



THE SCIENCE *of* POSSIBILITY



Validation for Continuous Manufacturing & Inspection Readiness

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Manufacturing & Process Automation

Informa's BioProduction Congress 2016

Vertex products filed in
2014 and beyond fully
continuous with RTRT

BHAG

Big
Hairy
Audacious
Goal

In 2011...





- 1st Fully Automated Processing Plant validated at the site
- 1st time Implementing RTRT & simultaneously with CM Rig
- Integrating work from ~9 Suppliers
- 1st time building a GMP/Commercial Mfg Facility
- 1st Internal Commercial site launch & Health Authority Inspection
- 1st CM NDA / MAA Submission
- 1st Process Validation at the site
- Multi-Process / Product



Vertex's Path to CM



CMO

Individual unit operations were purchased to allow the development and manufacture of clinical formulations in a “discontinuous” mode

2012



CMO

ConsiGma-25 unit was purchased and installed for continuous clinical batch manufacture

- Wet granulation, fluidized bed drying & compression.
- With PAT Support

2013



Boston

DLR designed with multiple processing technologies

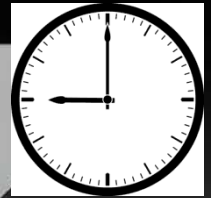
- Raw material blending to tablet film coating
- Wet Granulation, Dry Granulation, Direct Compression.
- PAT equipped: process monitoring / control & RTRT

2014

VERTEX

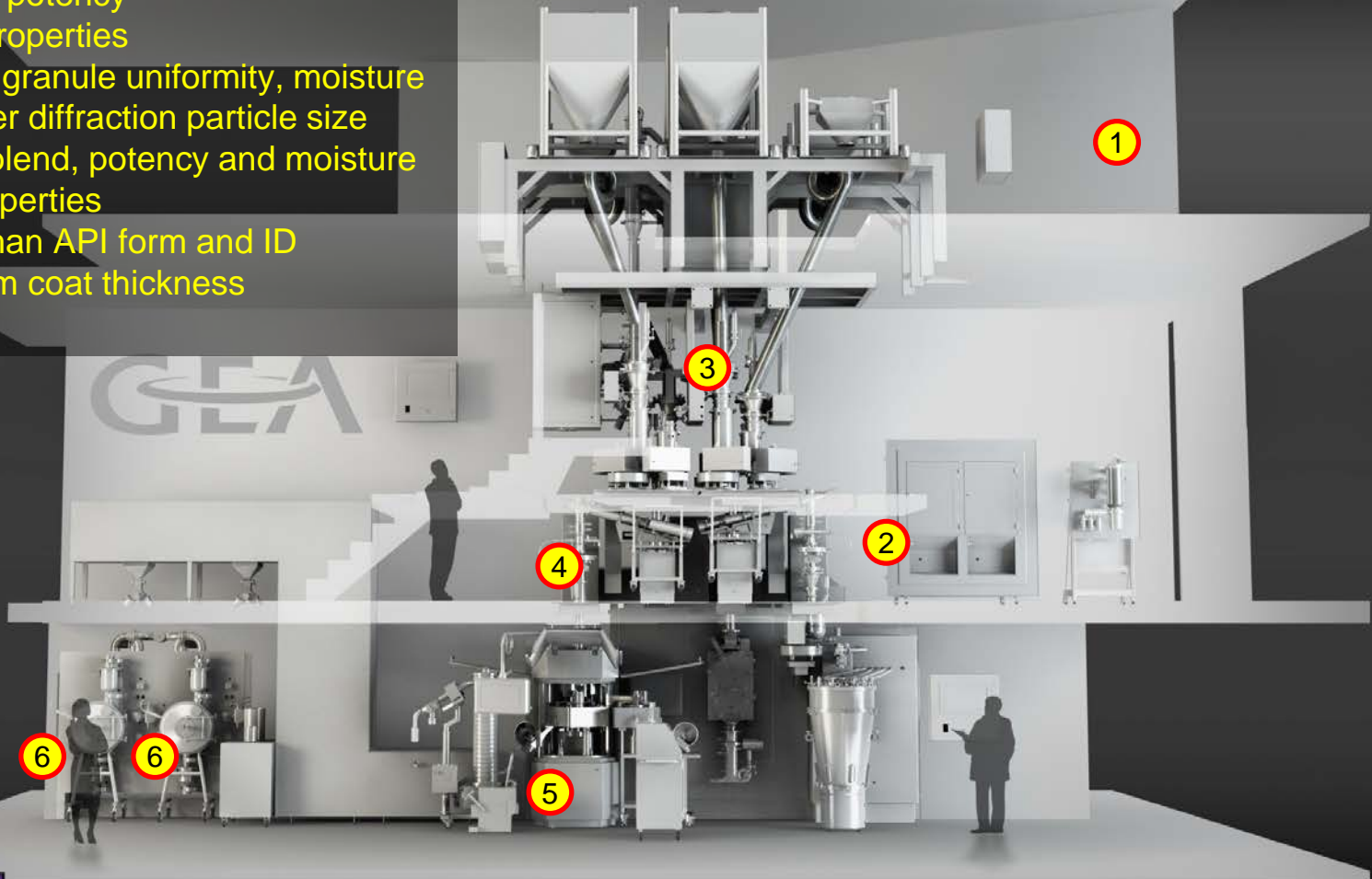
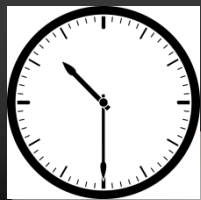
Vertex's Continuous Manufacturing Rig

