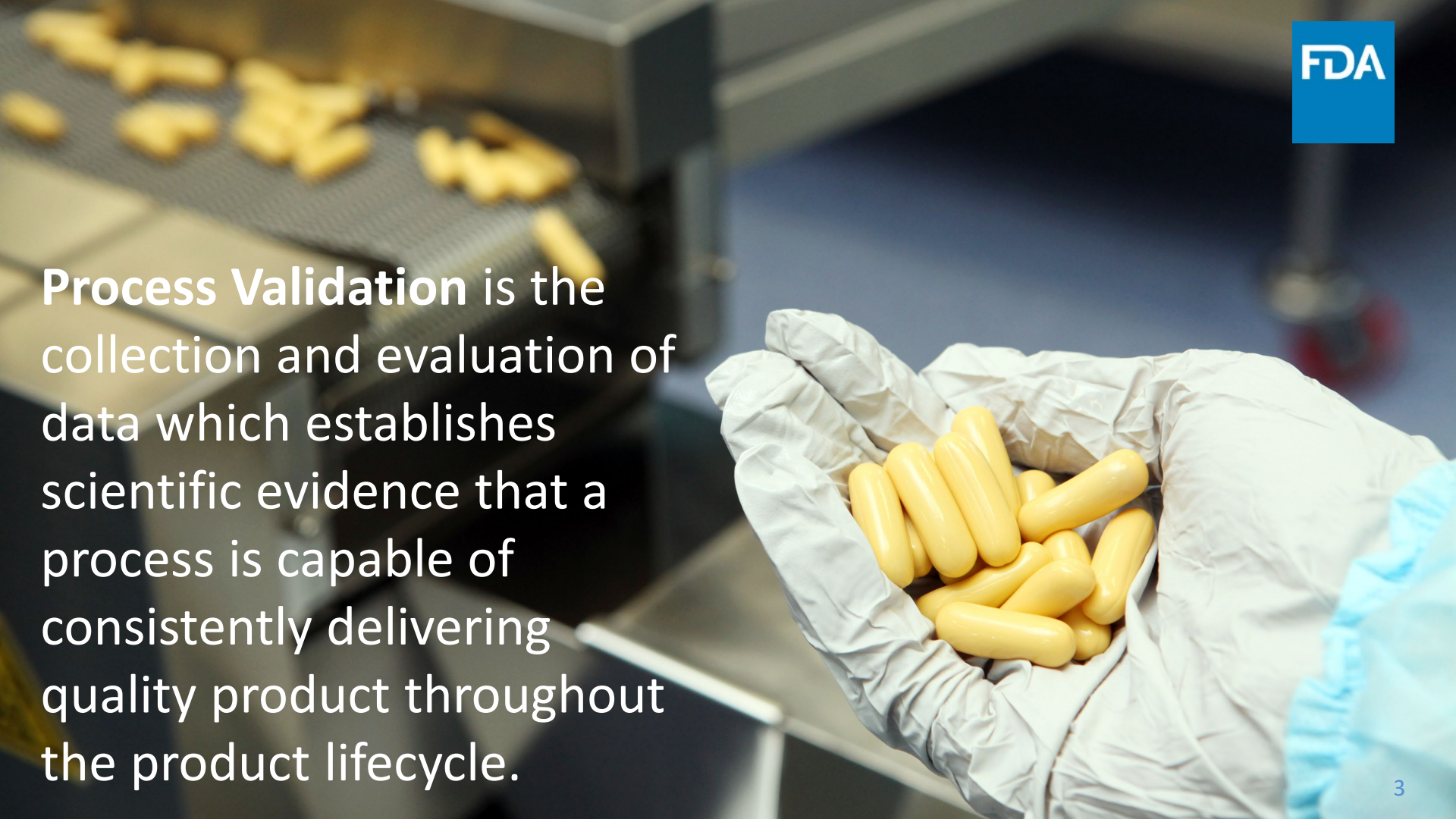
CGMP and Process Validation

CDR Tara Gooen Bizjak
Director, Manufacturing Quality Guidance and Policy Staff
Office of Manufacturing Quality
Office of Compliance, CDER

Compounding Quality Center of Excellence Virtual Conference: Working Together for Patient Safety **September 21, 2020**


FDA
Patients expect safe and effective medicine with every dose they take.



