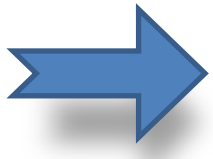
Welcome
Process Validation Guide
Regulatory Expectations & Best Practices

ISPE-Boston Area Chapter
February 20, 2014

ISPE®

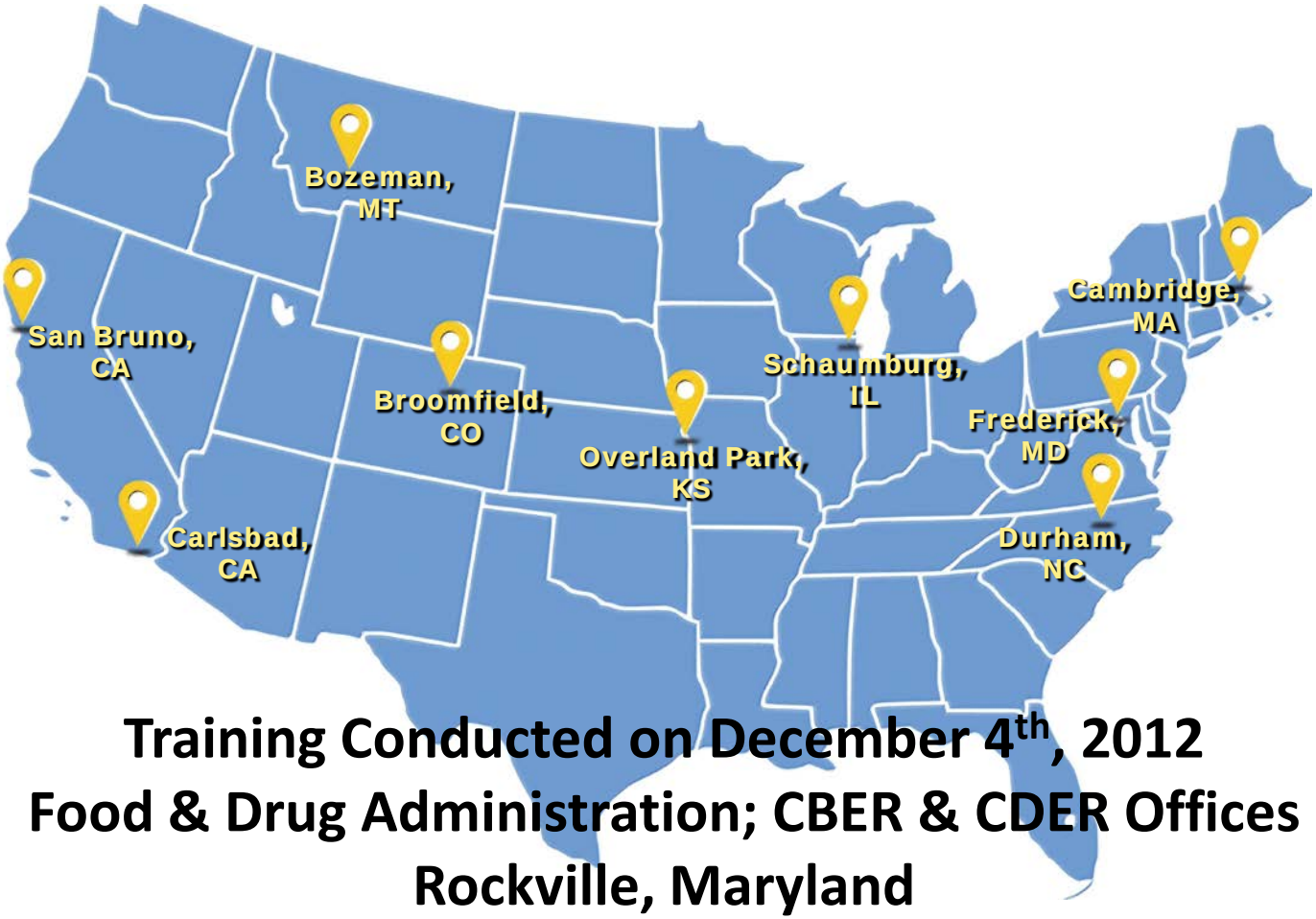
Process Improvement?



Grandpa's Car

Future Grandkid's Car

National & Product/Process-wide Approach (but how many have adopted it?)