- Smaller scale equipment / footprint
- All unit ops in one facility



1. At-line NIR incoming material attributes
2. NIR blend potency
3. Granule properties
 - a. NIR granule uniformity, moisture
 - b. Laser diffraction particle size
4. NIR final blend, potency and moisture
5. Tablet properties
 - a. Raman API form and ID
6. Raman film coat thickness

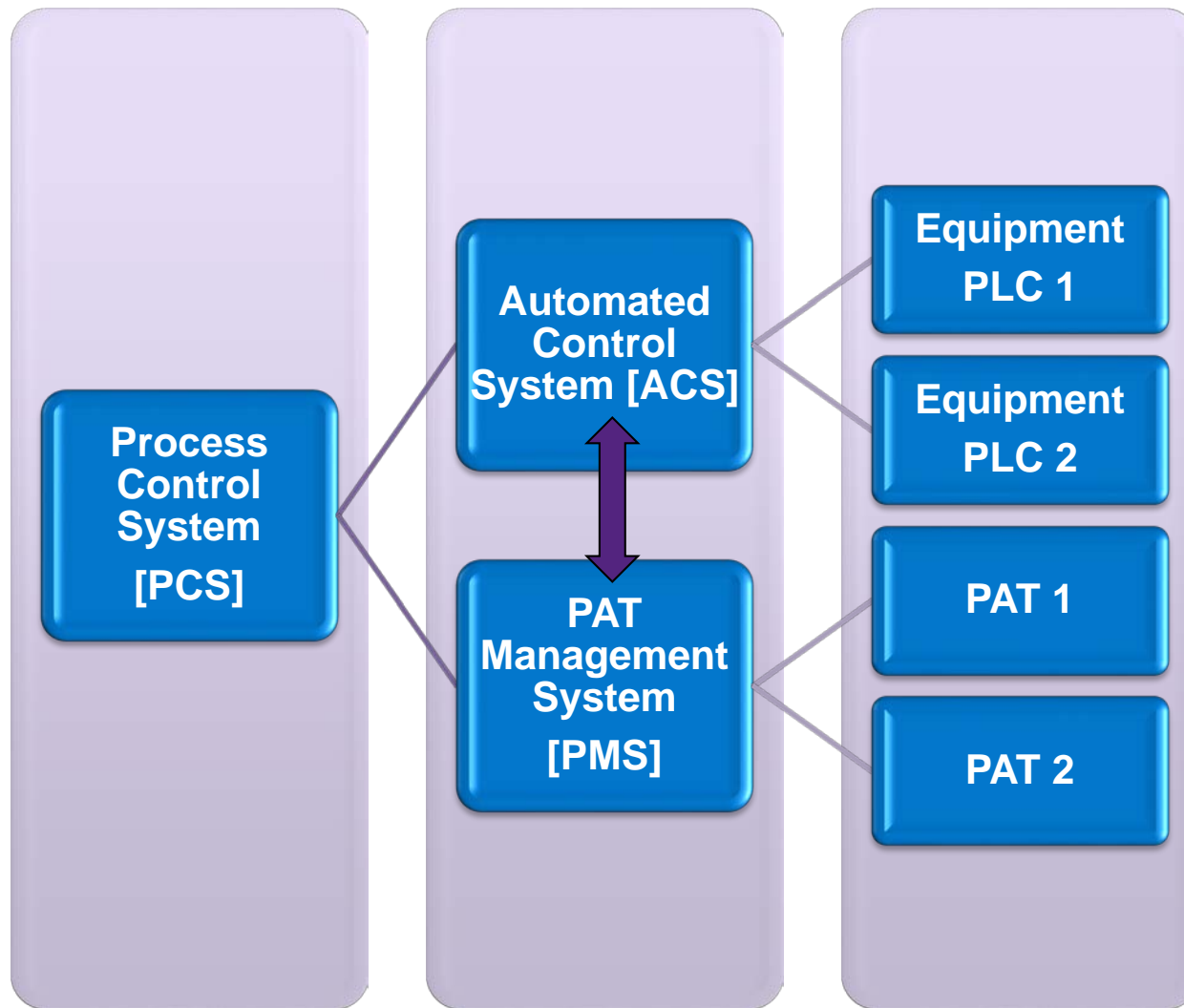
Powder In



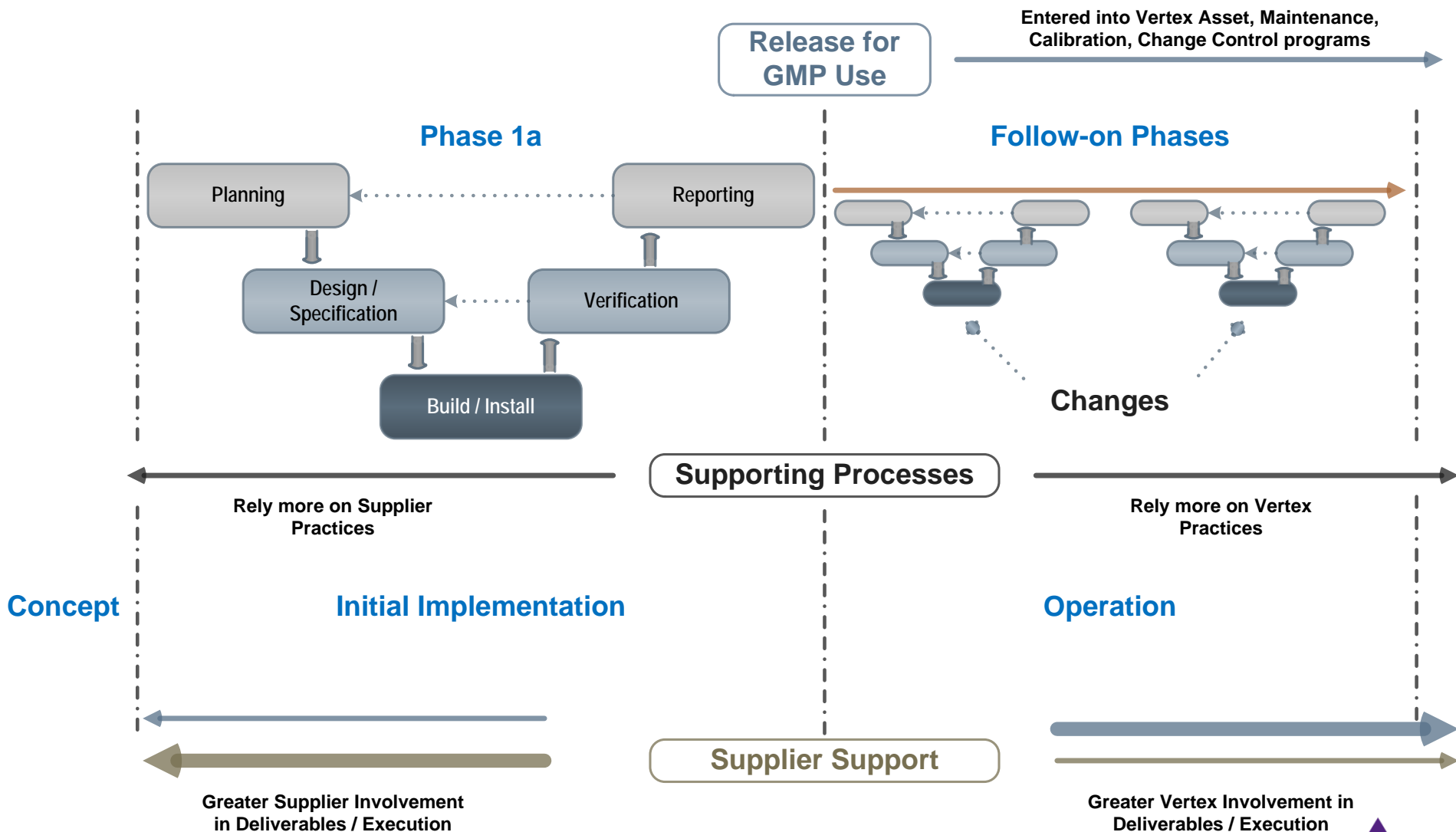
Coated Tablets Out

Continuous Monitoring => Real Time Release

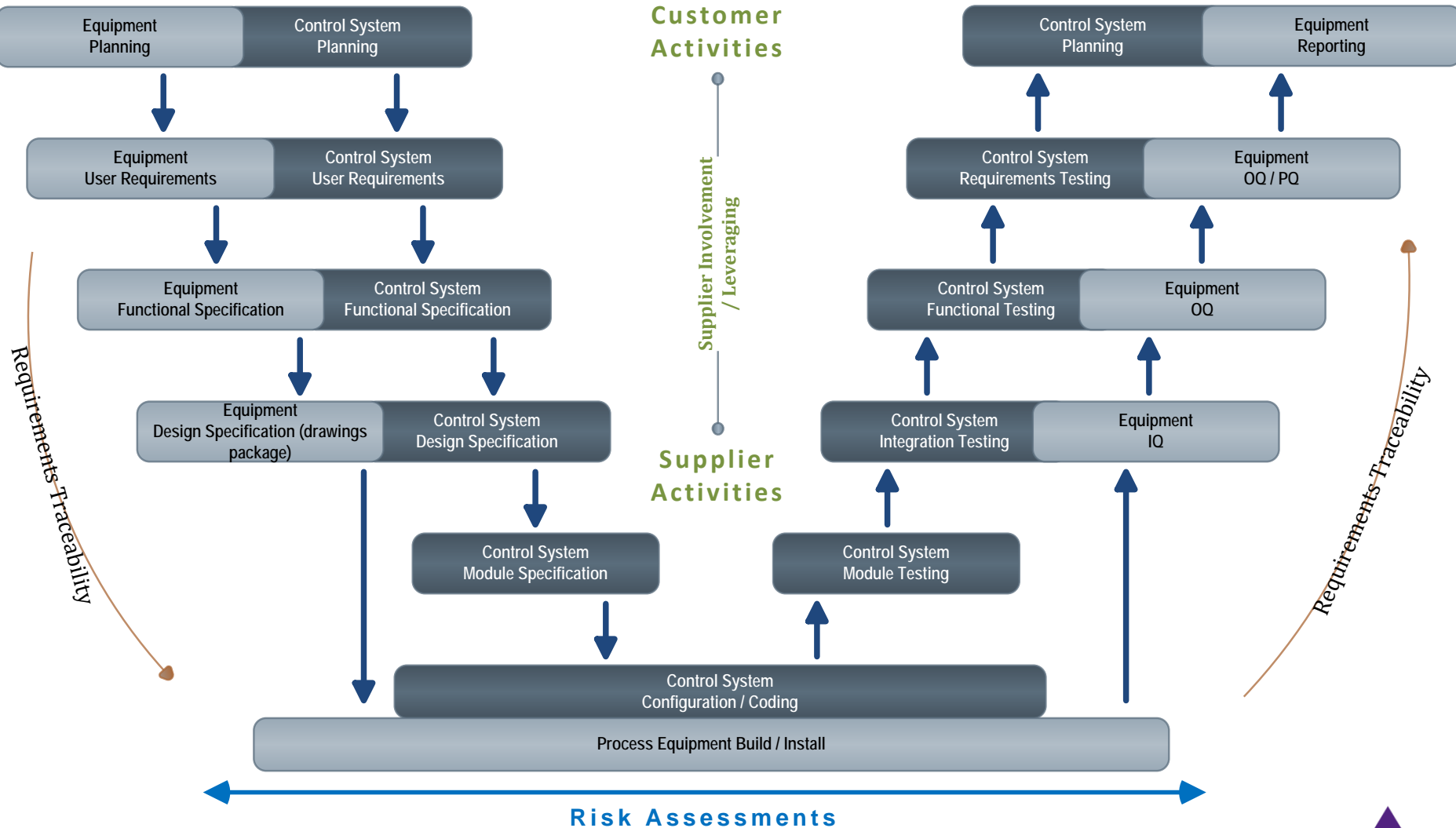
CM Rig Control System



System Implementation Life Cycle Overview



V-Model for CM Project



Concept & Initiation Phase

- Ensure all Suppliers are Adequately Represented
- Ensure all Key Customer Stakeholders are Adequately Represented
- Identify & Agree on **Clear Roles & Responsibilities**
- Identify and Assign an Overall **Integrator**



THE Critical Project Manager Role



Risk Assessments

- Product Impact (Direct / Indirect) **Direct**
- System Criticality (GxP criticality & Part 11) **High**
- System Category (complexity category based on GAMP 5) **5**
- System Detailed Functionality Assessment^{*}
 - Failure Mode and Effects Analysis (FMEA)
 - Explores failure modes for critical process parameters and high-risk aspects of the system
- Supplier Assessments

