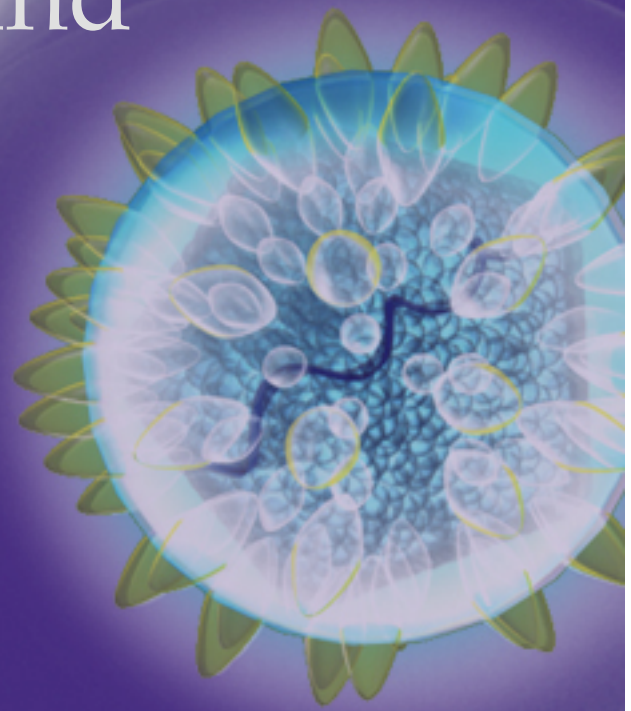
Effective Data Processing: Using QbD to Improve Product and Process Understanding



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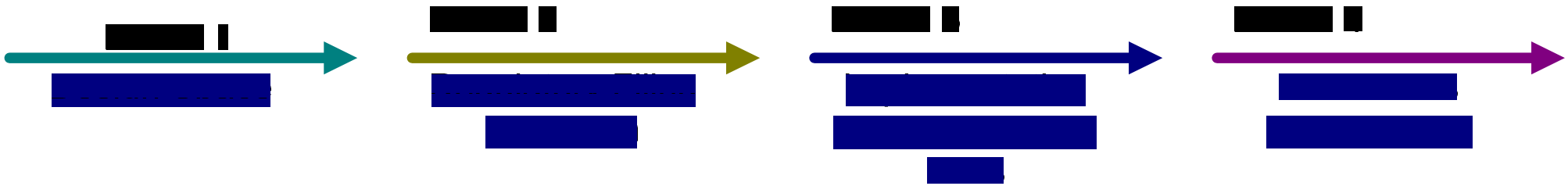
VERTEX

Implementation of QbD

- Pharmaceutical Development
  - Target product profile
  - Design space definition
- Technology transfer
  - Risk Assessment
  - Control Matrix
  - Design of Regulatory filings
- Commercial manufacturing
  - QbD in a commercial batch record
  - Implementation with traditional quality systems
- Lifecycle management
  - Trending
    - Data and information management
    - Process monitoring (on-line and off-line)
    - Monitoring key performance indicators
  - Continuous improvement
    - Management review
    - Change control
- References and resources

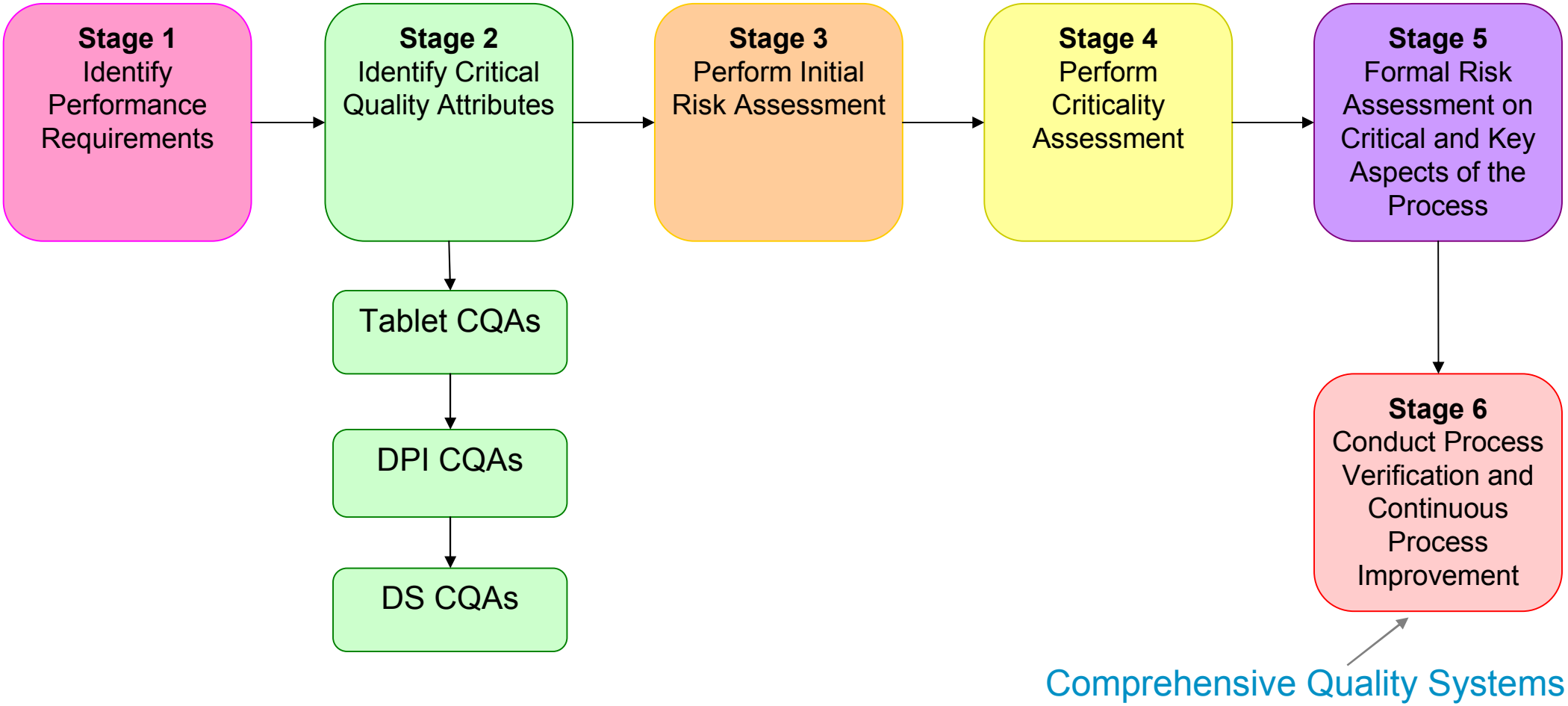
VERTEX

QbD is Implemented in Stages



Develop Product	Develop matrix showing material attributes, IPCs, and process parameter control that ensures CQAs are met	Agree on classifications of deviations	Perform trending
Understand product	Develop real-time release strategy	Agree on change classifications	Interpret results across trending parameters
Develop specifications	Develop post-approval change strategy	Agree on process for including NORs and PARs in batch record	Identify opportunities for improvement; implement as appropriate
Perform risk Assessment	Develop “product and process description” strategy for marketing application	Agree on overall control strategy	Publish trends and metrics
Define design space	Develop comparability protocol strategy	Agree on trending protocol and process	Set goals for continuous improvement

