Process Validation Guide
Regulatory Expectations & Best Practices

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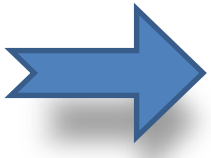
Process Improvement?

Grandpa's Car



Future Grandkid's Car

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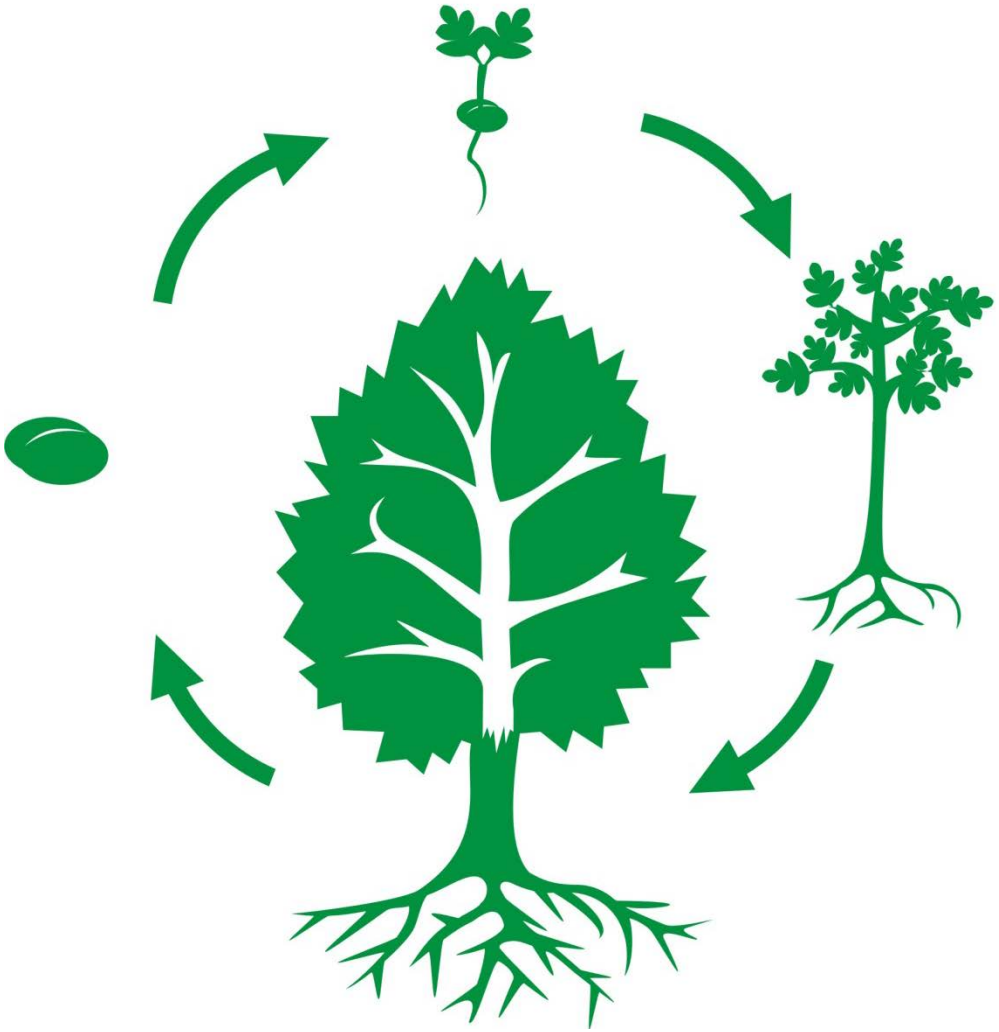
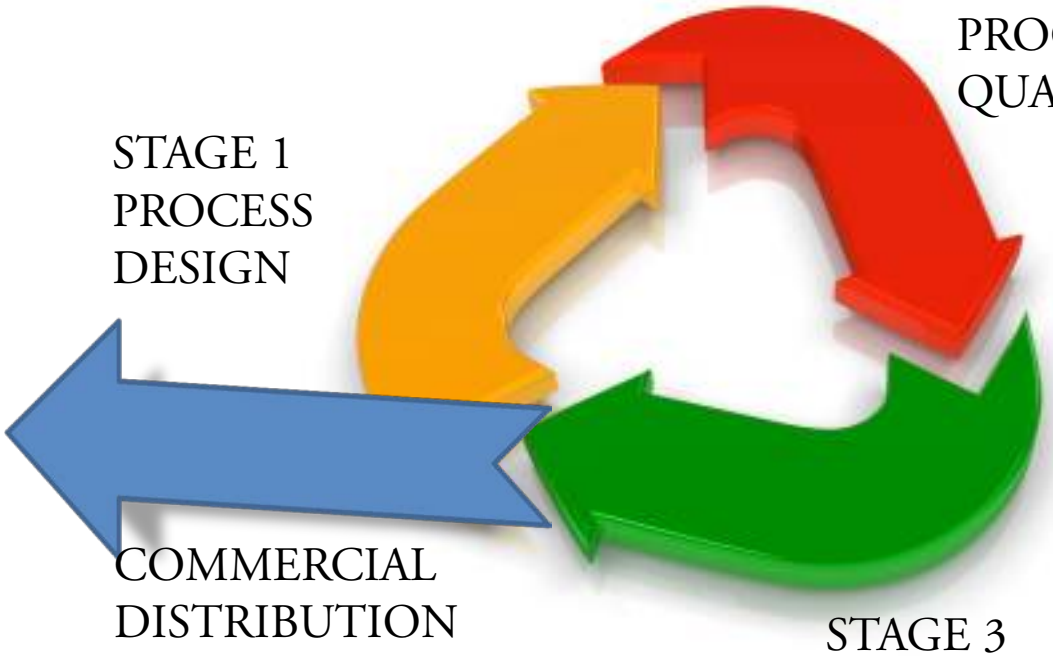
Linear Compartmentalization?