^{*}GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems



Risk Assessment Methodology

Risk Assessment Gamp 5 Methodology

TABLE 1

Severity		Probability		
	Impact	Low	Medium	High
	High (3)	Risk Class 2	Risk Class 1	Risk Class 1
	Medium (2)	Risk Class 3	Risk Class 2	Risk Class 1
	Low (1)	Risk Class 3	Risk Class 3	Risk Class 2
		Score 1	Score 2	Score 3

Example Severity (High) x Probability (Medium) = Risk Class 1

This is now used in table 2 with the detectability

Severity = Impact on Patient safety, Product Quality and Data Integrity. (Or other Harm)

Probability = likelihood of the fault occurring

Risk Class = Severity X Probability

TABLE 2

Risk Class		Detectability		
	Impact	High	Medium	Low
	Risk Class 1	Medium Risk Priority	High Risk Priority	High Risk Priority
	Risk Class 2	Low Risk Priority	Medium Risk Priority	High Risk Priority
	Risk Class 3	Low Risk Priority	Low Risk Priority	Medium Risk Priority
		Score 1	Score 2	Score 3

Detectability = Likelihood that the Fault will be noted before Harm occurs

Risk priority = Risk Class X Detectability

Example Risk Class (2) x Detectability (Medium) = Medium Risk Priority

The output of the risk assessment process, (risk priority) is used to decide upon appropriate controls. A range of options is available to provide the required control, depending on the identified risk.