Training Conducted on December 4th, 2012
Food & Drug Administration; CBER & CDER Offices
Rockville, Maryland
35-45 Inspectors present

Guidance Evolution from 1987 to 2011

1987

- Single protocol approach
- Static event, disconnected
- 3 batch requirement almost explicit
- More deliberately prescriptive
- Simply a confirmation
- Criticality is binary (yes or no)
- It is what it is
- Final report jumps to conclusions

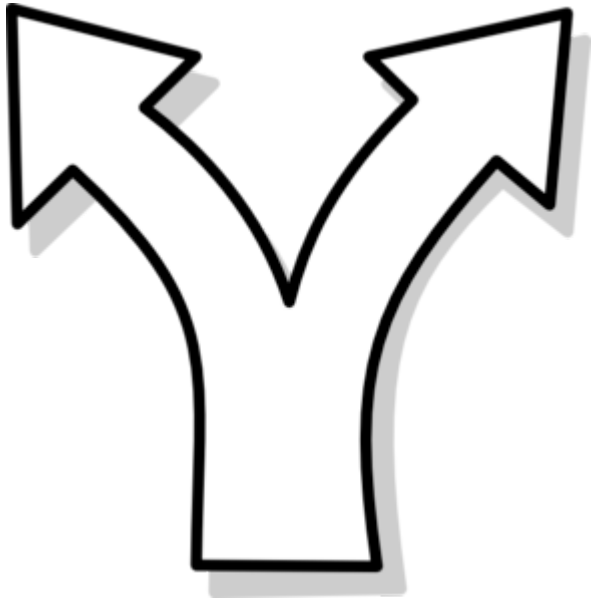
2011

- 3 phased approach
- Lifecycle evolution, sustainable
- No longer a magic run number
- Risk-based decision-making
- Emphasizes up front learning
- Criticality is a continuum
- Greater clarity of expectations
- Allowing the final report to "return" to process design allows for learning

Learning Progression

Poor design, planning, process and understanding

Good planning, expected result



Unexplained variation, Product and process problems, Process not in control. **Major Learning!** Potential substandard product on market

Continued Verification, Process Learning and improvement

PQ checklist exercise w/ little understanding

Sound, thorough process Qualification confirms design

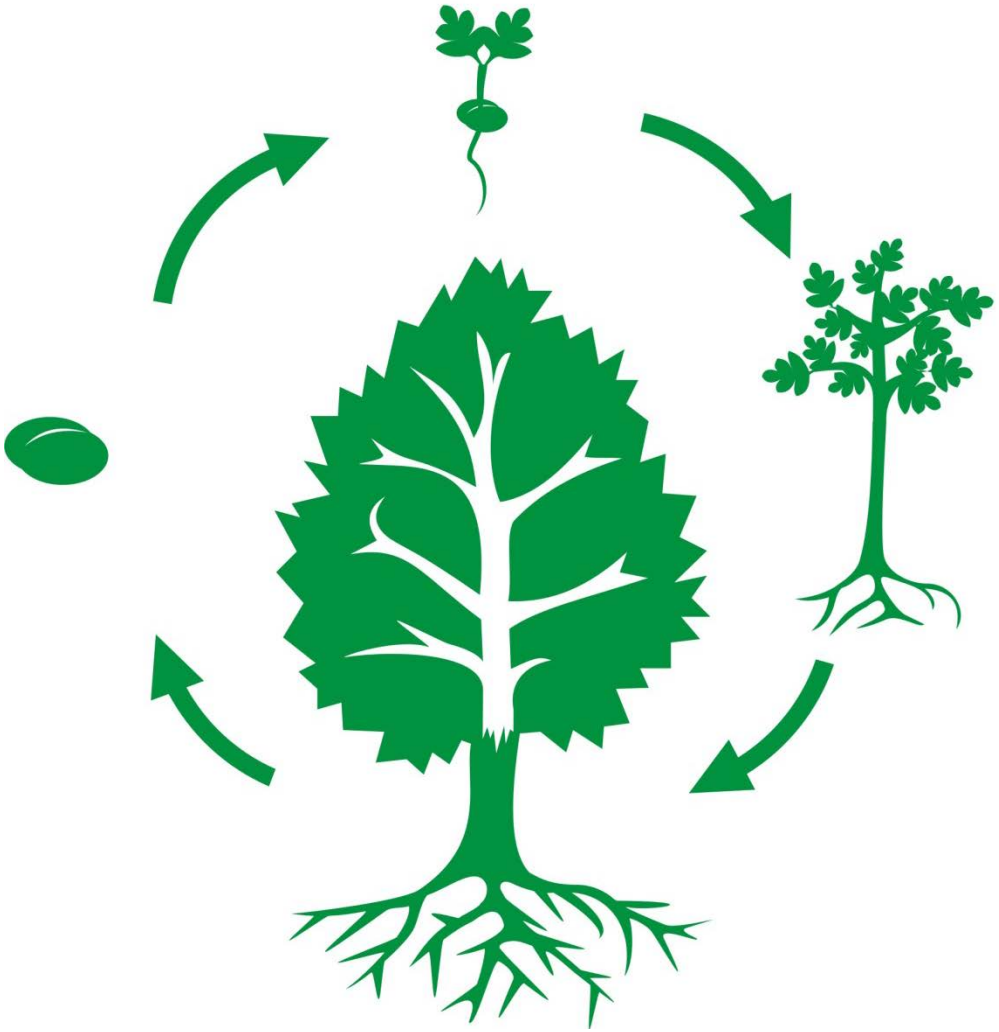
Poor, minimal design

Comprehensive process design, Scientific process understanding

Borrowed from Grace E. McNally

Linear Compartmentalization?