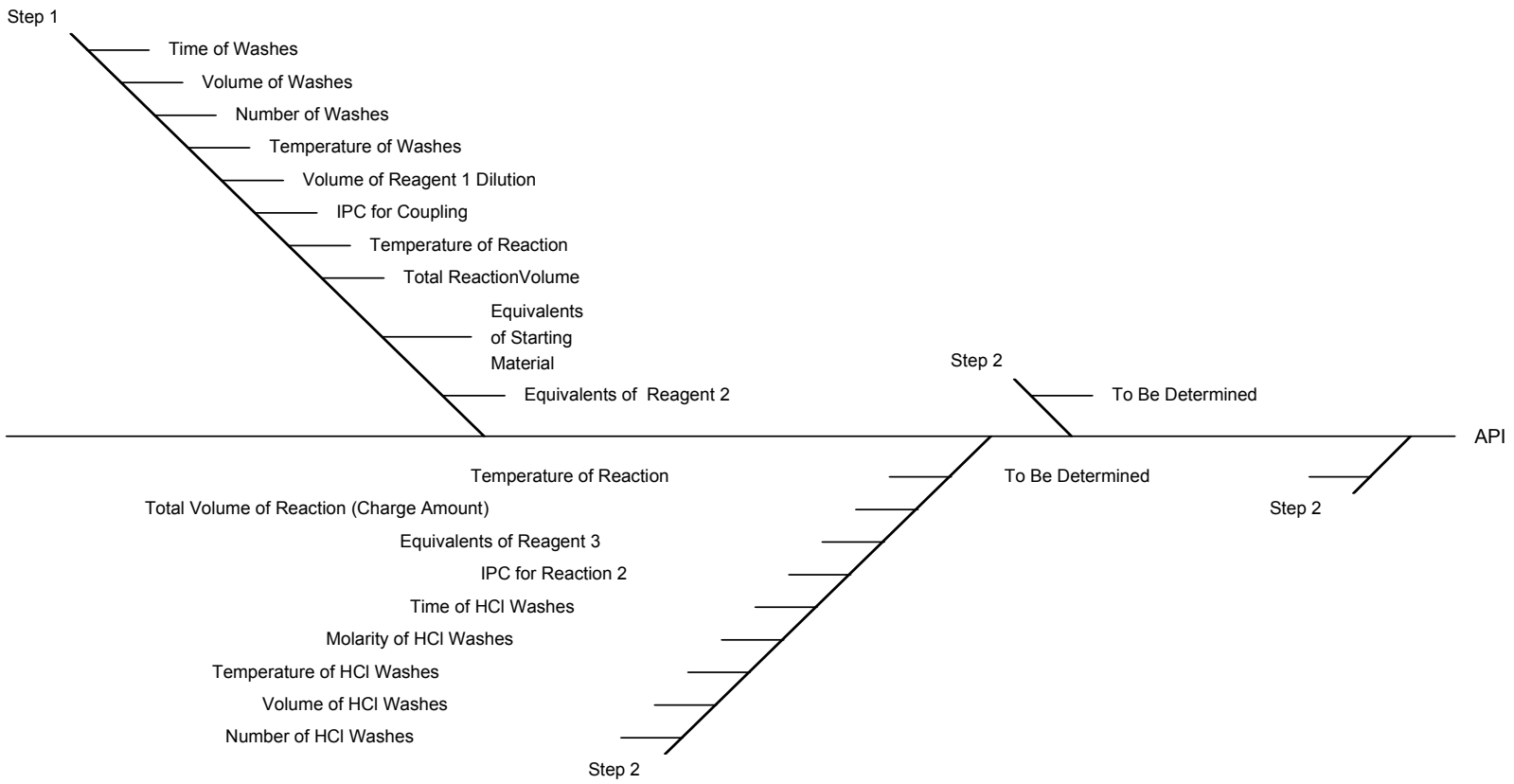
QbD Starts with a Target Product Profile



Traditional validation likely in initial QbD implementations because of uncertainty about expectations of inspectors, may not always be required since emphasis is on qualification rather than validation in QbD

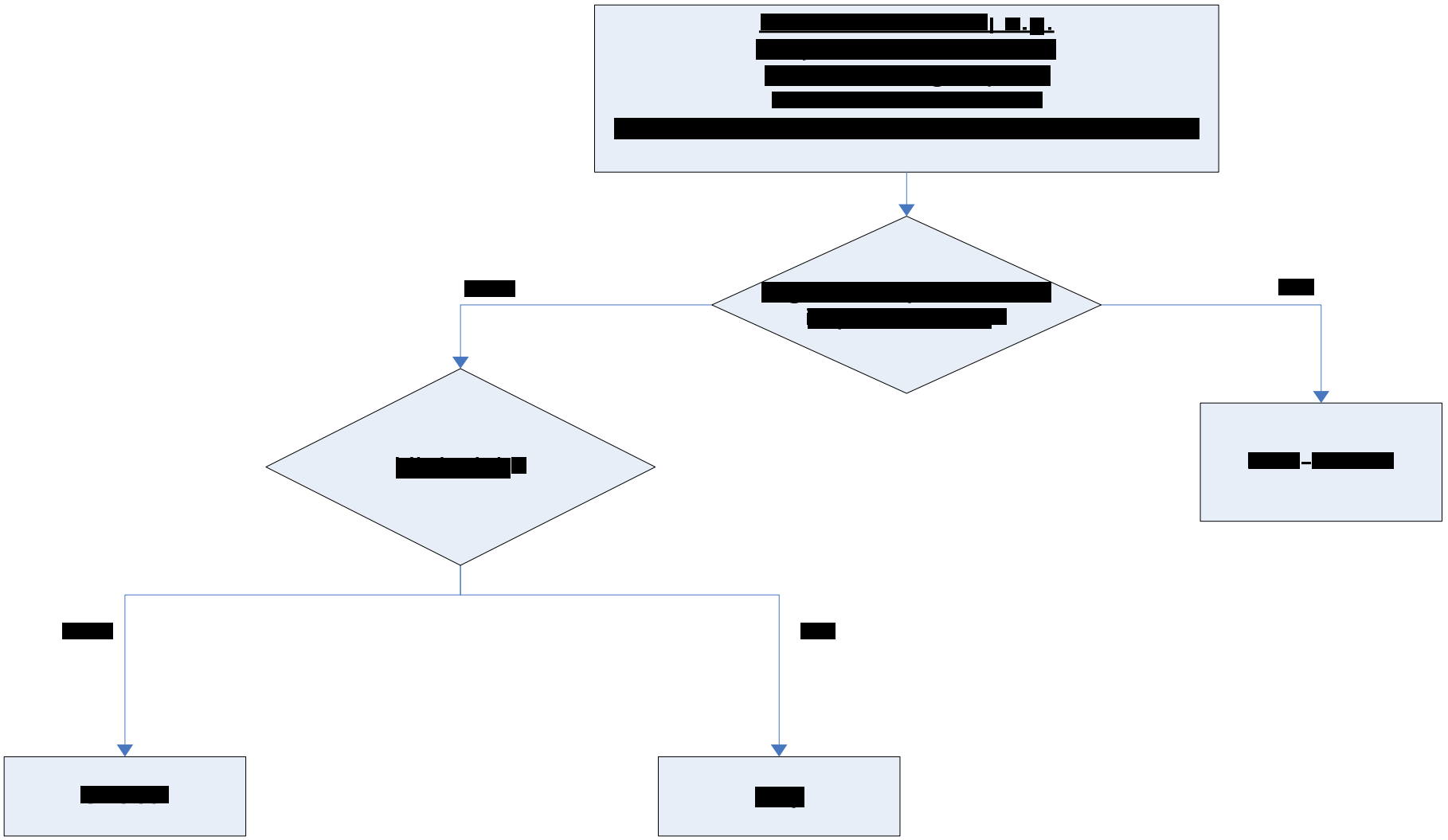
Initial Risk Assessment Defines Parameters to be Further Studied

Cause and Effect Diagram



- If initial assessment is low risk, assessment is documented and no further assessment is required
- If initial risk assessment is moderate or high, DOE is generally done to characterize NOR and PAR
- OFAT characterization of some low risk items may be done (optional)

A Single Process for Assessing Criticality is Used for all Aspects of the Process