Detailed Functionality Risk Assessment – Example

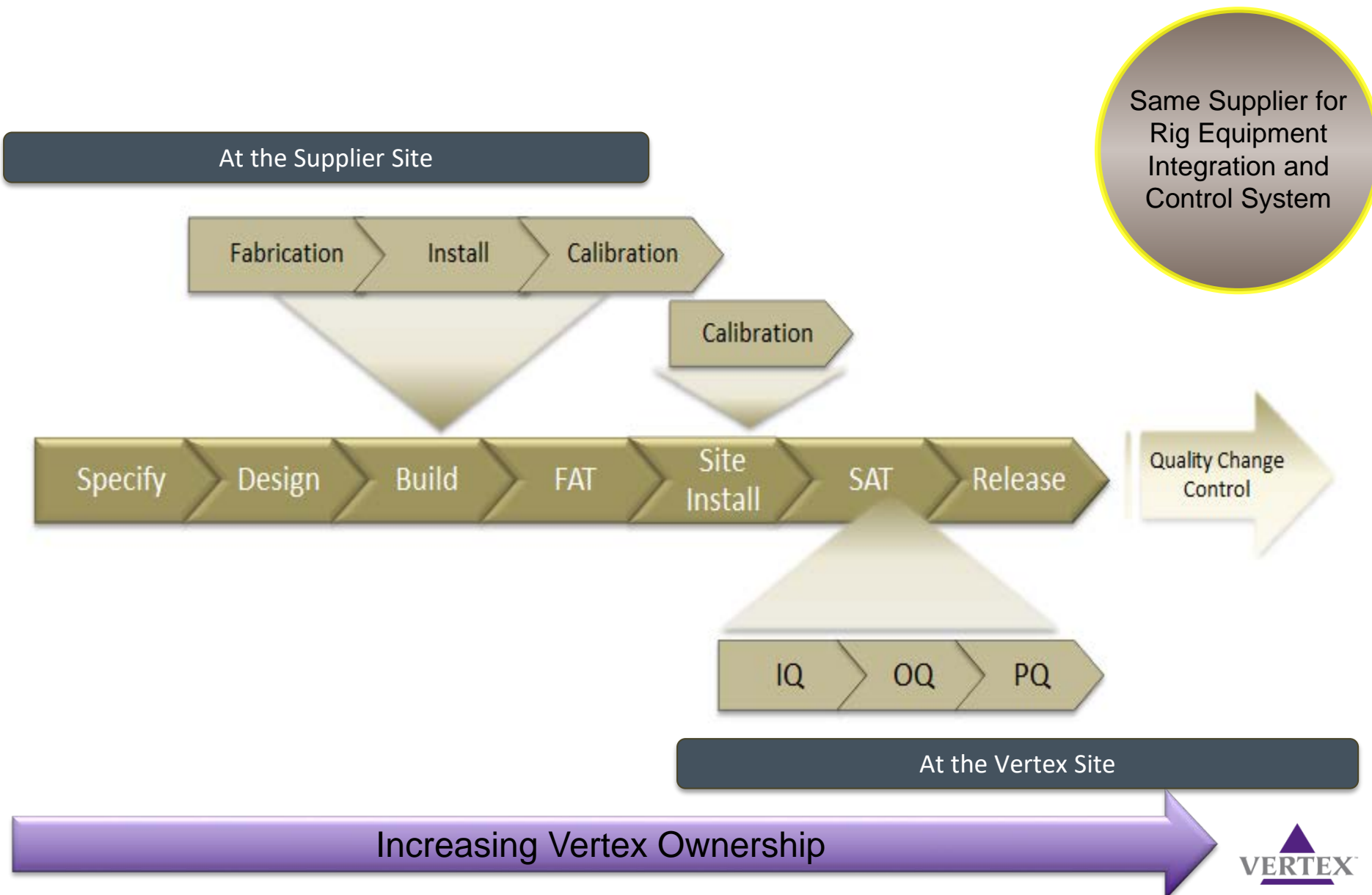
Granulator & FBD/AHU Wet Granulation Risk Assessment (See template for scoring method)													
No	URS Requirement	Unit EM Operation	Physical	Process	Process Condition	Identified Risk Scenario (Unwanted Transformations)	Product attributes	Servery of Impact (High = 3, Med = 2, Low = 1)	Likelihood of Occurance (High = 3, Med = 2, Low = 1)	Risk Class	Probability of Detection (3 = Low, 2 = Medium, 1 = High)	Risk Priority No (RPN)	Overall Risk Priority
1	3.4 - 003	Feeder 9	Screw Feeder with Hopper	Screw Feeding	No, Low Flow	The feeder is delivering insufficient amount of material to the granulator. (Density, agglomerate, insufficient accuracy)	(Quality) Non - Conforming Material	3	2	1	2	12	High Risk Priority
2	3.4 - 004/8	Feeder 9	Screw Feeder with Hopper	Screw Feeding	High Mass Flow	The feeder is delivering too much material to the granulator. (Density, agglomerate, insufficient accuracy)	(Quality) Non - Conforming Material	3	2	1	2	12	High Risk Priority
3	3.4 - 0010	Feeder 9	Screw Feeder with Hopper	Screw Feeding	No Level, Low Level	The feeder hopper is empty or low level is detected during operation of a batch (Density, agglomerate, insufficient accuracy)	(Quality) Non - Conforming Material	3	2	1	2	12	High Risk Priority
4	3.4 - 0010	Feeder 9	Screw Feeder with Hopper	Screw Feeding	High Level	The feeder hopper is over full and detected during operation of a batch (Density, agglomerate, insufficient accuracy)	(Quality) Non - Conforming Material	3	2	1	2	12	High Risk Priority
5	3.4.2	Granulator Bridge Breaker	Bridge Breaker	Material Conditioning	No Flow, Low Flow	Bridge Breaker runs slow/stops/stalls during operation (Density, agglomerate, insufficient accuracy)	(Quality) Non - Conforming Material	3	2	1	2	12	High Risk Priority
6	3.4.2	Granulator Bridge Breaker	Bridge Breaker	Material Conditioning	High Flow	Bridge Breaker runs fast during operation (Density, agglomerate, insufficient accuracy)	(Quality) Non - Conforming Material	3	2	1	2	12	High Risk Priority
7	3.4 - 026	Liquid Addition 1	Pump to granulator	Liquid Transfer	No Flow, Low Flow	Metering pump 1 stops/stalls or the flexible tubing is not connected to the pump (solids addition and moisture errors)	(Quality) Non - Conforming Material	3	2	1	2	12	High Risk Priority