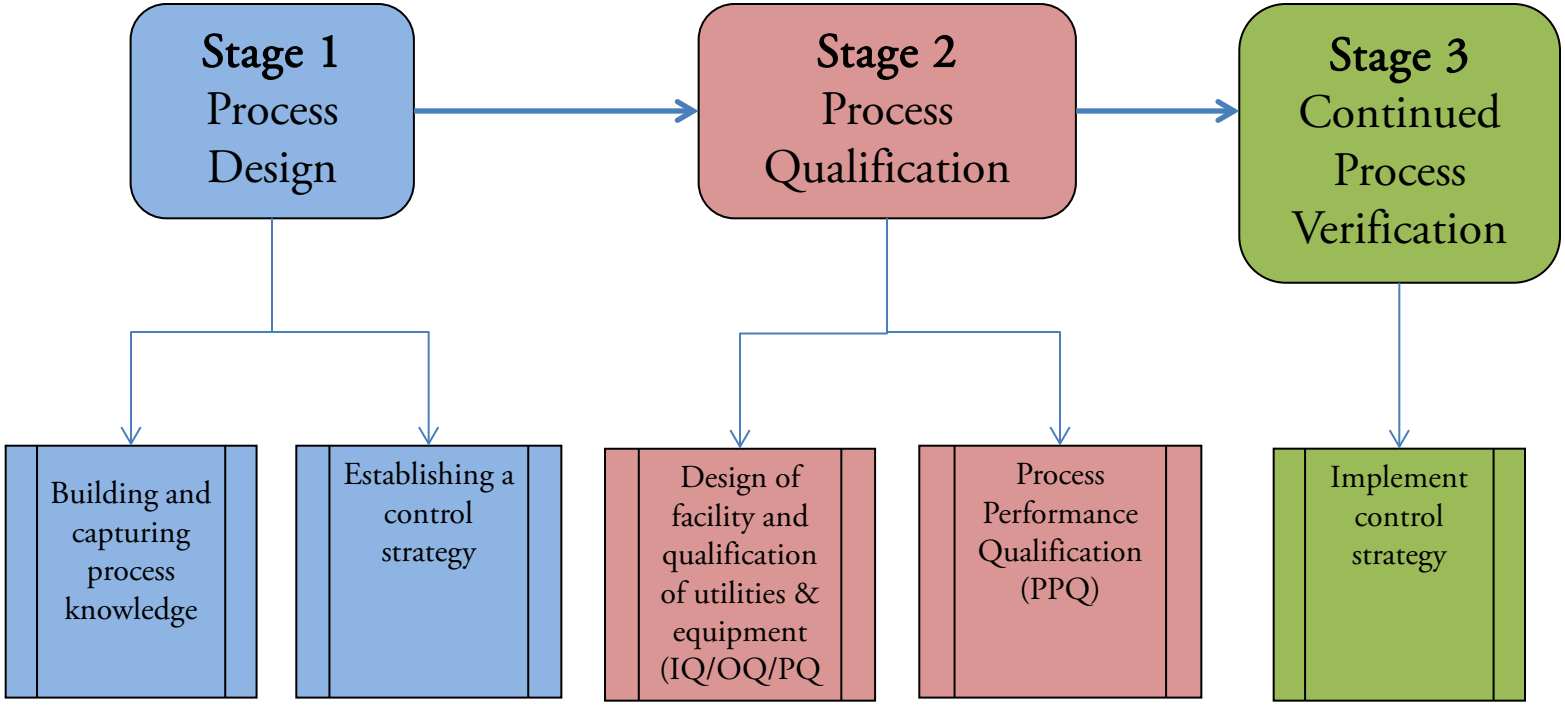
Lifecycle Approach



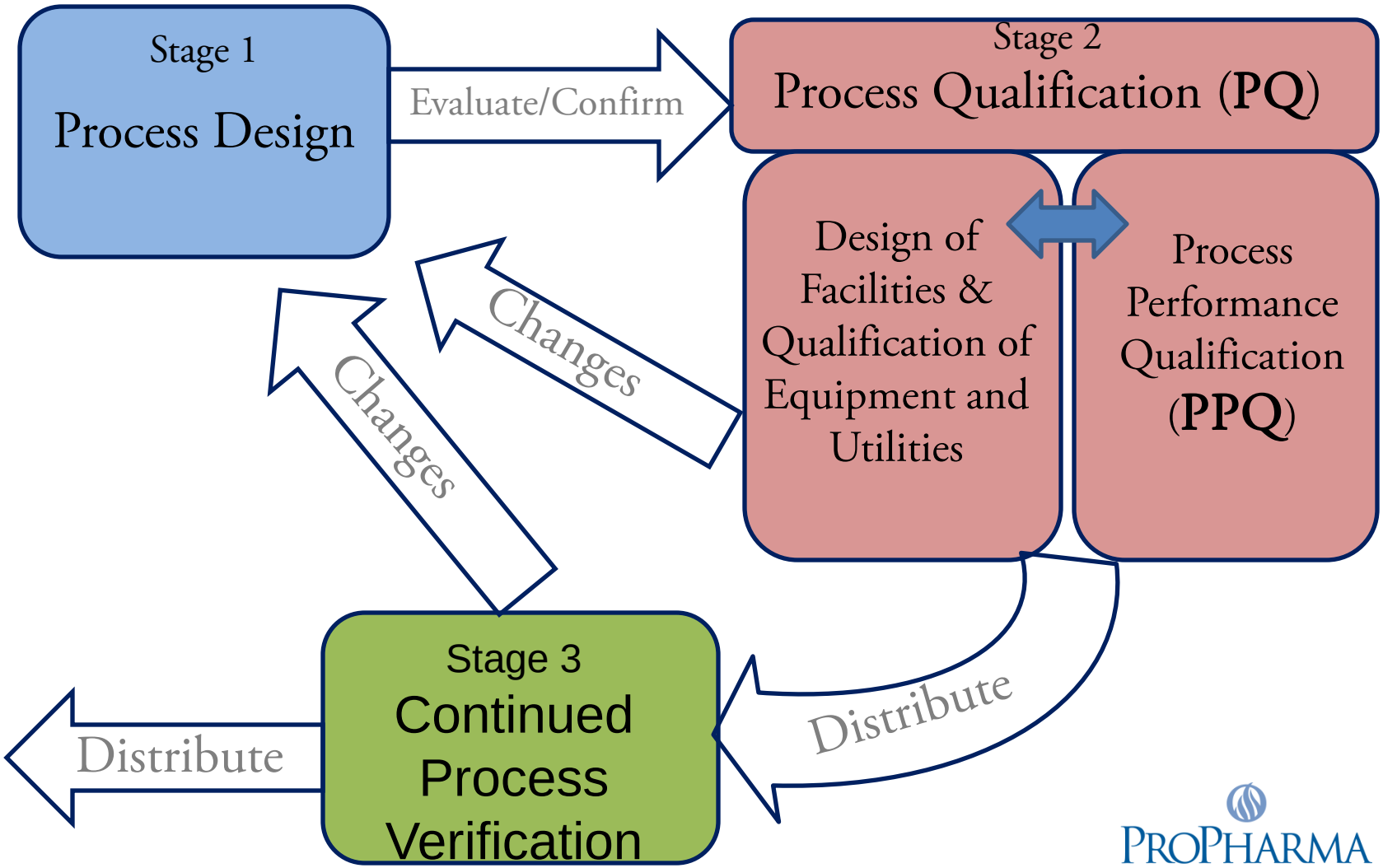
Lifecycle Staged Approach



Process Validation Stages



Schematic of Stages
(New Process or Product)