Defining Critical, Key, and Non-critical Parameters from Operating Ranges

Non-critical parameter – No effect on CQA

Parameters affecting CQA – Continue to Monitor through Product Lifecycle

Key process parameter – modifications effect CQA but NOR is well within PAR

Critical process parameter - NOR and PAR are similar at upper range

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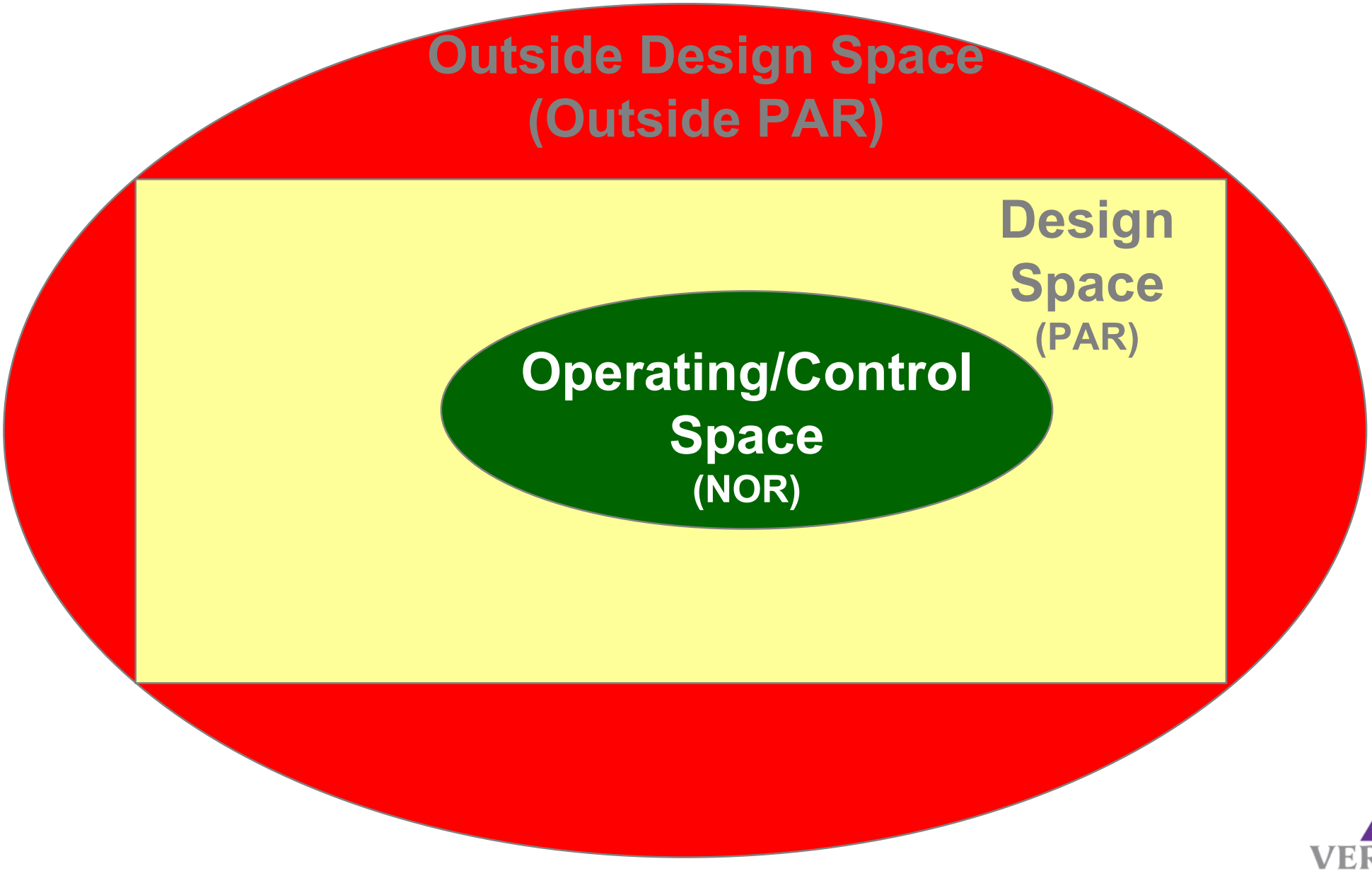
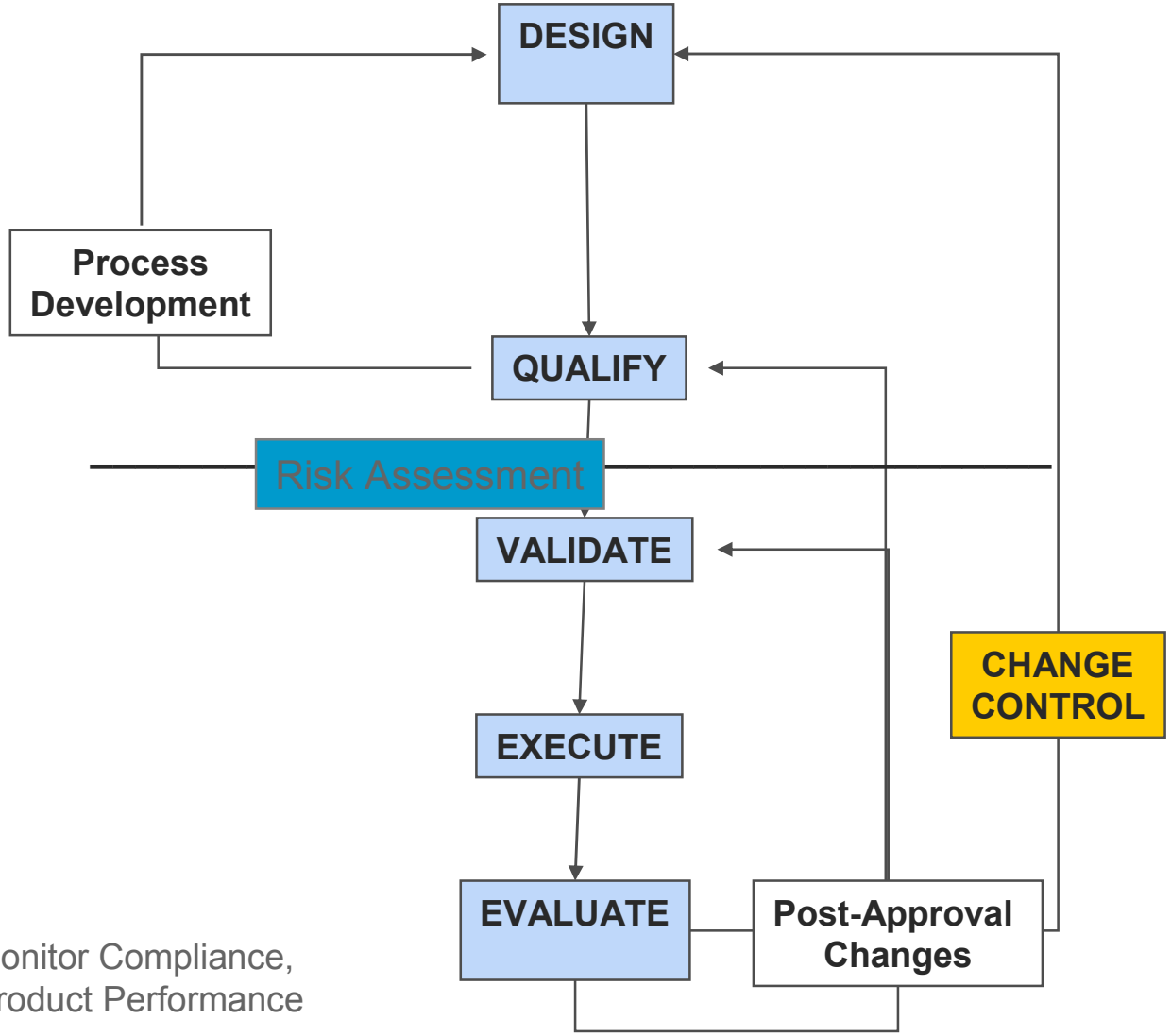
Defining the Design Space



Technology Transfer Ensures Quality Commercial Product



Validation per QbD covers the entire product development; registration includes all development activities that are part of defining design space

Start of traditional validation; pre-validation activities not part of registration

Monitor Compliance, Product Performance

Failure Mode Analysis and Risk Assessment when the Design Space is Defined

- Determine level of risk
  - On Critical and Key Process Parameters
  - On Critical and Key In-Process Controls
  - On Critical and Key Material attributes
  - On any process step that produces a Critical Impurity
- Numerical risk score documented in the Risk Assessment
- Where risk is above a predefined threshold, mitigate
  - Tighten NOR
  - Modify the process
  - Modify the equipment
- Reassess during lifecycle management

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Control Matrix: Process Control Points Ensure Drug Substance Quality

Potential Critical Quality Attribute	Starting Material	Step 1	Step 2	Step 3	Specification
Appearance	Spec			IPC	
Identification	Spec				
Purity	Spec	CPP		Real-time release	
Impurities	Spec			CPP	
Residual Solvents				Real-time release	
Physical Form				KPP	
Inorganic Impurities	Spec			KPP	

VERTEX

Implementation of QbD in Batch Records:

- NORs are intended for routine commercial manufacturing.
- The batch record includes NORs for critical and key process parameters and in process control (IPC) tests
- Tighter operating ranges or a mid-point rather than NORs may be implemented
  - to avoid excursions outside the NOR
  - to maximize product performance
- PARs for critical and key process parameters and in process control (IPC) tests are included in a separate supplemental document
  - referenced in the batch record