Corrective Action	None witnessed FAT	Witness Testing at FAT	SAT (IQ / OQ) Testing Required	Comments	Corrective Action Completed (Yes/No)	Servery of Impact (High = 3, Med = 2, Low = 1)	Likelihood of Occurance (High = 3, Med = 2, Low = 1)	Risk Class	Probability of Detection (3 = Low, 2 = Medium, 1 = High)	Risk Priority No (RPN)	Overall Risk Priority	Risk Reduction
Review of Servery impact by Vertex & SOP to maintain the feeders correctly, test control	Yes	No	Yes	Providing the KTron feeder actual kg/hr feedback (kg/hr) is accurate then the control system should detect and alarm low flow rates based on the alarm and warning values set in the recipe. (This also applies to the material leaving the feeder matching the actual feedback)		3	2	1	2	12	High Risk Priority	E.G. High to Medium
Review of Servery impact by Vertex SOP & to maintain the feeders correctly, test control	Yes	No	Yes	Providing the KTron feeder actual kg/hr feedback (kg/hr) is accurate then the control system should detect and alarm low flow rates based on the alarm and warning values set in the recipe. (This also applies to the material leaving the feeder matching the actual feedback)		3	2	1	2	12	High Risk Priority	
Review of Servery impact by Vertex	Yes	No	No	Alarms will be generated for feeder hopper low level		3	2	1	2	12	High Risk Priority	
Review of Servery impact by Vertex	Yes	No	No	Alarms will be generated for feeder hopper high level		3	2	1	2	12	High Risk Priority	
Review of Servery impact by Vertex	Yes	No	No	Should the Bridge Breaker block or the feeder 9 transfer line not be connected there is no means of detecting this in the control software,		3	2	1	2	12	High Risk Priority	
Review of Servery impact by Vertex	Yes	No	No	Should the Bridge Breaker block or the feeder 9 transfer line not be connected there is no means of detecting this in the control software,		3	2	1	2	12	High Risk Priority	
Review of Servery impact by Vertex	Yes	No	Yes	The liquid flow rates are monitored by the control system via the flow meter and will generate low flow alarms if low flow is detected.		3	2	1	2	12	High Risk Priority	