Ref: Grace E. McNally FDA (Guide Leader) Sept 15, 2010

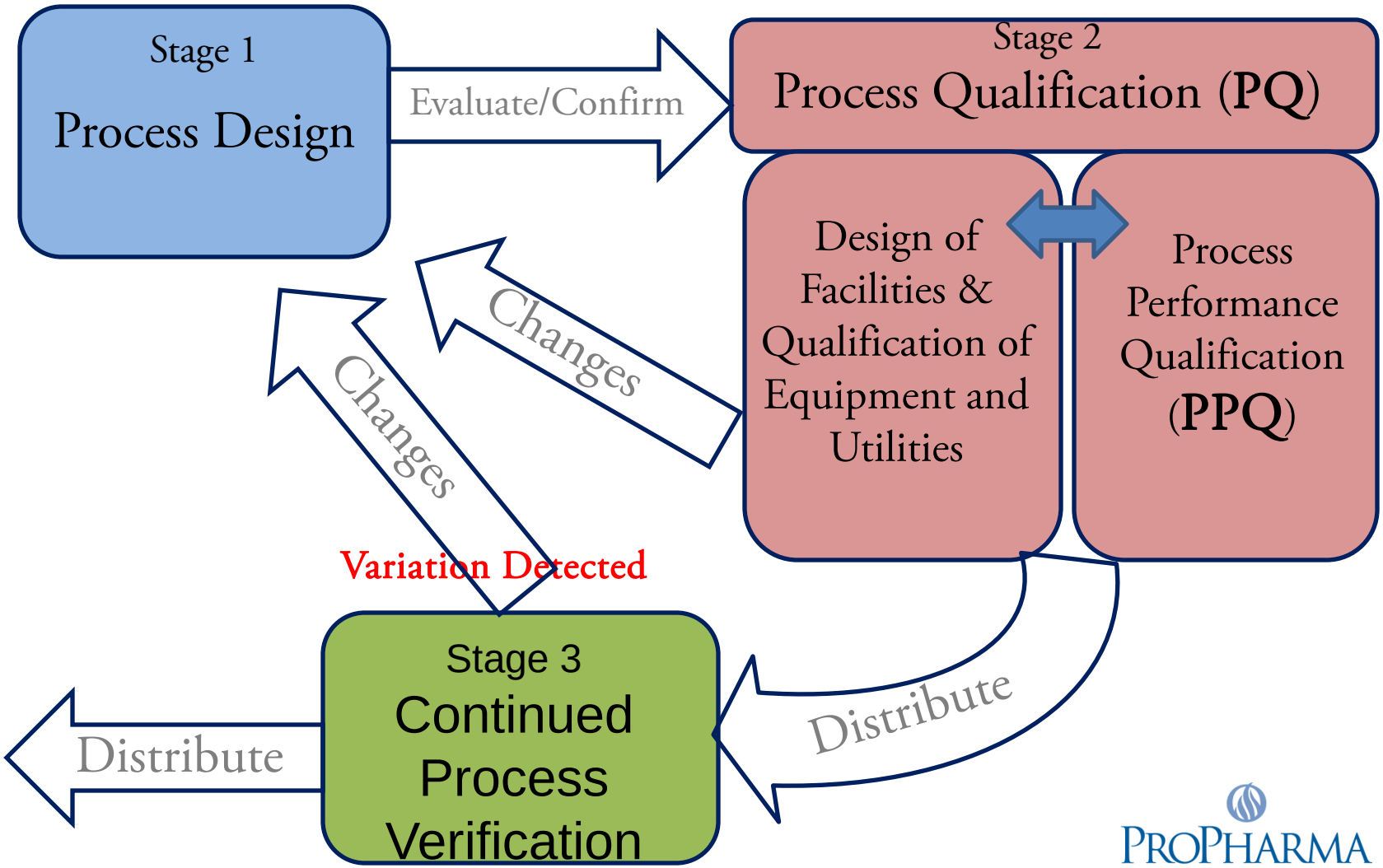
What does this mean?

- Lifecycle approach – product conception through commercialization

Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality.

