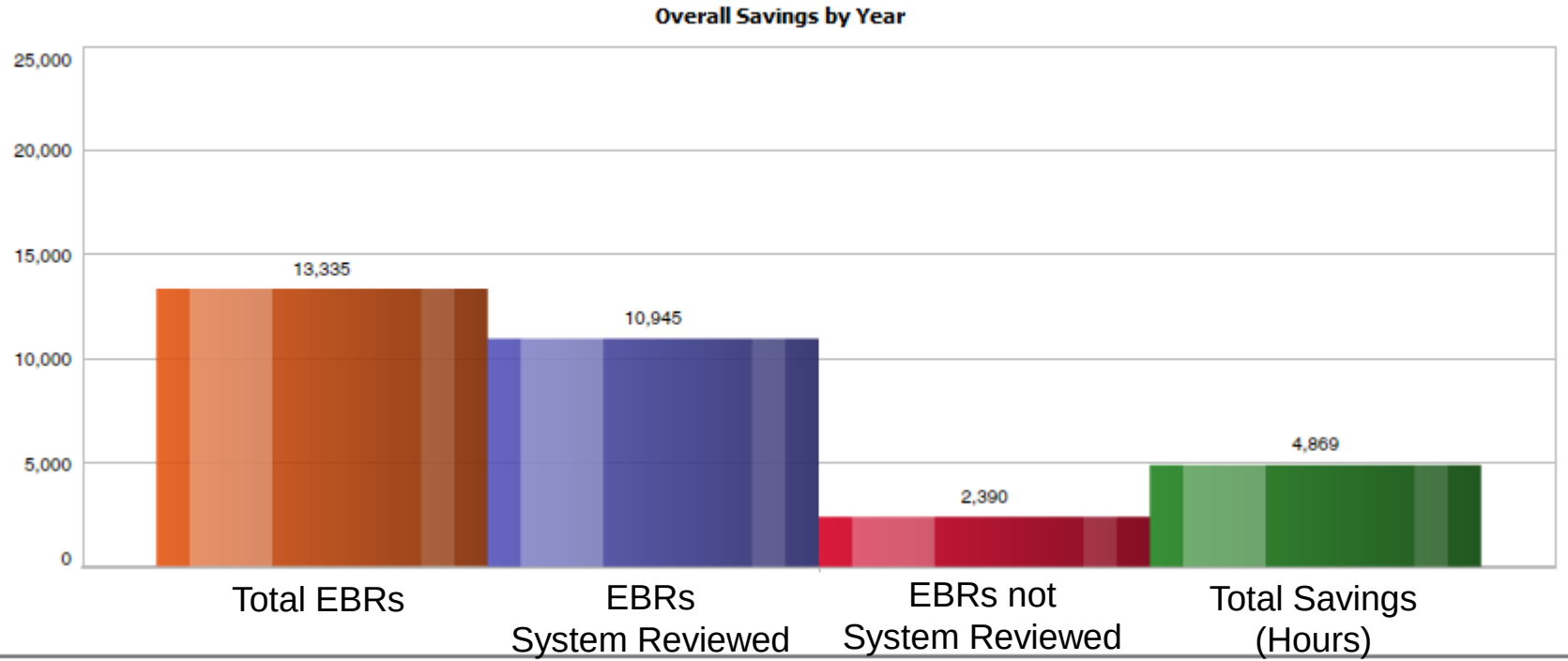
After Integration:



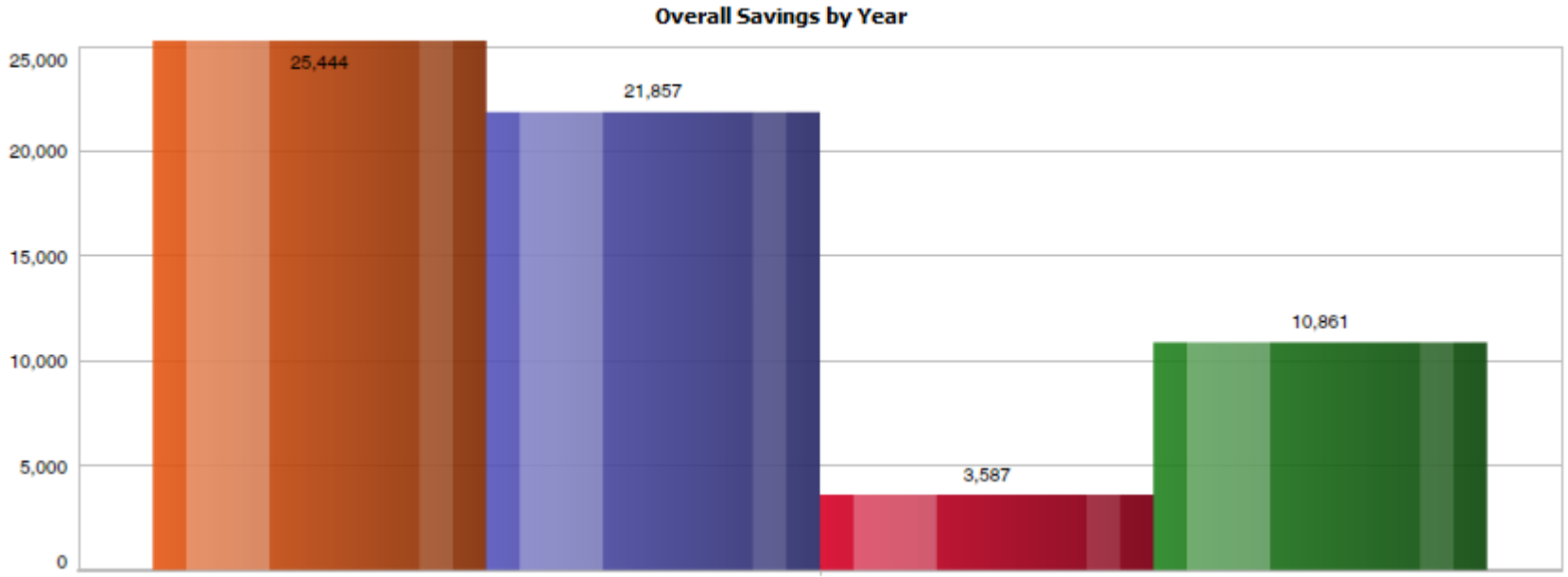
- Elimination of 45 minute manual review by MFG and QA
  - Since Q1 2015: 7000 of 8000 EBRs automatically reviewed → 5000+ hours saved
- Elimination of paper Equipment Use Records (EURs)
- Reduction in deviations

Benefit Realization – Primary, 2014

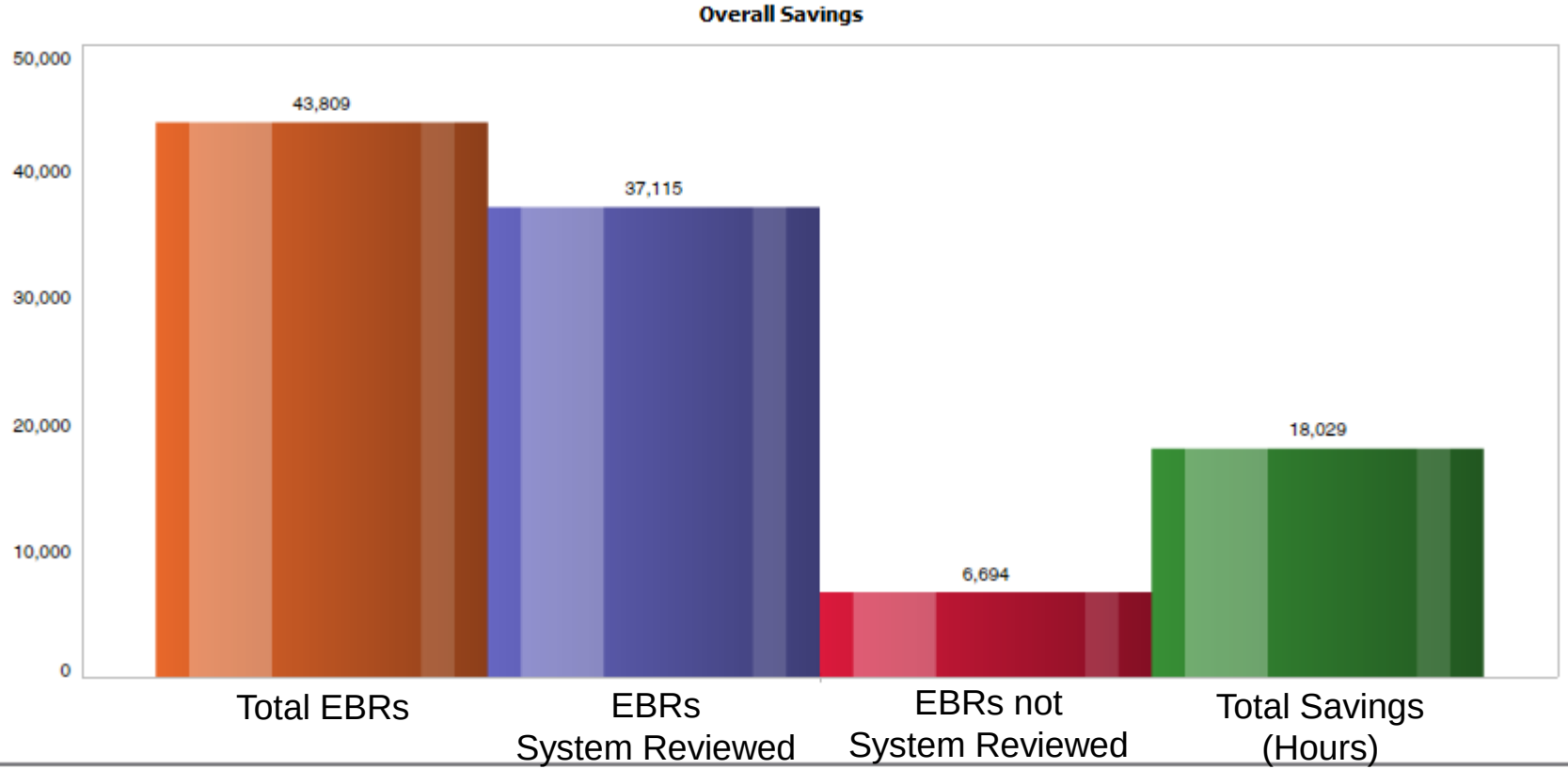
Primary Objective: Reduce manual reviews of batch records