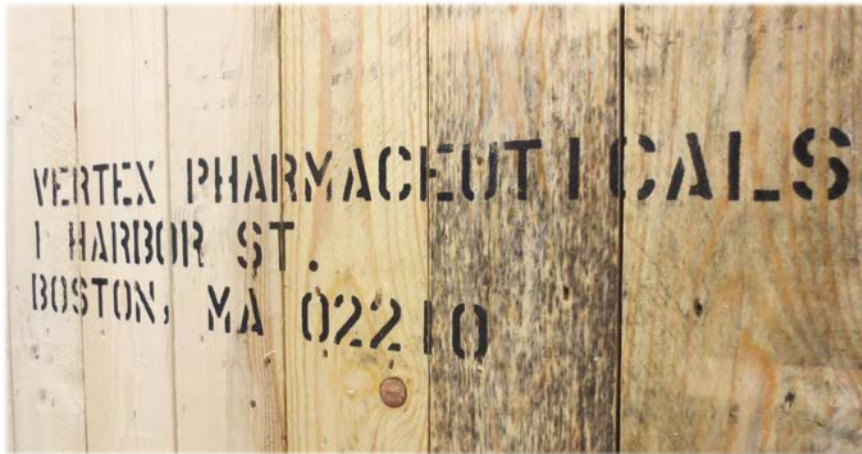
Validation Planning – Example

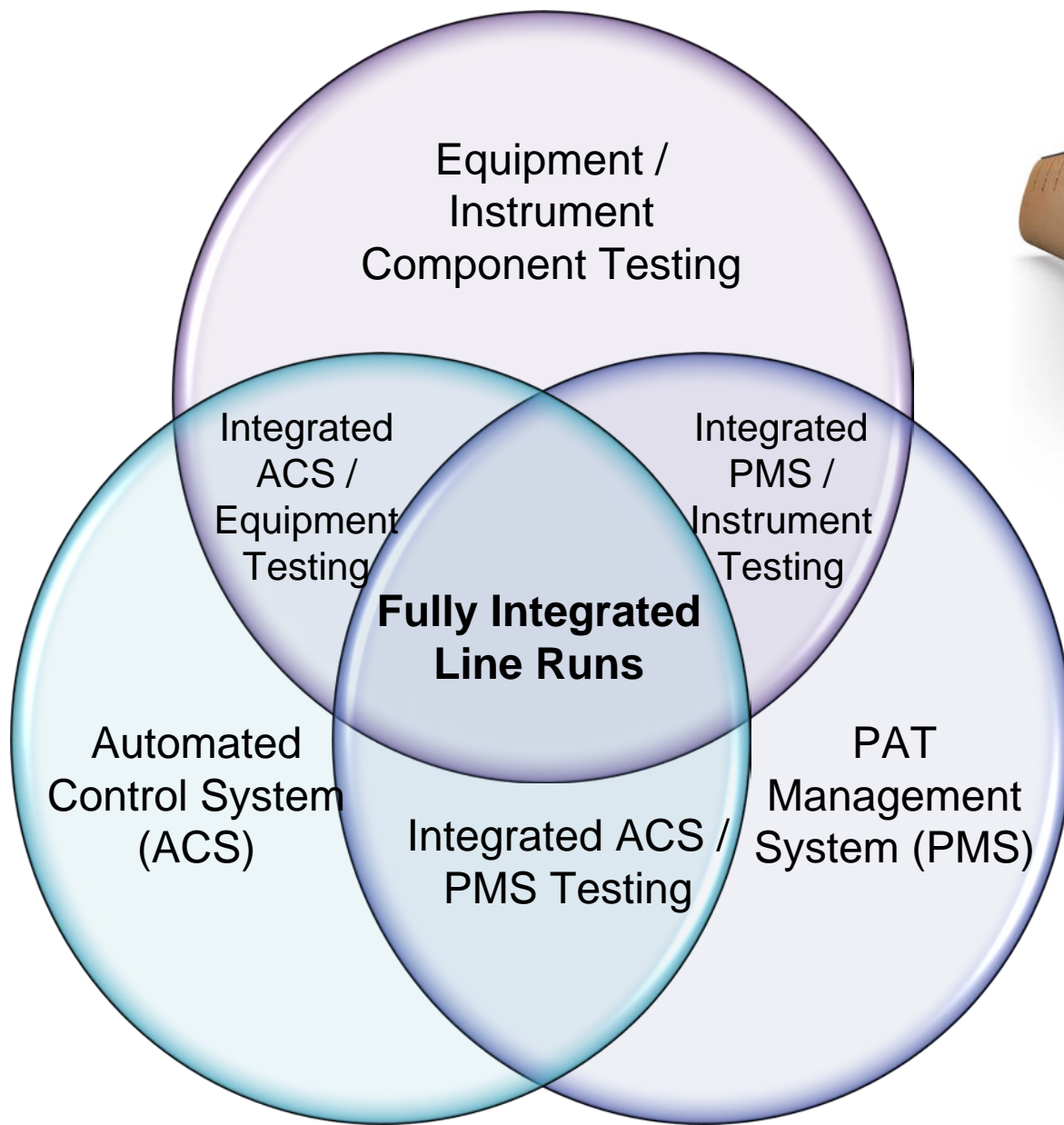
- 1.0 → Introduction
- 1.1 → Purpose
- 1.2 → Business-Need
- 2.0 → Scope
- 2.1 → Validation-Scope
- 2.2 → DLR-System-Description
- 2.3 → PAT-Lab
- 2.4 → System-Rollout-Scope
- 2.5 → Out-of-Scope
- 3.0 → Project Team Organization & Roles
- 4.0 → Risk Determination
- 4.1 → System-Impact-Assessment
- 4.2 → Categorization-based-on-GAMP
- 4.3 → Product-Impact
- 4.4 → Detailed-Risk-Assessment-for-Critical-Aspects
- 5.0 → Qualification & Validation Strategy
- 5.1 → Overview
- 5.2 → Supplier-Quality-System-&-Assessment
- 5.3 → Supplier-Leveraging
- 5.4 → User-Requirements-and-Traceability
- 5.5 → DLR-Design-&-Build
- 5.6 → FAT-Commissioning-Phase-at-GEA-Sites
- 5.7 → Post-FAT
- 5.8 Installation & Calibration at Vertex
- 5.9 Onsite Testing – Qualification & Software Validation
- 5.10 Onsite Testing – Equipment Performance Qualification (PQ)
- 5.11 Issues and Changes during Onsite Testing
- 5.12 Summary Reports
- 5.13 Post Onsite Testing
- 6.0 Good Documentation Practices (GDP) and Execution Guidelines during Qualification
- 7.0 Test Incident Management during Qualification
- 8.0 Change Management during Qualification
- 9.0 Deliverables
- 10.0 ACS Software Handover to Vertex
- 11.0 Training Plan
- 12.0 System Procedures
- 13.0 System Release for Operational Use & Process Validations
- 13.1 Acceptance Criteria
- 13.2 Validation Summary Report (VSR)
- 14.0 Post Release for GMP Service
- 15.0 Definitions, Abbreviations & Acronyms
- 16.0 References
- 17.0 Revision History