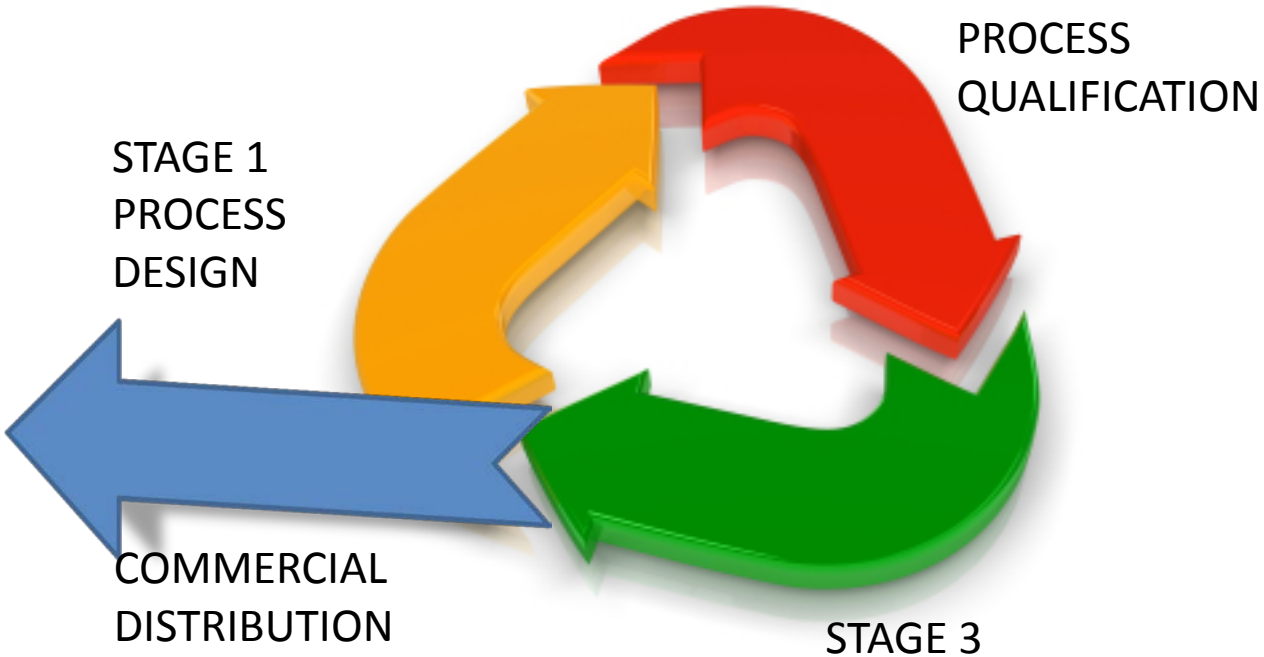
Lifecycle Approach



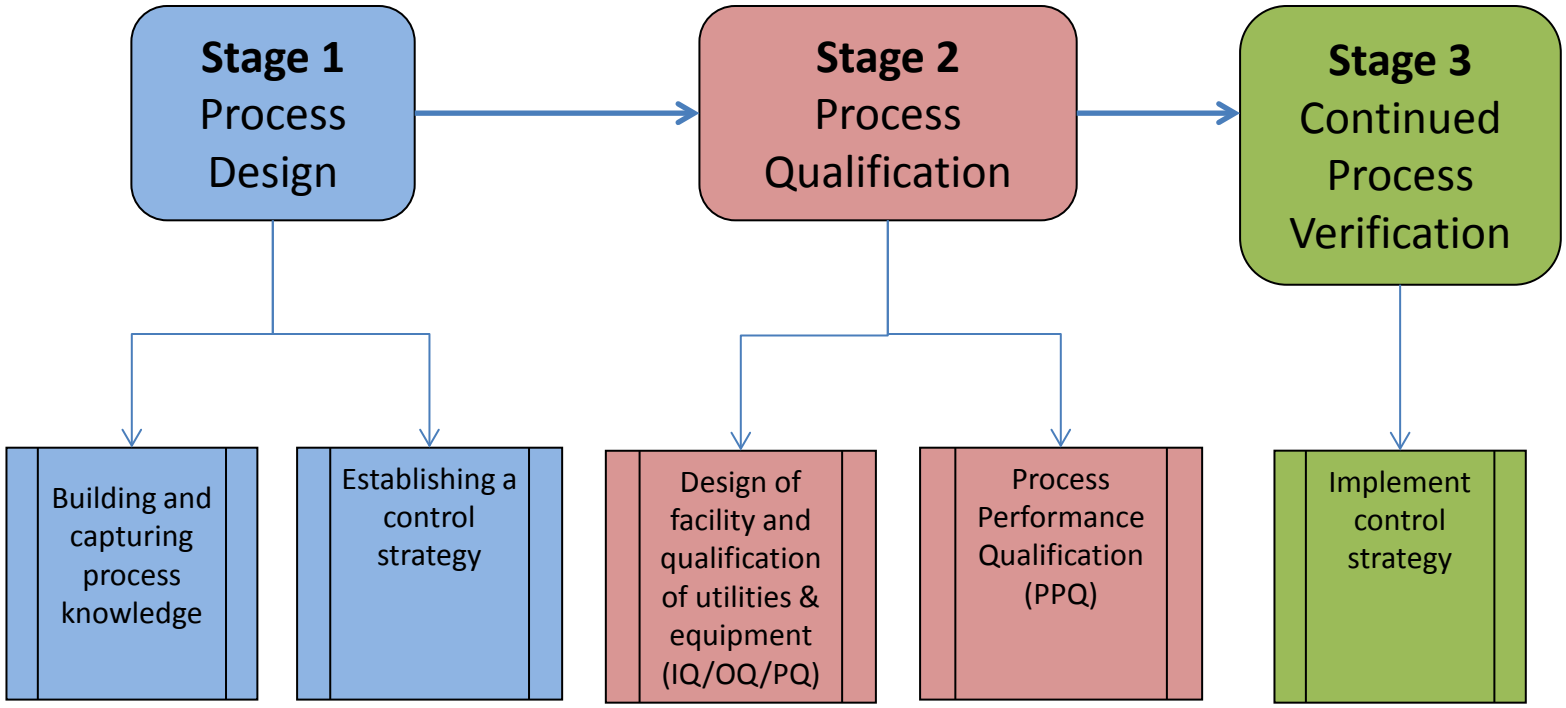
Approach to Process Validation

Process validation involves a series of activities taking place over the lifecycle of the product and process. The guidance describes the process validation activities in three stages.