Process Validation is the collection and evaluation of data which establishes scientific evidence that a process is capable of consistently delivering quality product throughout the product lifecycle.

Process Validation Links the Patient, Product & Process

Patient

Drug Product

Process

Clinical Outcome

Critical Quality Attributes

Material Attributes & Process Parameters

Inputs: **Personnel, Machines, Materials, Methods, Measurements, Environment**

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

4

General Principles and Practices

- Quality must be designed into the manufacturing process (i.e., in-process and release testing is a verification) (21 CFR 211.110(a))
- **Variation** is a key focus of process validation
  - Understanding
  - Detecting
  - Responding
  - Controlling from input through output

"Uncontrolled variation is the enemy of quality." Dr. W. Edwards Deming

Regulatory Foundation

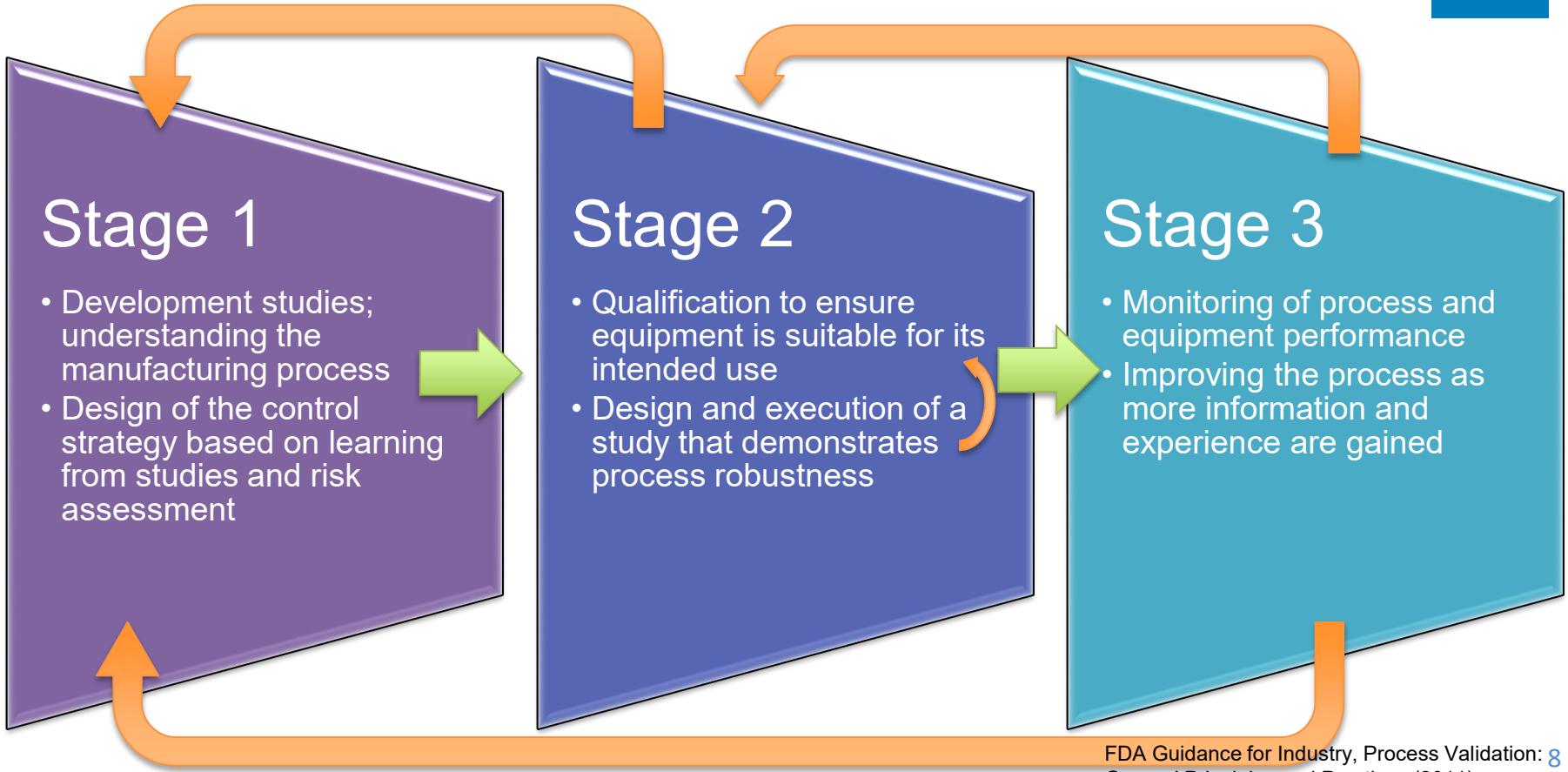
The CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet pre-determined quality requirements, and do so consistently and reliably. (21 CFR 211.100(a))