Validation Activities Supplier vs. Onsite – Initial Build



DLR – Annex Installation: Oct 2013



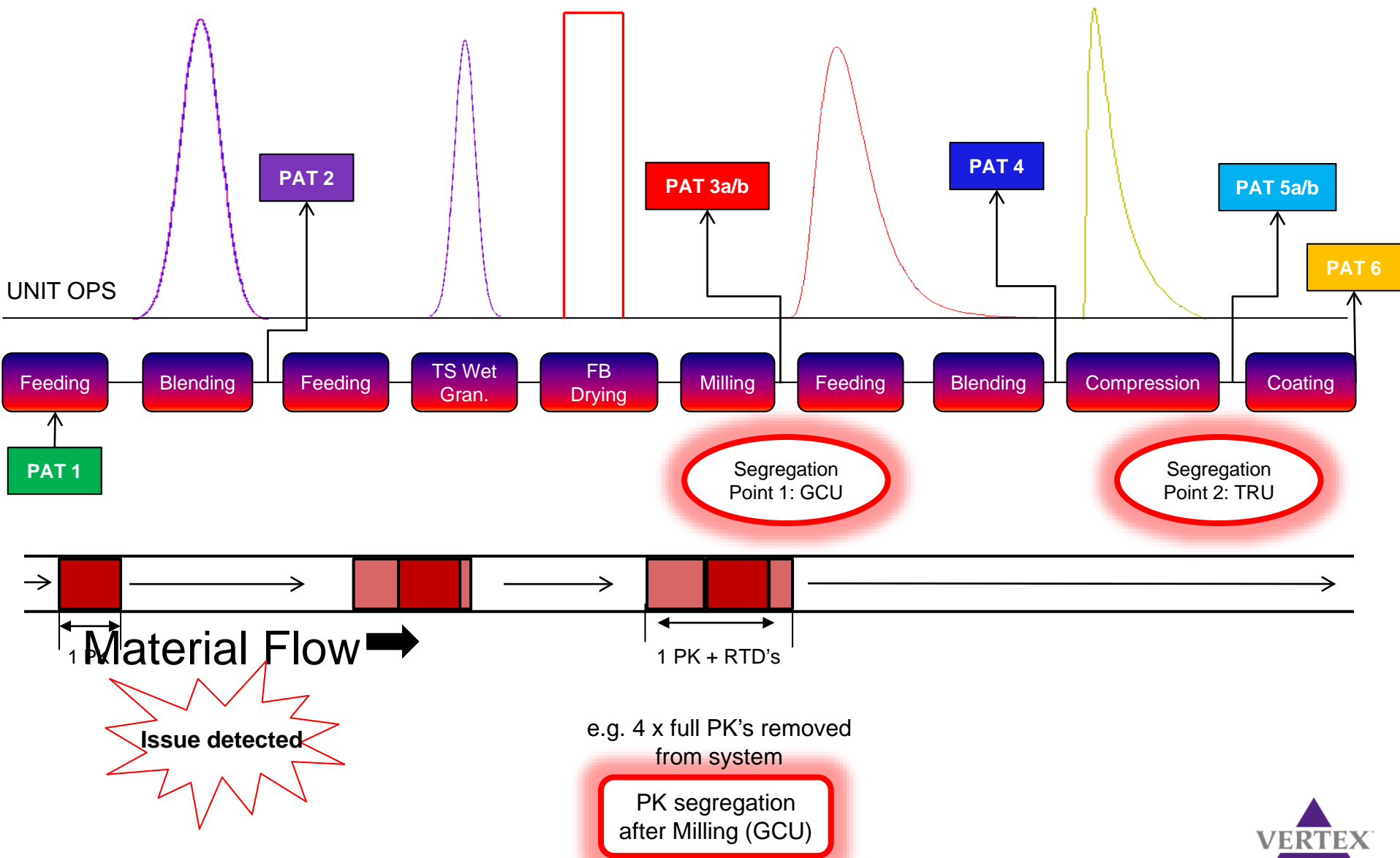


- Testing of functionality against requirements / specifications
- Comprehensive alarm testing
- Comprehensive product tracking & segregation testing