Lifecycle Staged Approach

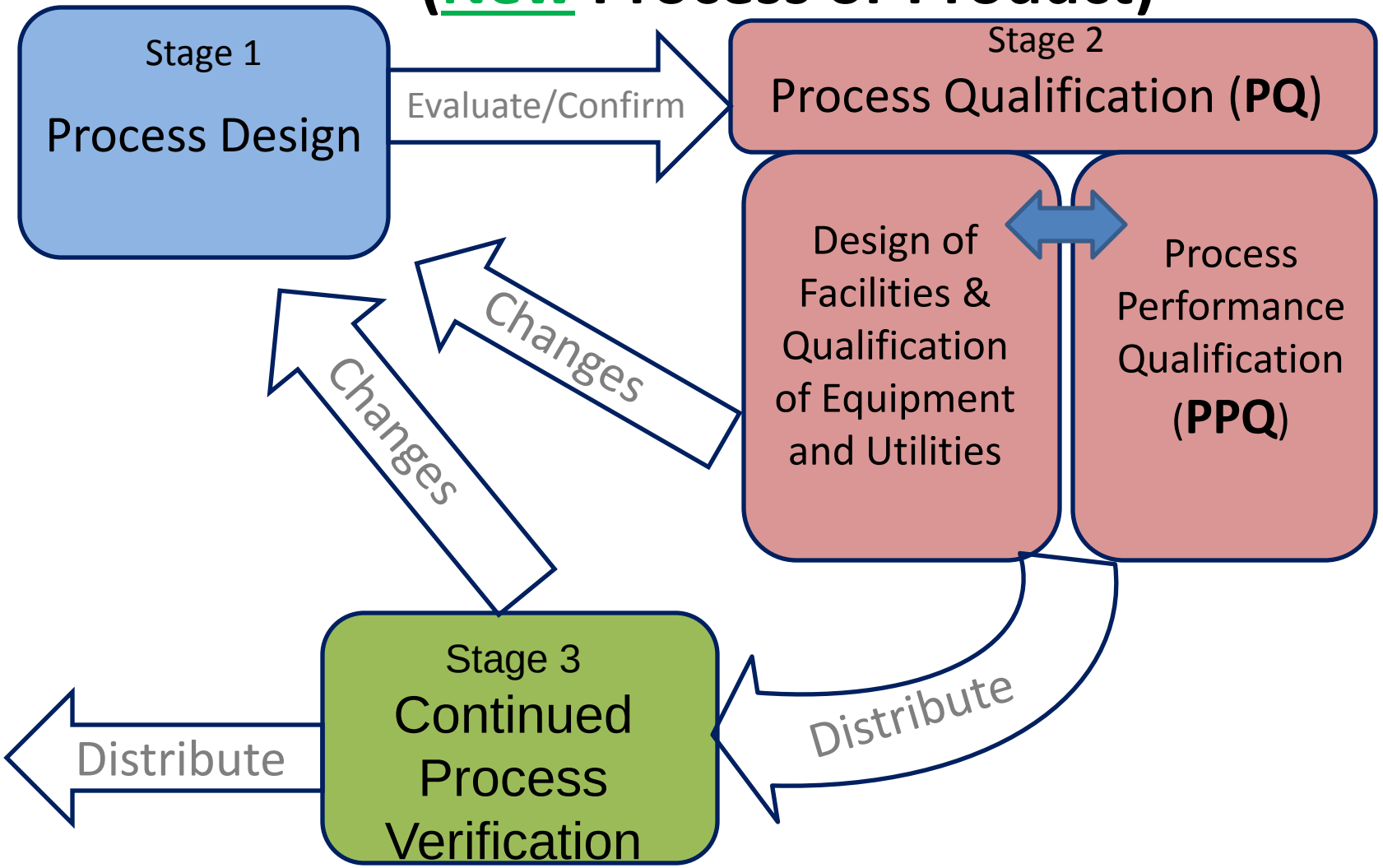


Process Validation Stages



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

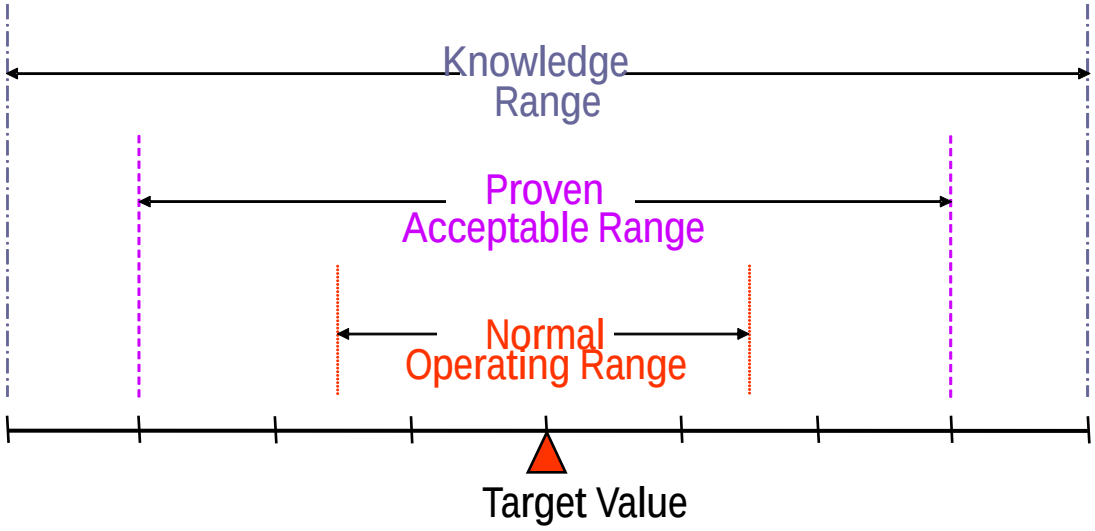
Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality.

- FDA Guideline Section IIB

Process Validation Benefits to Industry

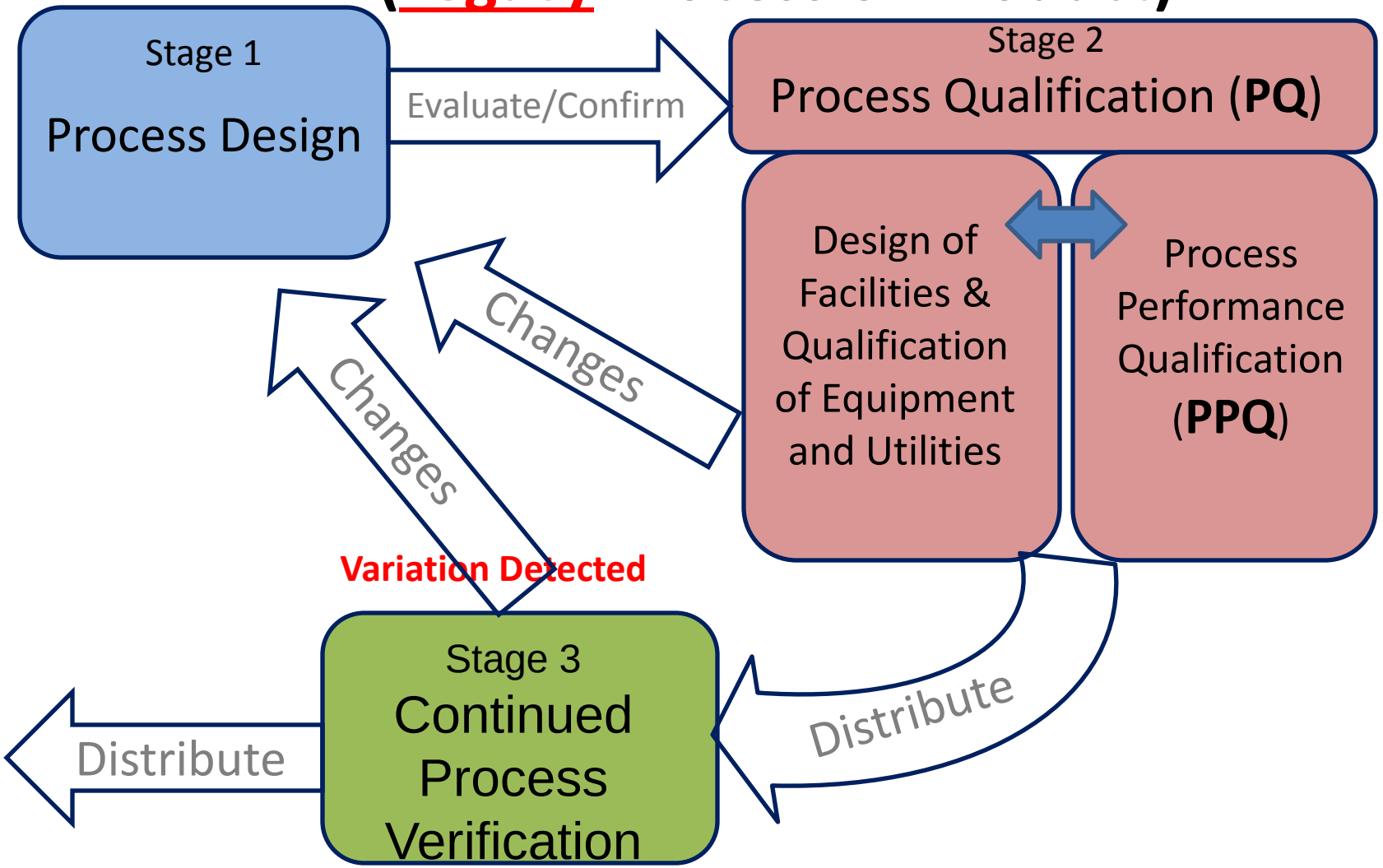
Knowledge vs. Proven Acceptable vs. Normal Operating Range