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Regulatory Foundation

- Written procedures designed to assure product quality attributes (21 CFR 211.100(a))
- In process controls to monitor the output and to validate the performance of those processes that may cause variability (21 CFR 211.110(a))
- Equipment must be of appropriate design and suitable for its intended use (21 CFR 211.63)
- Representative sampling with statistical confidence and predetermined acceptance criteria (21 CFR 211.110(b))
- Product quality data is periodically reviewed to determine whether any changes to the established process are needed (21 CFR 211.180(e))

Process Validation Overview



FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Process Validation: Lifecycle Stages

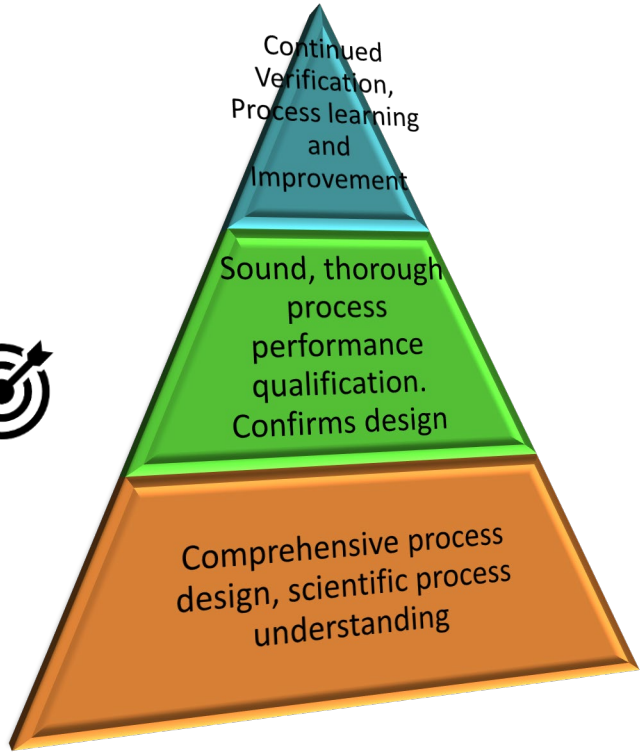
Description of Activities	*Goals*
Stage 1: Process Design	
Lab, pilot, small scale and commercial scale studies to establish process based on knowledge	**Functional understanding between parameters (material and process) and quality attributes**
Stage 2: Process Qualification	
▪ Facility, utilities and equipment ▪ Performance Qualification (Confirm commercial process design)	Scientific measurable evidence that ▪ product meets specifications consistently and ▪ process performance meets acceptance criteria; reproducible
Stage 3: Continued Process Verification	
▪ Monitor, collect information, assess during commercialization ▪ Maintenance, continuous verification, process improvement	Maintain or improve control and reduction in product and process variability

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Journal of Pharmaceutical Sciences, Vol. 55, No. 1, January 1966

- The new era for quality control statistics may well be in product design, control system design, or quality control simulation – all things to be done before the product is ever manufactured”
  - Olson, T. and Lee, I., “Application of Statistical Methodology in Quality Control function of the Pharmaceutical Industry”