VERTEX

Lifecycle Management – QbD in Regulatory Filings

- Include more complete picture of development data in QbD filing vs. traditional filing
  - Specifications set at “PAR”
  - Extensive use of predictive tools (models) to justify design space
- Product control supported by control matrix
  - Coordination of starting material specifications, in-process controls, and process parameters to ensure product meets all specifications
- Post-approval changes classified and prior approval to implement changes obtained
  - Predefine parameters to be changed and process for changing
  - Submit comparability protocols for post-approval changes to design space
    - PAS to CBE-30 or CBE
  - No regulatory filings needed for changes within design space
- More detailed description of quality systems included in application
- Inspections will review changes and process used to implement

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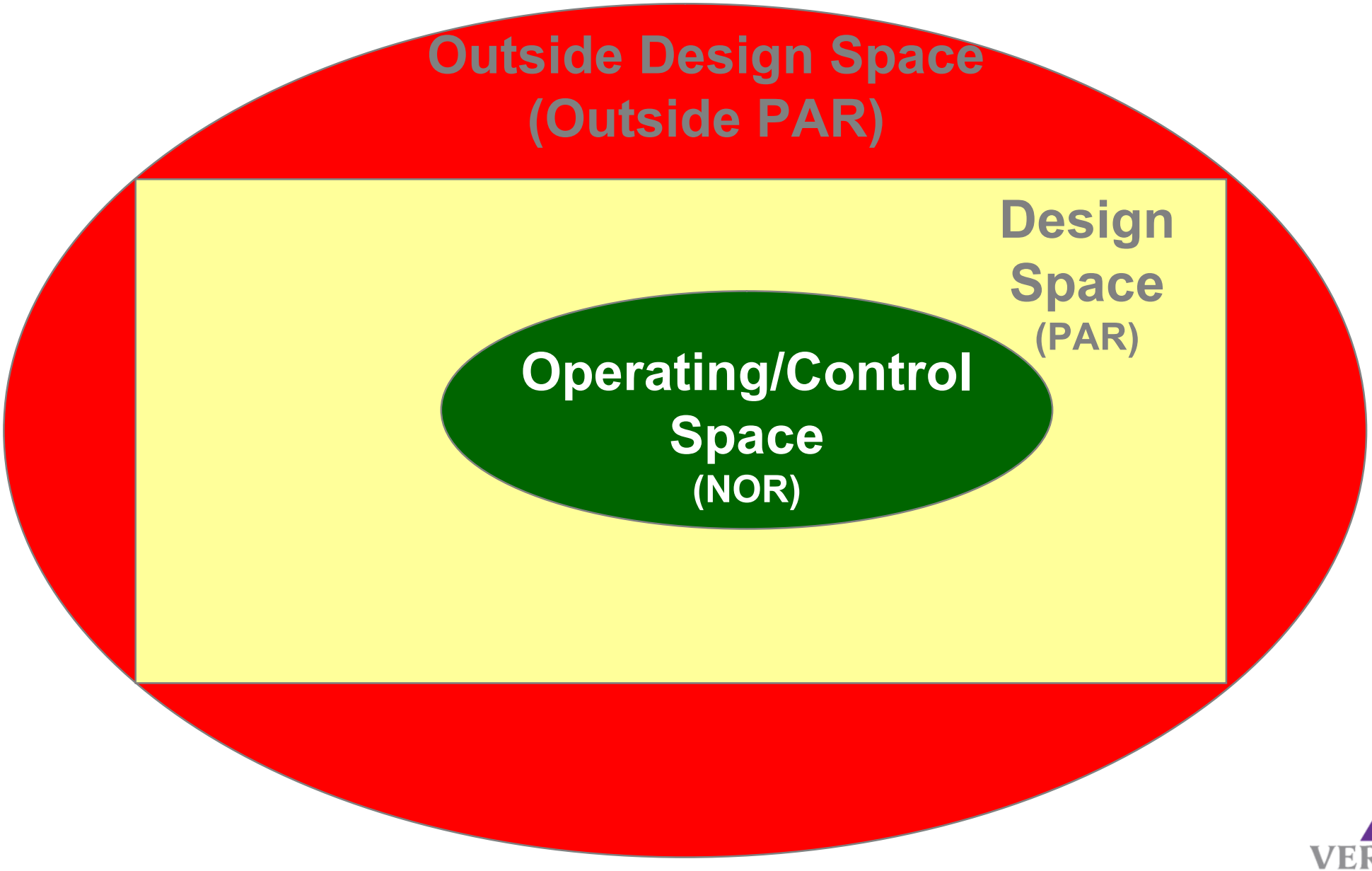
Commercial Manufacturing - Implementation of QbD with Traditional Quality Systems

- Vertex Quality systems completely embrace QbD
- Vendor Quality systems should not be different for QbD and "traditional" products
  - Changes to supplier Quality systems should be minimized
  - Use change management procedures to drive implementation of changes
  - Use nonconformance and process monitoring to identify potential changes and drive continuous improvement
- Vertex drives continuous process improvement with the support of and input from the supplier(s)

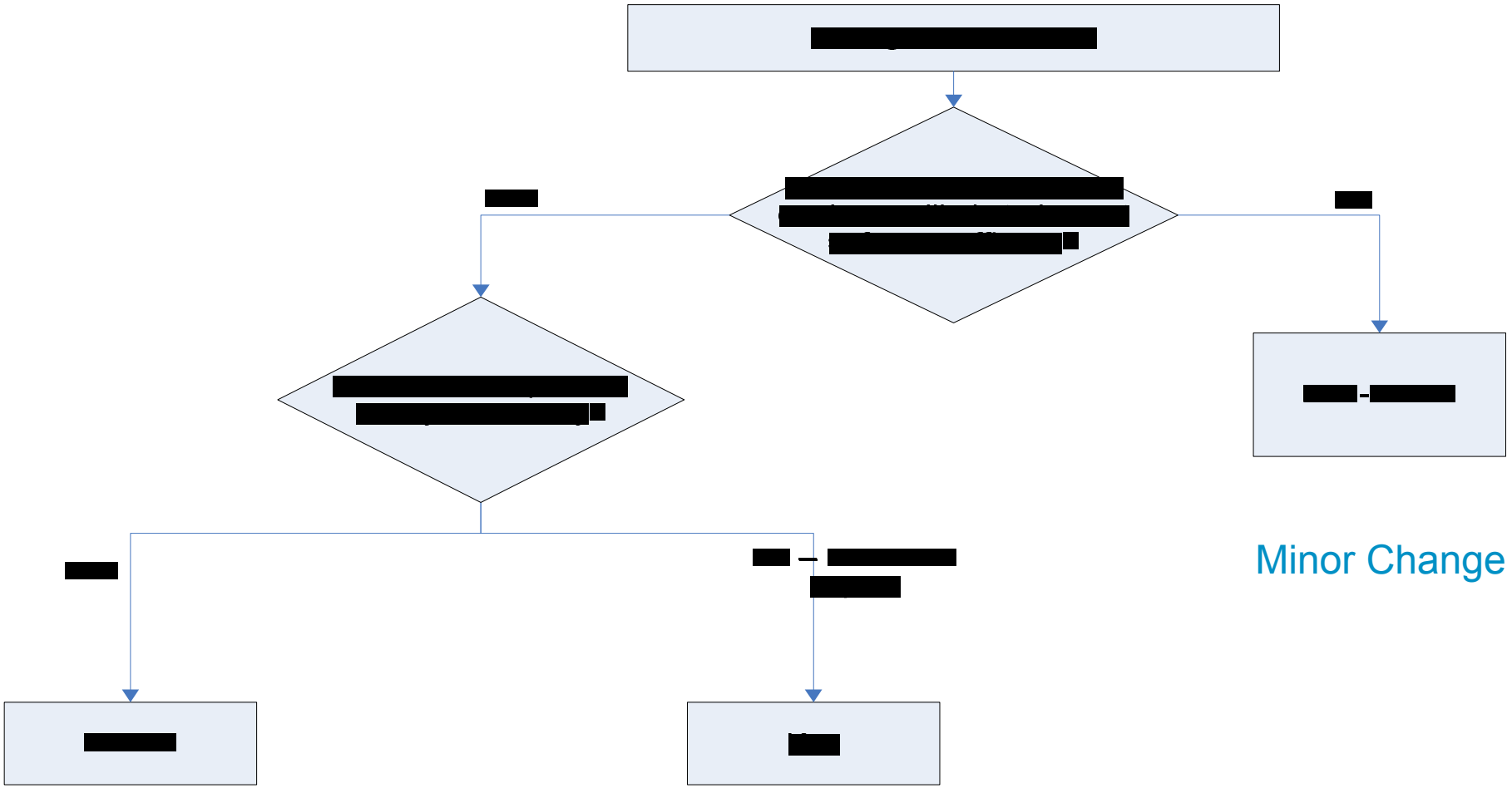
All assumptions have been valid to date

VERTEX

Implementation of QbD: Defining Deviations relative to NORs and PARs



Classification of Post-Approval Changes is Consistent with Traditional SUPAC Definitions