- Knowledge that the product will meet requirements
- Ability to predict product quality / assess impact of changes prior to OOS
- Reduced deviations – Reduce time to market, reduce release time
- More efficient / effective deviation resolution



Schematic of Stages

(Legacy Process or Product)



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

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) Design of Experiments & Quality by Design
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

Process Risk Assessment Tracking

Process Flow	CPP	Risk	Measure System Validated	Spec Rationale	Process Quality Data updated	Statistical Capability Assessment					CQA Monitor In Normal Product (Yes / No)
		RPN < 100	Yes / No	Yes / No Spec Range	Yes / No	Control Charts			Capability Assessment		
						Pattern Analysis	Average / Standard deviation	Distribution analysis	K2	PPK	
Raw Material Release –	**Alkylating Agents**	48	Yes – MVR - 1234	Yes – USP 1280	Yes – Report 102	NA	99.3/ 0.4	X - Normal	3.0	1.49	No – NIR planned for 2015
Mixing	RPM Time Feed rate Impeller selection	383	No Yes No Yes	Linearity Matrix Limits Tech sheet	Mix - Report 1200	Due 12/13	Due 11/13	Due 10/13	4.26	0.93	Protein– No pH- Yes
Filter	Bubble point	110	Yes – MVR 4321	Tech sheet	Yes - Report 102	In process		Chi Square	3.1	0.99	No – flow meter due 9/13

STAGE 1: PROCESS DESIGN

Expectations

1) Defined process
2) Completed CPP/CQA Matrix including rationale
3) Completed risk assessment
4) Defined control strategy including limits and monitoring methods
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 “fit for purpose” check
2) Develop PPQ Protocol including:
   a) Definition of testing 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