Benefit Realization – Primary, 2015



Benefit Realization – Primary, to date



Benefit Realization - Secondary

1. Additional time savings
   - Execution time of batch records
2. Improves the **Right First Time** performance of batch record reviews
3. Reduces non-value added paperwork and associated GDP errors
   - **Elimination of paper printouts** from Level 1 systems (PLCs and FITs)
   - **Elimination of paper logbooks** for Parts Washers, Autoclaves, and FITs
4. Increased compliance and reduced deviations due to reduction in manual decision points and entries
   - **Prevented** at least 26 deviations (that occurred in 2012 and 2013)

Project Recap

- 3 years
- 55 directly impacted Master Batch Records (MBRs)
- >250 document updates (SOPs and specification documents)
- >70 test plans (including qualification protocols)
- 8 change controls
- >25 project team members

Project Recap – Success Factors

- Not an IS project
- Define the RBE philosophy up front
- “Do Your Job” – Bill Belichick
  - Let the appropriate system do their own job
  - K.I.S.S.
- Batch Record now needs to be treated like an automated recipe
  - Configuration based on pre-approved FS
- Core team consistency
- Challenge the current way
  - Why?

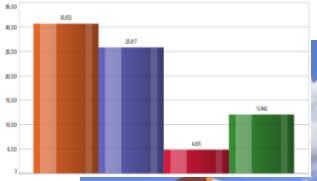
Project Recap – Lessons Learned

- Validation system testing ≠ Production system testing
  - Always conduct “Integration” field test prior to roll-out
- Anticipate all possible failure scenarios and non-routine operations
  - Build contingency plans into SOPs

Moving Forward

- Core solution developed for system integration
- Culture changed
- RBE is the new expectation
  - Future projects on site being designed with RBE as a guiding principle

Batch Record Review-By-Exception (RBE) Implementation



Sanofi Genzyme

"To enable Review By Exception (RBE), we needed to integrate our MES system with both our DeltaV system and our PI Data Archive historian system."

Ryan Greeley, Lead Automation Engineer
David Maglaya, Historian/Automation Engineer

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CHALLENGES

- Time-consuming traditional batch record review
- Increasing amount of Electronic Batch Record (EBR) executions to review
- Significant amount of non-value added paperwork, causing GDP errors

SOLUTION

- Deployment of a RBE program in 3 phases, to automate most of the reviews
- Based on the ISA S95 structure, using the PI System to integrate process and batch data for DCS/PLC and MES

RESULTS

- Saved to date, over 12,000 hours of manual review time
- Integrated operations are now paperless on Manufacturing floor
- Reduction in the number of deviations (>12/year)

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Questions

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谢谢

Danke

Gracias

Merci

Thank You

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