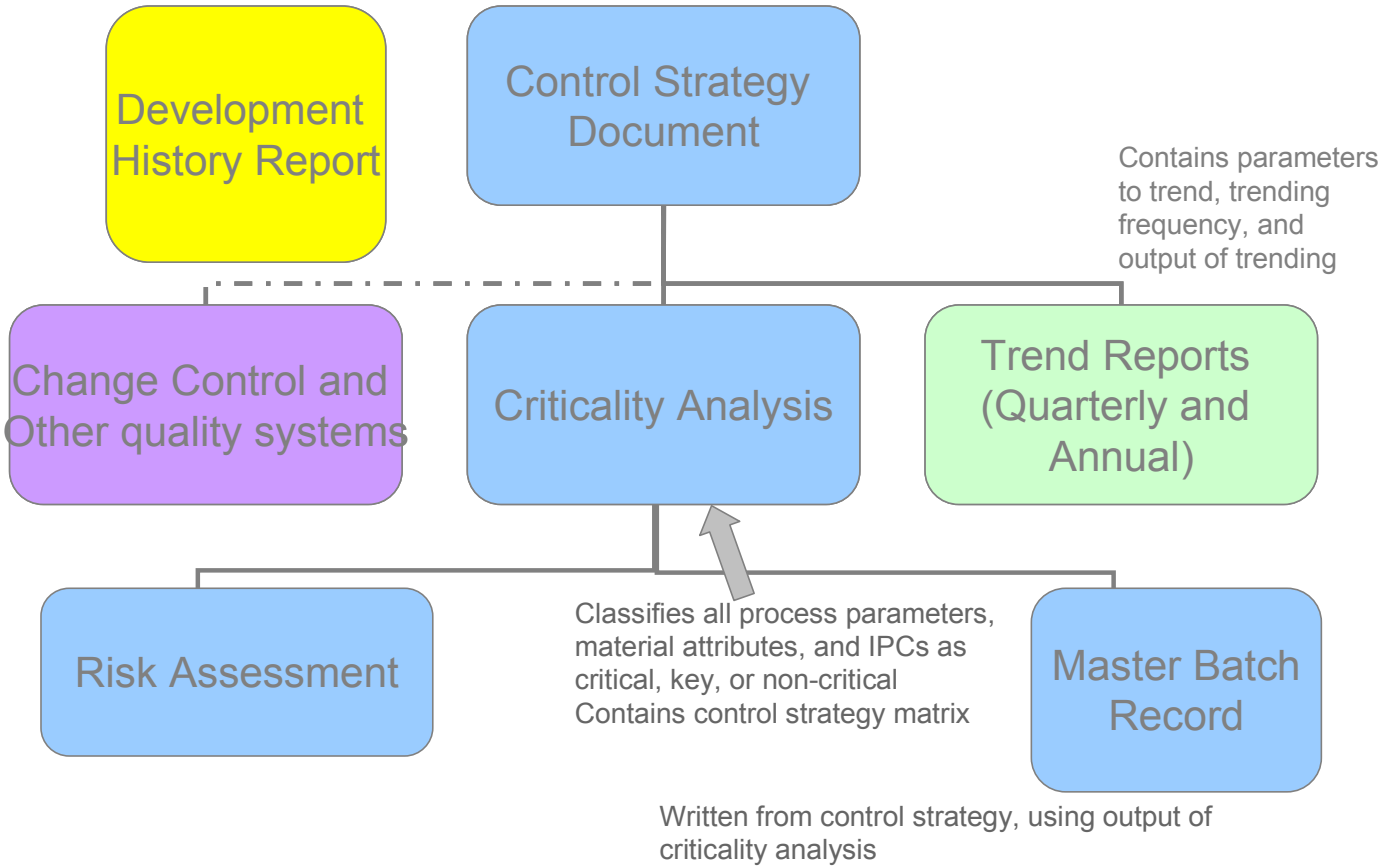
Minor Change

Major Change

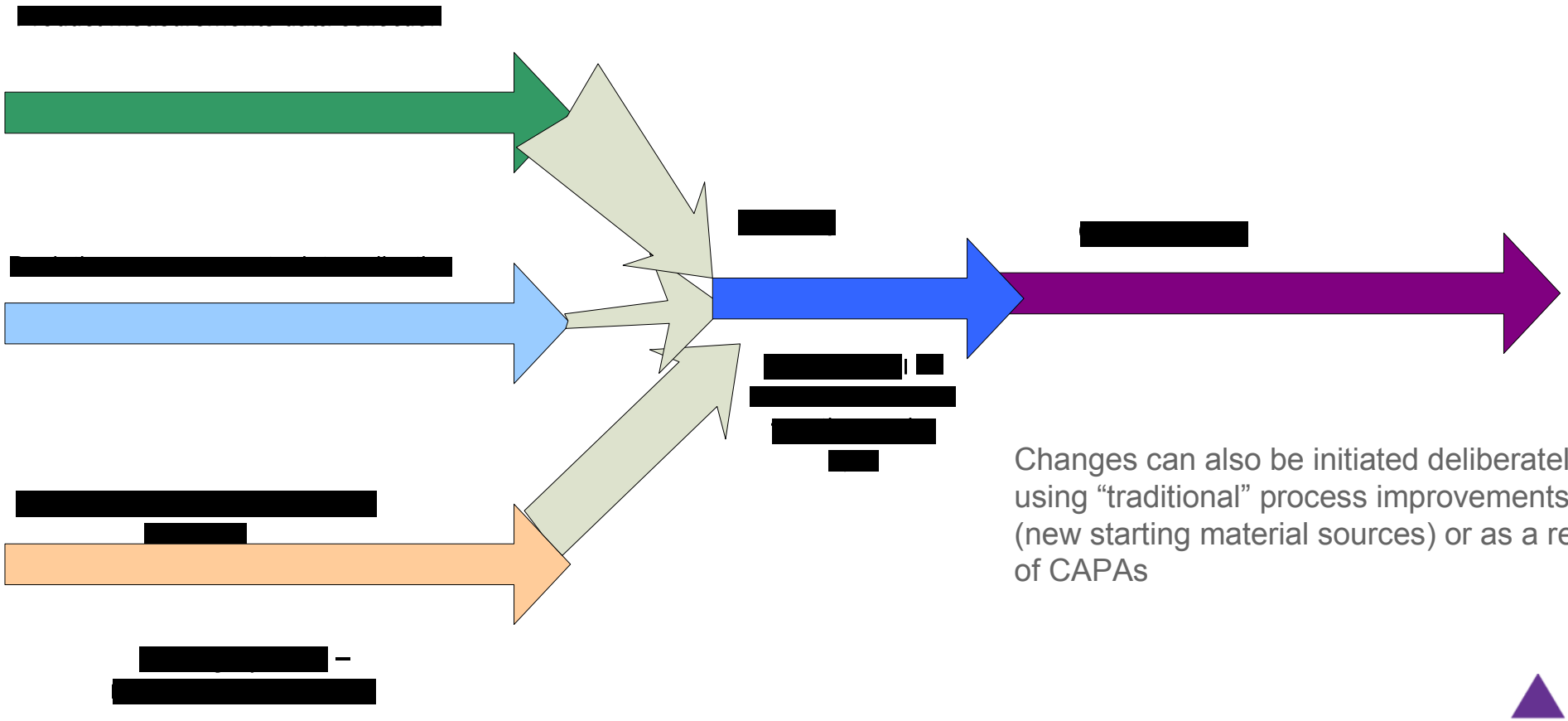
Moderate Change

Commercial Manufacturing under QbD

QbD Document Relationship



Lifecycle Management - Traditional Performance Measures are Trended using Statistical Tools and Changes Identified and Implemented under Existing Systems



Changes can also be initiated deliberately using “traditional” process improvements (new starting material sources) or as a result of CAPAs