- FDA Guideline Section IIB

Schematic of Stages
(Legacy Process or Product)



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Activities for Legacy Products

- Demonstrate **control over variation** through the examination of data from previously manufactured product
- BEST PRACTICE:
  - Review a minimum of 10 lots over the last 3 years or at least thirty (30) batches
  - Examine data for critical process parameters for each step of the process and include:
    - all in-process testing and QC results
    - final product testing results
    - specifications.
  - Examine data for critical parameters for overall state of control for each batch

STAGE 1: PROCESS DESIGN

Expectations

1) Define risk based methodology and team structure
2) Define CQA
3) Perform Risk Assessment
4) Define applicable CPP's
5) Determine analytical process variation
6) Demonstrate variation correlation
7) Establish control strategy
8) Assess data

Best Practice

1) Engage Process Development Scientist & Engineers early
2) Get it in writing
3) Ensure scalability
4) Create event driven Process Flow
5) Get an early start on Method Validation

STAGE 1: PROCESS DESIGN

Expectations

1) Defined process
2) Completed CPP/CQA Matrix
3) Completed risk assessment
4) Defined control strategy
5) Defined risk reduction plan
6) Summary of test method validation
7) Statistical assessment
8) Process variation

Stage 1 Summary Report

Best Practice

1) Make it accessible
2) Make it searchable
3) Make it clear!
4) Allow amendments

STAGE 2: PROCESS QUALIFICATION

Expectations

1) Confirm Facility, Equipment, Utilities
2) Develop PPQ Protocol including:
   a) Definition of methodology and team structure
   b) Definition of statistical terms and formulas
   c) Applicable references to stage 1 summary report
   d) Control strategy
   e) Number of batches
   f) Sampling Plan
   g) Create control charts
   h) Acceptance Criteria / Investigation process for both intra and inter batch variability.
   I) Training record

STAGE 2: PROCESS QUALIFICATION

Expectations

3) Train Operations and Analytical Team
   a) Manufacturing Processes
   b) SPC trending
   c) Updated SOP's
   d) Batch record review
   e) Risk assessment review
   f) CPP/CQA Matrix review
4) Execute Protocol
5) Revise risk assessment and CPP/CQA

Best Practice

1) Plan extra runs
2) Prepare for deviations
3) Follow in-process results closely

STAGE 2: PROCESS QUALIFICATION

Expectations

1) Summary of results
2) Confirm Process Performance value
3) List of CPP's by Risk Priority Number
4) Control system
5) Determine confidence intervals
6) Justification for reduced testing

Stage 2 Summary Report

Best Practice

1) Compile results in real time
2) Utilize someone well versed in statistical methods
3) Leave a well documented rationale as to which Attributes to monitor and why

Commercial Distribution

- Basis for Commercial Distribution

  "Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product."

  FDA Guideline Section IIB

STAGE 3: CONTINUED PROCESS VERIFICATION

Expectations

1) Revise Batch records
2) Establish an SOP / Methodology
3) Revise CAPA / Change control process
4) Utilize CPP/CQA matrix
5) Record and trend CQA batch results
6) Report CQA trends

Best Practice

1) Create a Program
2) Hire a Full Time manager
3) Be proactive!
4) Review OOS, CAPA, Deviations
5) Make results visible to all
6) Bring the Cross Functional Team together – Often

STAGE 3: CONTINUED PROCESS VERIFICATION

Expectations

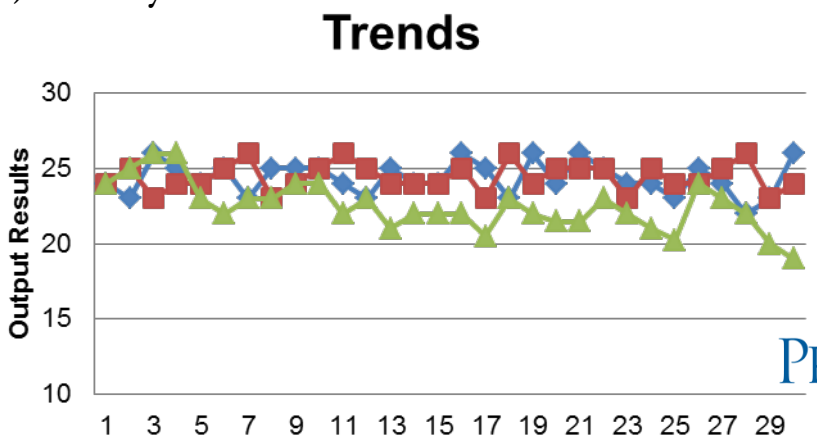
1) Summary of results
2) Routine monitoring
3) Control system
4) Justification for continued testing of CPP's

Process Metrics Report

Annual Product Report

Best Practice

1) More than just annual requalification
2) Analysis of



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Is there a conclusion?

- Know your process
- Understand your variability
- Build a Control Strategy early
- Establish a lifecycle
- Monitor the process and analyze your results
- Continued process improvement will lead you to the Future!