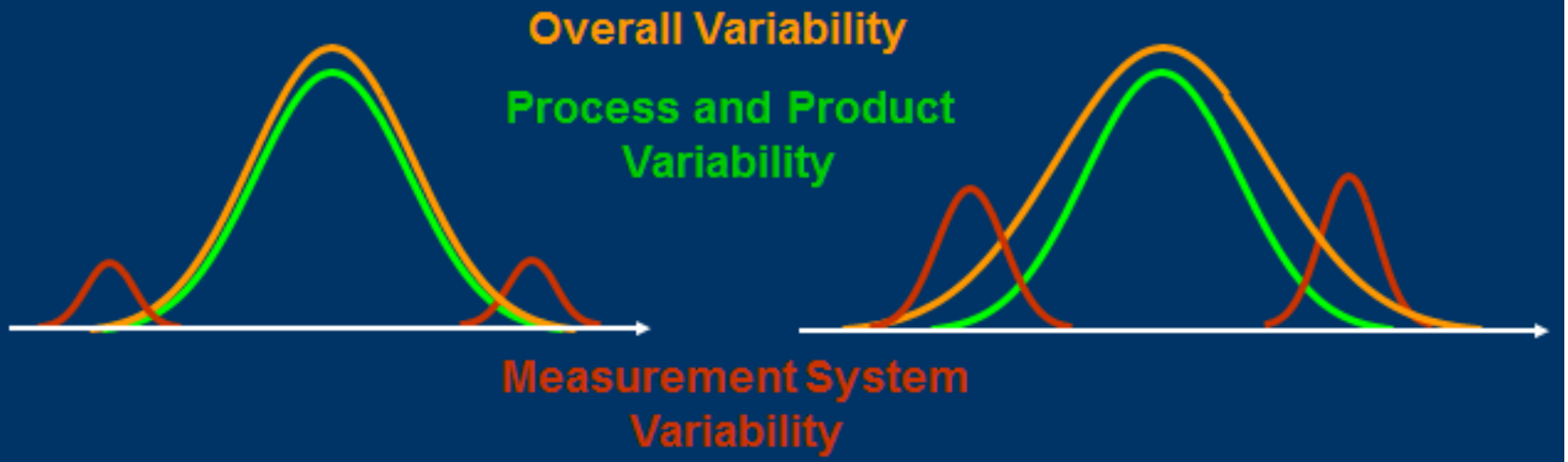
Expectations

3) Train Operations and Analytical Team
   a) Manufacturing Processes
   b) Statistical Process Control trending or charting begins
   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 & conduct 'in control' approvals
3) Follow in-process results closely

Variability Assessment

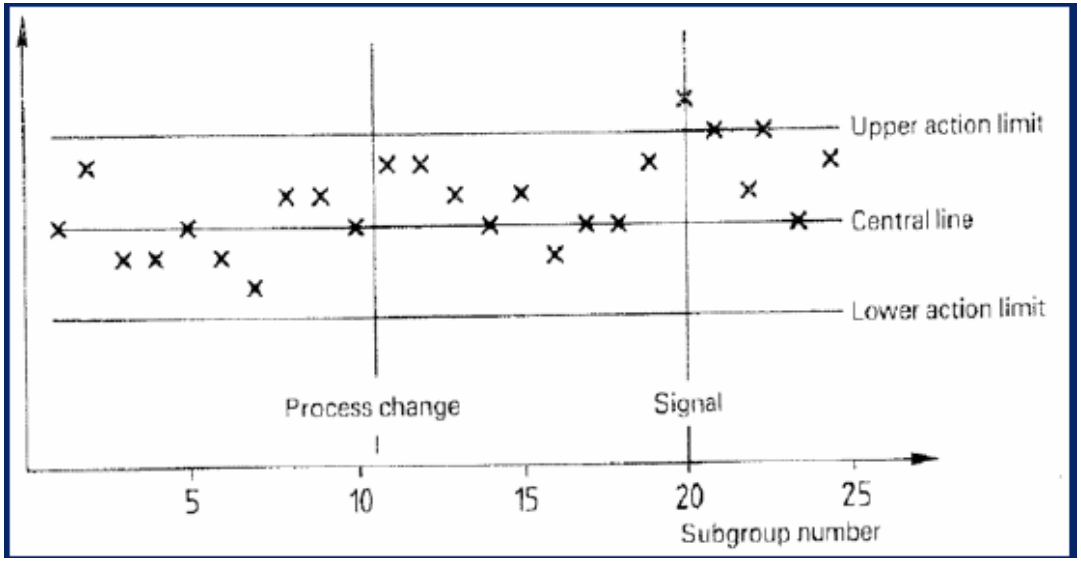


- $Variability_{Overall} = Variabillity_{Process\ \&\ Product} + Variability_{MeasurementSystem}$
- Measurement System Analysis Objectives
  - Estimation $Variability_{MeasurementSystem}$
  - Comparison $Variability_{MeasurementSystem}$ vs. $Variability_{Overall}$

PPQ and example control chart

- Confirms process design and demonstrates performance
- Completed before commencing commercial distribution
- Supported by data from commercial scale batches (+ lab and pilot studies)

- Used to qualify manufacturing conditions established in development
- Strongly recommend objective measures (e.g. statistical)



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 ("hand-shake" to Stage 3)

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

How many runs?

TECHNOLOGY/APPLICATION

Risk-based Methodology for Validation of Pharmaceutical Batch Processes

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ABSTRACT: In January 2011, the U.S. Food and Drug Administration published new process validation guidance for pharmaceutical processes. The new guidance debunks the long-held industry notion that three consecutive validation batches or runs are all that are required to demonstrate that a process is operating in a validated state. Instead, the new guidance now emphasizes that the level of monitoring and testing performed during process performance qualification (PPQ) studies must be sufficient to demonstrate statistical confidence both within and between batches. In some cases, three qualification runs may not be enough. Nearly two years after the guidance was first published, little has been written defining a statistical methodology for determining the number of samples and qualification runs required to satisfy Stage 2 requirements of the new guidance. This article proposes using a combination of risk assessment, control charting, and capability statistics to define the monitoring and testing scheme required to show that a pharmaceutical batch process is operating in a validated state. In this methodology, an assessment of process risk is performed through application of a *process failure mode, effects, and criticality analysis* (PFMECA). The output of PFMECA is used to select appropriate levels of statistical confidence and coverage which, in turn, are used in capability calculations to determine when significant Stage 2 (PPQ) milestones have been met. The achievement of Stage 2 milestones signals the release of batches for commercial distribution and the reduction of monitoring and testing to commercial production levels. *Individuals, moving range,* and *range/sigma charts* are used in conjunction with capability statistics to demonstrate that the commercial process is operating in a state of statistical control.