Trending Protocol

- Prospective, documented plan for monitoring during routine manufacturing
  - Critical and key process parameters
  - Critical and key material attributes
  - Activities where frequency of failure is above a threshold
  - Key performance indicators, e.g.
    - Complaints
    - Confirmed OOS
    - Deviations (Major and Minor)
    - Observations
- Predefined responsibility for monitoring, frequency of reporting, statistical tools to be used, and thresholds for key performance indicators
- Describes content of trending report

VERTEX

Trending Report

- Comprehensive and cumulative
- Trend reported for all product performance measurements and all key performance indicators
  - Evaluation of observed trend to predicted trend
  - Evaluation of discrete “events” that can signal other issues
  - Conclusion about changes needed to the process, material attributes, operations, or key performance indicators
  - Risk assessment (actual vs. predicted frequency) revisited

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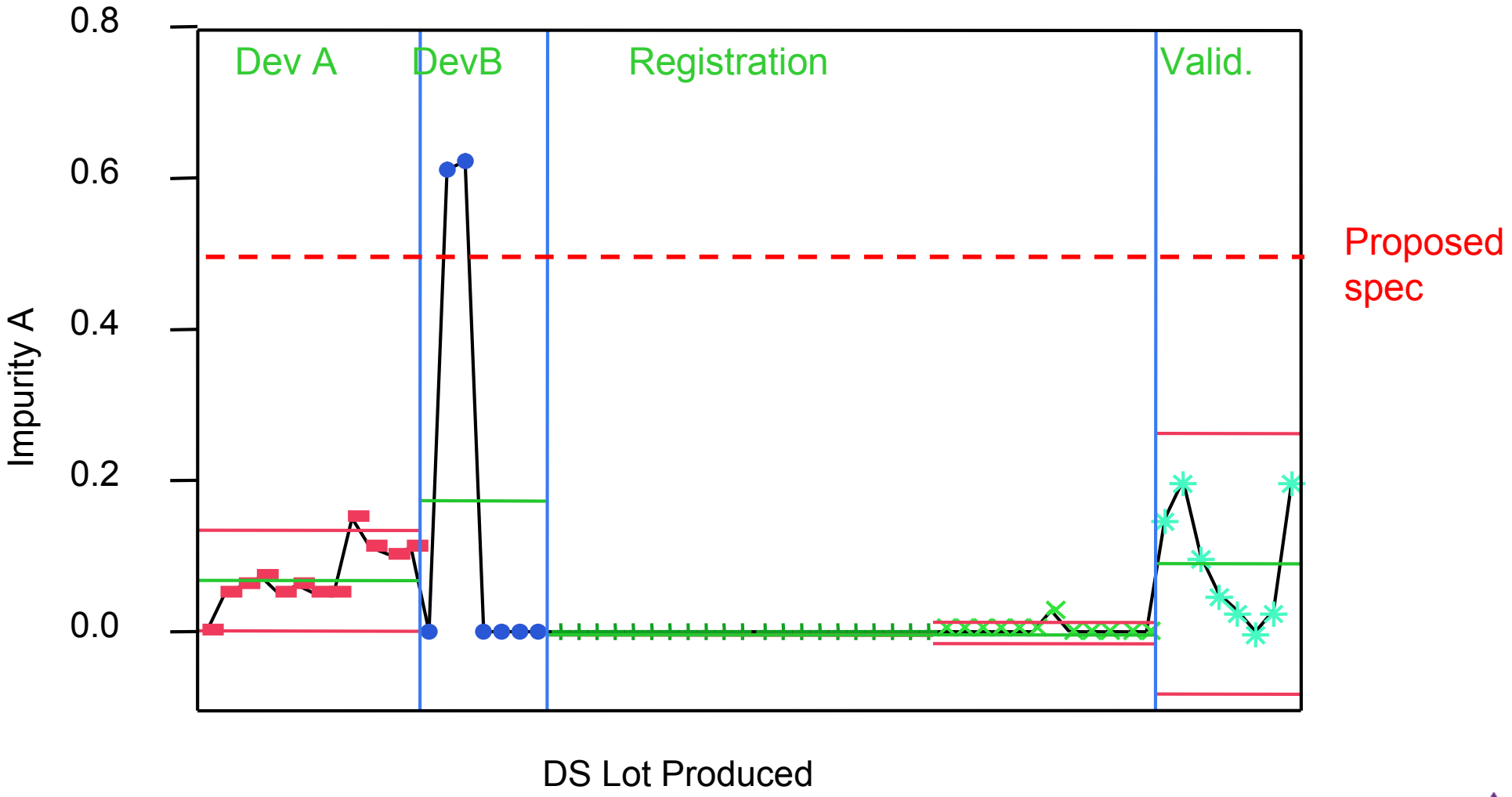
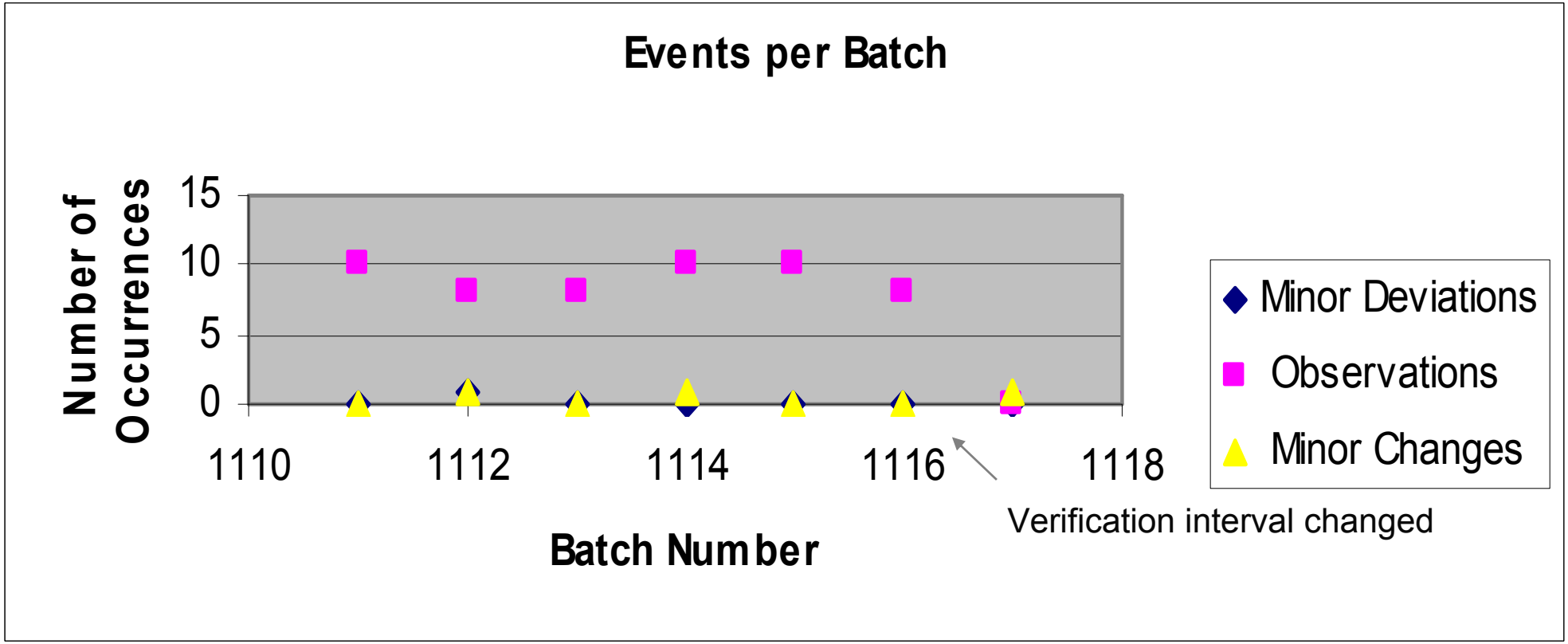
Trending drives continuous improvement through increased process understanding