CM Testing Considerations

- Control Strategy
 - Product Tracking
 - Product Status
 - Product Segregation
 - Waste-by-Range
- Alarms / Warnings
 - Equipment
 - Instrument
 - Process (DSL, IPC & CPP)
- Different Line Rates
 - 10 – 30 Kg/Hr
- Process Control
 - Initializing
 - Production
 - Line Pauses
 - Controlled Stops
 - Emergency Stops
 - Empty Line

Control Strategy Testing: Identification & Traceability of Product Segments (Product Keys - PKs)



Control Strategy System Testing: Example

		Off-line	Placebo Line Run	Product Line Run
Testing to Support the DLR Wet Granulation Control Strategy	Automated Control System (ACSWinCC)	<p>General PMS-to-ACS communication via OPC.</p> <p>ACS PCA/PCW visualization on HMIs</p> <p>ACS PCA/PCW PK Status, segregation and Waste-by-Range.</p> <p>OPC Tags configured correctly for synTQ Warning locations and work when simulating PMS inputs.</p>	<p>Segregation based on PK Status and application of Waste-by-Range.</p> <p>PK Tracking and Location in system.</p> <p>ACS Process Critical Alarms/Warnings tested during DLR WG run to confirm HMI visualization, correct PK Status, Segregation and Waste-by-Range.</p>	<p>Legend:</p> <p>Tested as part of DLR CM Phase 1a</p> <p>Tested as part of DLR CM Phase 1d</p>
	Integrated Process Control System (PCS) = PMS + ACS	Not Applicable	<p>General PMS-to-ACS communication via the OPC layer.</p> <p>PMS Data Collection of Process Parameters on DLR equipment from the ACS.</p> <p>Wet Granulation Control Strategy per PMS configuration using various data logic scenarios and confirm HMI visualization of Alarms/Warnings, correct PK Status, and Segregation.</p> <p>Wet Granulation regression testing to ensure WG Line continues to run as expected after change.</p>	Product Orchestration Loads and Initializes successfully.
	PAT Management System (PMS/synTQ)	<p>Verify PMS Data Collection from DLR PAT Instruments.</p> <p>Orchestration configurations assess data against IPC warning and acceptance criteria, CPP NOR and DSL limits and non-critical PP against DSL correctly and that they send the appropriate alarm/warning strings, alarm/warning enabled outputs and PK status output.</p>	Not Applicable	PMS (synTQ) Reports.

Test Execution Challenges

- Testing provided & executed by **multiple** parties
- Many 1st timers to validation
- Significant amount of in parallel testing and high number of persons involved in testing
- Incidents & Change Happens
- Different practices
 - Date format
 - Labeling test evidence
 - Real time recording

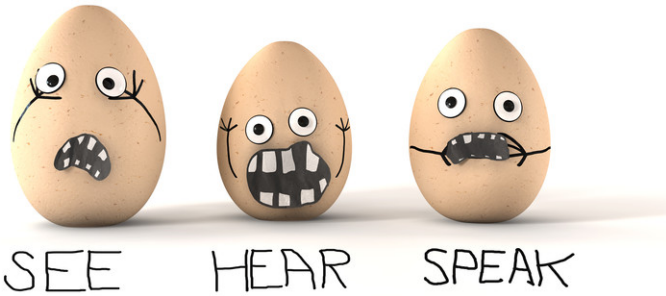


Test Execution

- Ensure all Testers are trained and aligned on the *preferred GDP practices*
 - Use the international date format (e.g. 16Jun2016)
 - Use a Signature Register (Log)
- Have a well defined process for handling Test Incidents & Changes
 - Use *smart forms in electronic format*
 - Use predefined Error codes, Severity categories etc. for greater consistency across completed forms



Challenge with Changes

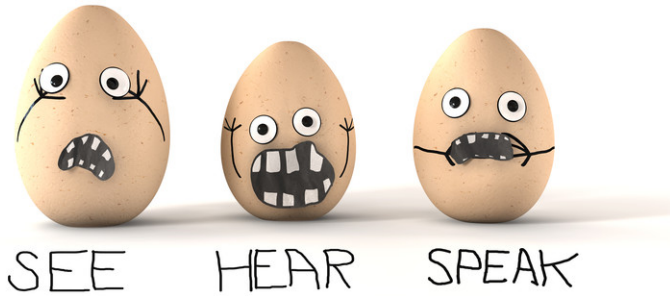


99 little bugs in the code
99 little bugs in the code
Take one down, patch it
around

127 little bugs in the code...

- Robust change handling practice for *during* validation
 - Ensure all are trained and aligned on the preferred change handling practice
- Good tracking mechanism for both incidents and changes

Challenge with Changes



99 little bugs in the code
99 little bugs in the code
Take one down, patch it
around

127 little bugs in the code...

- Supplier systems are often different from yours – *integrate them*
- ‘Debugging’ step in the process to ‘try out’ changes before implementing them

What's Your Story



Achieving Readiness

- **Have an RTM!**
- Approach equipment/system validation with PV in mind
- Perform a Detailed Functionality Risk Assessment
- Ensure Integration ssis adequately addressed
 - Components no longer operate independently

What's Your Story



Achieving Readiness

- Have robust practice for incident & change handling
- Have robust project management and tracking tools
- Have a clear and well documented Story Line
- **Organize** the Validation Package for ease of review
- Consider a Playbook for the Team to use during an Inspection

Contributor to Our Success





- Supplier Integrations
- Implemented RTRT simultaneously
- 2 successful PAI inspections for ORKAMBI (US & EU)
- Installed and Validated Initial Rig onsite in 8 months
- 1st Commercial site launch & Approval was on CM
- Wet Granulation and Dry Granulation Tableting Lines implemented / validated for GMP use