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) Establish an SOP / Methodology
2) Variable monitoring frequency, alert & action levels reviewed for 'in-control' approval
3) Revise Batch records
4) Revise CAPA / Change control process
5) Utilize CPP/CQA matrix including potential revision of alert & action levels
6) Record and trend CQA batch results
7) 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

Example of Critical Process Summary Table

Critical Operating Parameter	Normal Operating Range	CPV Strategy
Carbon feed rate	Target ± 15%	Not subject to SPC; however, Important to monitor controller variability, so will plot glucose feed profile for comparison (overlay) with previous batches
In-Process Control	**Limit(s)**	**CPV Strategy**
DO	≥ 10%	Not subject to SPC; characterization data shows that any value above 10% is sufficient for consistent fermentation performance; no routine trending required, but any IPC failure will be fully investigated for impact to the validated state
Total Acid Addition Volume	≤ 6.0 kg	Known to have direct impact on product quality and subject to SPC; parameter will be control charted
In-Process Acceptance Criterion	**Acceptance Criterion**	**CPV Strategy**
Final Wet Cell Weight	> 250 g/L	Important indicator of process consistency and subject to SPC; parameter will be control charted
Culture Purity (Plating Method)	No Contaminating Organisms	Not subject to SPC; existing quality systems would ensure that a failure would result in batch termination.
Final Product Titer	≥ 3.0 g/L	Important indicator of process consistency and subject to SPC; parameter will be control charted

Unit Operations Risk Assessment

CQA	Process Step					
	Granulation	Drying	Milling	Blending	Compression	Coating
Assay	Low	Low	Low	Medium	Low	Low
Blend Uniformity	Low	Low	Medium	High	High	Low
Impurity	Low	Low	Low	Low	Low	Low
Appearance	Low	Low	Low	Low	Medium	High
Dissolution	Low	Low	Low	Medium	Medium	High
Justification (High Rating Only)	NA	NA	NA	Blending can affect blend uniformity, assay and dissolution profile	Compression can affect content uniformity based on PS variability, flow and weight variation	Coating can affect final appearance and release rate

STAGE 3: CONTINUED PROCESS VERIFICATION

Expectations

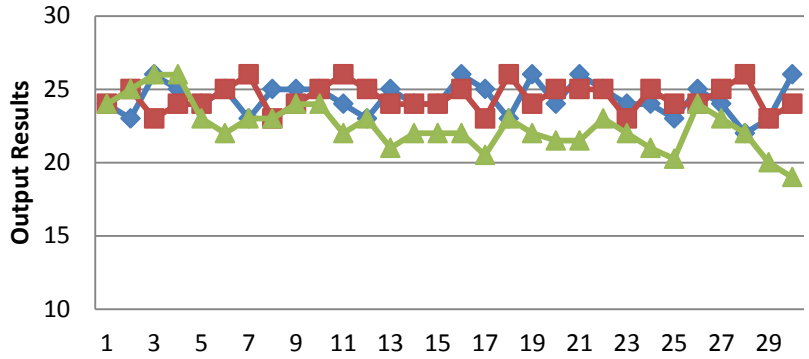
1) Summary of results including assessment and interpretation
2) Routine monitoring with warning of 'significant' trends
3) Control system augmented through investigative learning
4) Eliminates testing into compliance
5) Justification for continued testing of CPP's

Process Metrics Report

Annual Product Report

Best Practice

1) More than just annual requalification
2) Analysis of **Trends**



Continued Process Verification

CGMP requirements:

The collection and evaluation of information and data about the performance of the process **will allow detection of undesired process variability.** Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control

(§ 211.180 (e).

Continued Process Verification

- Goal – to continually assure that process remains in a state of control
- Collection and evaluation of data will allow detection of process drift
- Evaluation should determine whether action must be taken
- On-going program to collect and analyze data must be established
- Statisticians can develop the data collection plan & methods

EU Continuous Process Validation

- An alternative approach in which manufacturing process performance is continuously monitored and evaluated.
- Incoming materials or components, in-process material and finished products
- Verification of attributes, parameters and end points, and assessment of CQA and Critical Process Parameter (CPP) trends
- Use of tools to support (PAT, NIR, MSPC, etc.)

EU Continuous Process Validation

- Other Factors
  - Compliance with GMP principles & requirements
  - Prior development & manufacturing knowledge
  - Complexity of product/manufacturing process
  - Process should be verified on commercial-scale batches prior to marketing

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!