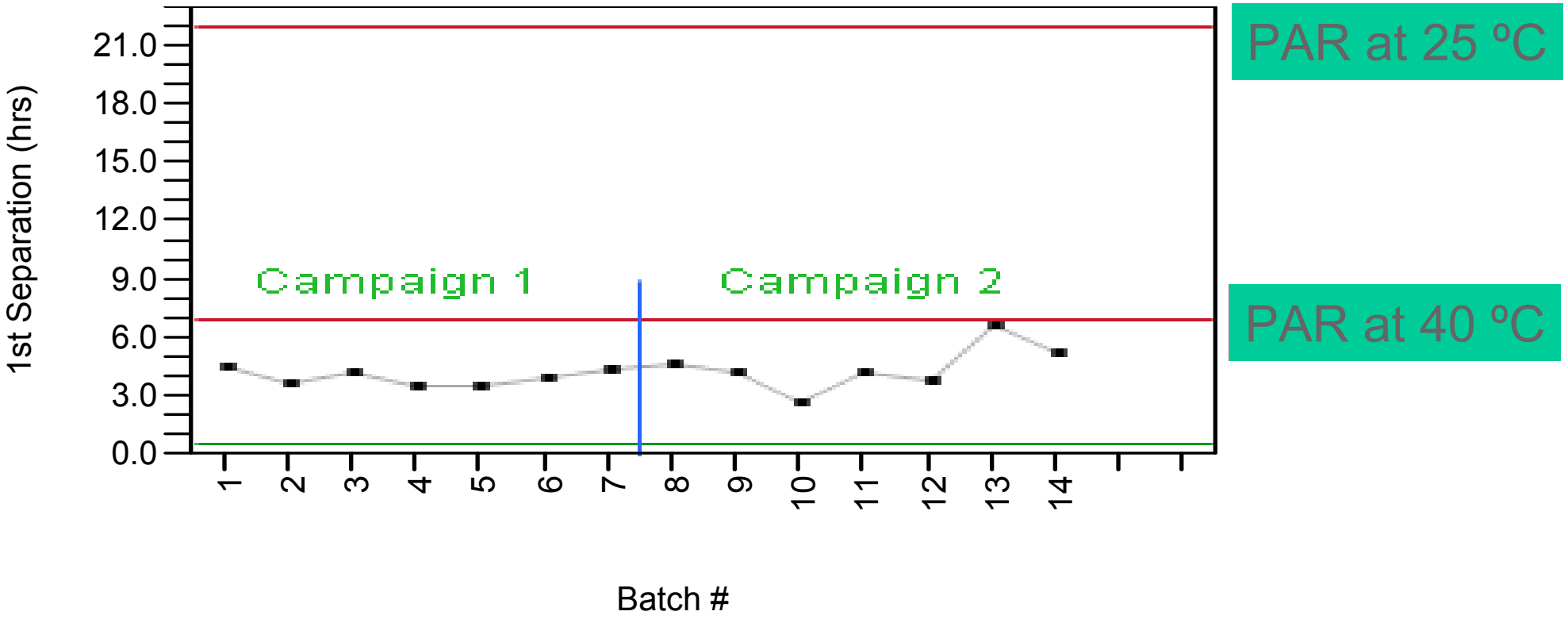


Trending Key Performance Indicators Gets to Root Cause



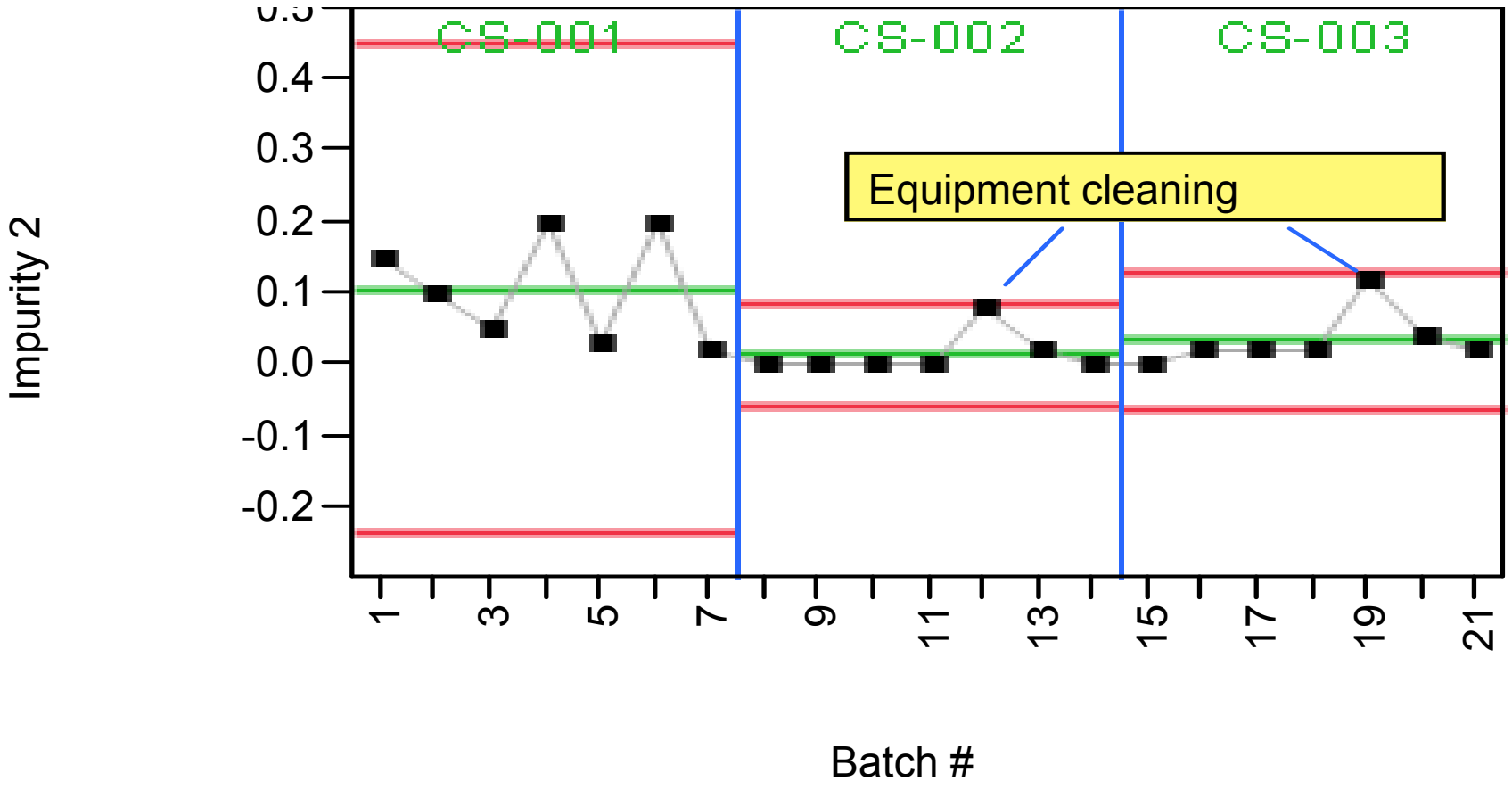
- Increased number of observations traced to increased rate of instrument failure
- Correlated with recent change in performance verification interval
- Performance verification interval reduced to 6 months

Trending Based on Process Criticality Decreases Risk of Product Failure



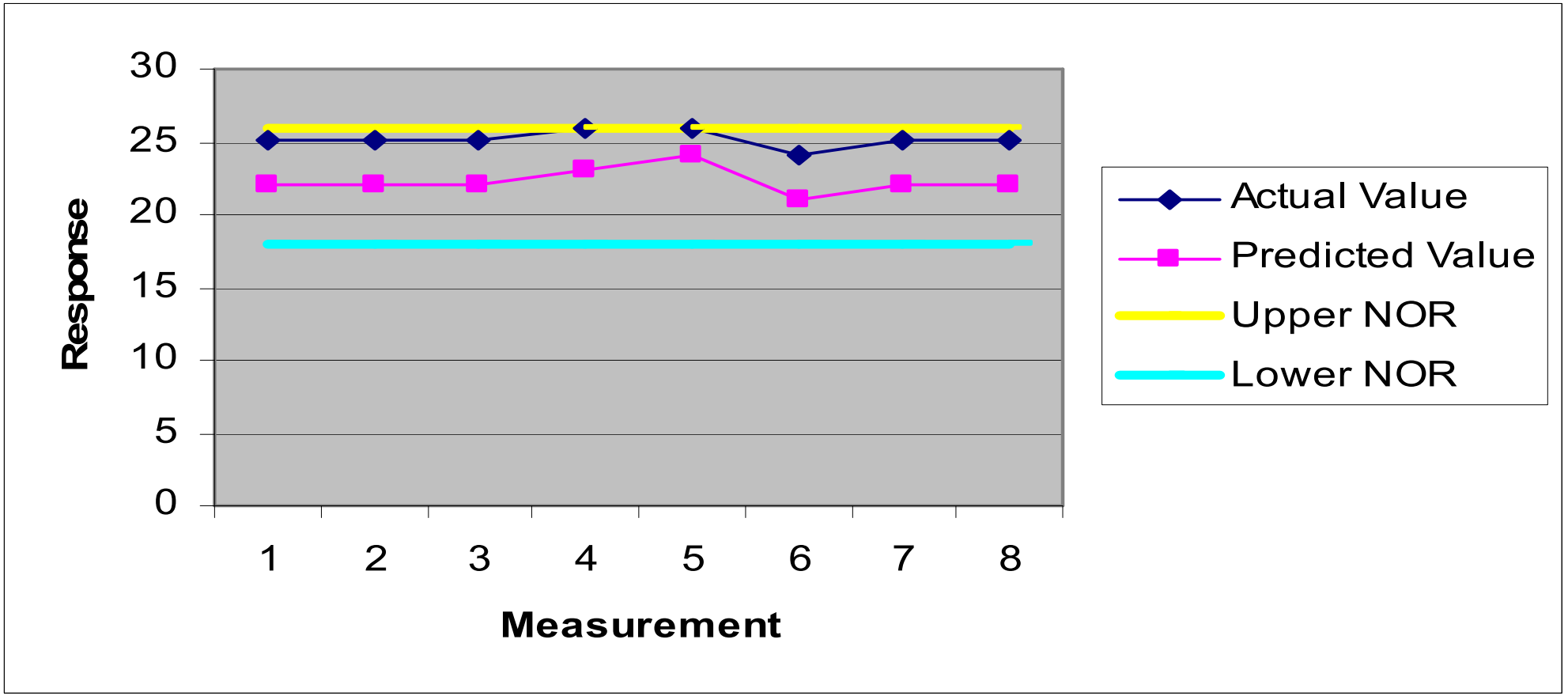
- Maximum temperature monitored as key process parameter
- Automated equipment records temperature every hour
- Batch record modified to instruct operator to record maximum temperature
- Further equipment modifications being considered

Trending Can Identify Process Issues



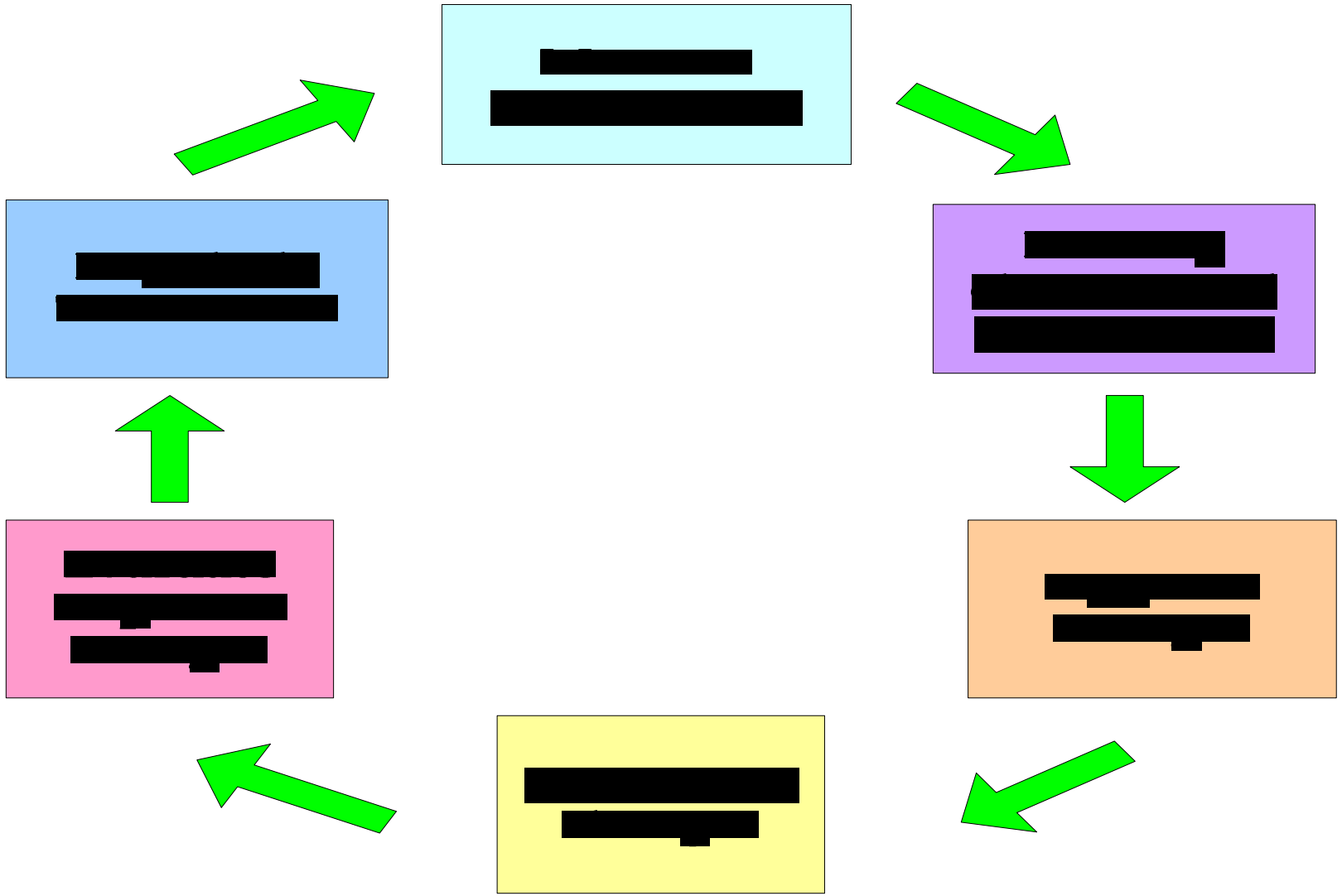
- Increased level of impurity 2
- Correlated with periodic equipment cleaning
- Process modified to verify all piping rinsed before contact with product

Process Changes Can Result from Trending



- Predicted value based on model from development runs
- During scale-up a bias in actual vs. predicted results was observed
- NOR modified to reflect change in the model

Continuous Improvement is Part of Product Lifecycle



Effective Data Processing Ensures Continuous Improvement in Process and Product Understanding

- Pharmaceutical development ensures commercial product is more robust
  - Process and product understanding built into control strategy and change management systems
  - Better predictability of product performance
- Regulatory specifications ensure product safety, quality, and efficacy
  - PAR can be non-rectangular
- QbD manufacturing processes are compatible with traditional quality systems
  - Change management system assesses changes to NOR and PAR
  - Routine manufacturing can be designed to operate within a traditional-looking range
- Lifecycle management is achieved through routine, coordinated trending
  - Key and critical process parameters, IPCs, and critical quality attributes
    - "Out of trend" results are investigated and addressed
  - Ensures continuous improvement in product performance and product knowledge

VERTEX

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- Kelly Tolton
- Antoinette Paone
- Drew Barlow
- Adam Looker
- John Goldthwaite
- Martin Warman

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Related Links

- Overview of Risk-Based Quality Assessment System
  - http://www.fda.gov/CDER/gmp/gmp2004/ONDC_reorg.pdf
- FDA's PAT Guidance
  - http://www.fda.gov/cder/guidance/6419fnl.pdf
- FDA Report on Risk Based Approach to cGMPs
  - http://www.fda.gov/cder/gmp/gmp2004/CGMP%20report%20final04.pdf

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QbD Regulatory references

- Q8(R1) Pharmaceutical Development (Drug Product)
  - Step 5 (November 2008)
- Q8 Annex
  - Step 5 (November 2008)
- Q9 Quality Risk Management
  - Step 5 (November 2005)
- Q10 Pharmaceutical Quality System
  - Step 5 (June 2008)

- http://www.ich.org/cache/compo/276-254-1.html

- Q11 Development and Manufacture of Drug Substances (Chemical and Biotech)
  - Final concept paper approved April 2008
  - http://www.ich.org/cache/compo/276-254-1.html
- Q8-Q10 Quality Implementation
  - Final concept paper approved November 2007
  - http://www.ich.org/LOB/media/MEDIA4457.pdf
- Q8, Q9, and Q10 Questions and Answers
  - Approved April 2009
  - http://www.ich.org/MediaServer.jser?@_ID=5290&@_MODE=GLB

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