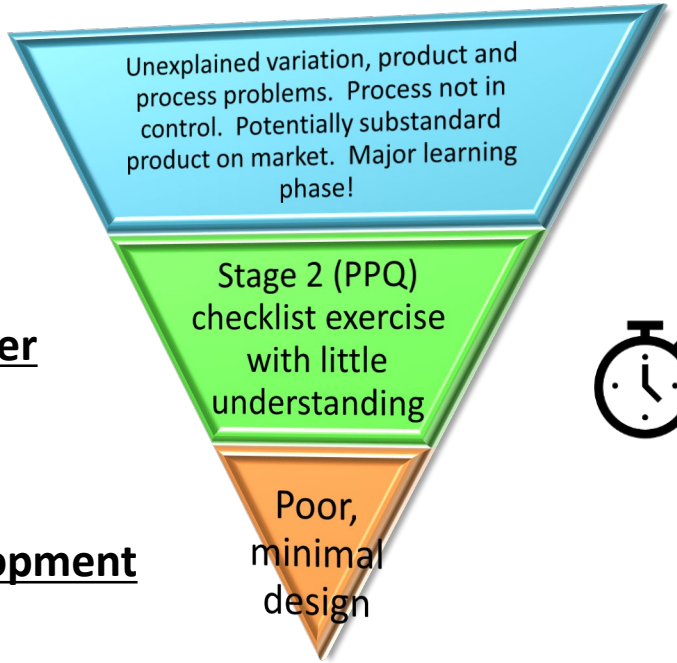
Two approaches to learning



Commercial

Tech Transfer

Development



Good planning, expected path

Poor design, planning, process understanding

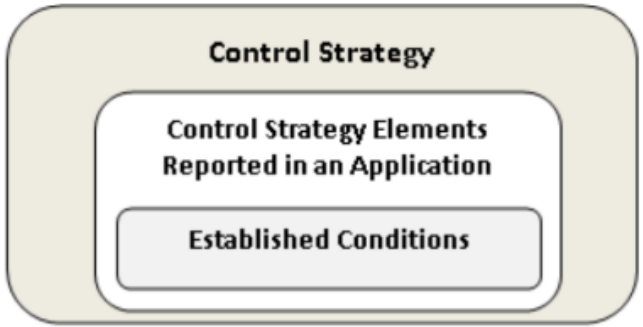
Stage 1: Process Development

- Connection of incoming and intermediate material attributes to Critical Quality Attributes (CQAs)
- Connection of process parameters to CQAs
- Can be accomplished by understanding failure modes, through Quality Risk Management and Design of Experiment (DOE) studies
- Enhance process understanding with scale up and technology transfer activities
- Consider principles in FDA Guidance on Pharmaceutical Development (Q8), Quality Risk Management (Q9), and Pharmaceutical Quality System (Q10)

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Stage 1: Control Strategy Development

- Identify process controls for critical points using development data and quality risk management principles
- Establish monitoring appropriate for each level of the control strategy
- The filed regulatory control strategy is built on a foundation of acceptable CGMP systems and the facility's broader controls
- Q8(R2) Pharmaceutical Development



FDA Guidance for Industry, Q8(R2) Pharmaceutical Development, 2009

Draft FDA Guidance for Industry: Established Conditions, May 2015

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Process Validation: Lifecycle Stages

Description of Activities	*Goals*
Stage 1: Process Design	
Lab, pilot, small scale and commercial scale studies to establish process based on knowledge	Functional understanding between parameters (material and process) and quality attributes
Stage 2: Process Qualification	
▪ **Facility, utilities and equipment** ▪ **Performance Qualification (Confirm commercial process design)**	**Scientific measurable evidence that** ▪ **product meets specifications consistently and** ▪ **process performance meets acceptance criteria; reproducible**
Stage 3: Continued Process Verification	
▪ Monitor, collect information, assess during commercialization ▪ Maintenance, continuous verification, process improvement	Maintain or improve control and reduction in product and process variability

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Stage 2a: Equipment Qualification (21 CFR 211.63)

- Appropriateness, capability, and reliability of equipment
- Establish typical variation of equipment and whether this is suitable for the process
- Study design should consider the expected demands of the commercial manufacturing conditions

- Consider commercial phase activities during process/equipment design (e.g., cleaning, calibration, maintenance)

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Stage 2b: PPQ Study Design

- Thoughtful design of the Process Performance Qualification (PPQ) protocol is important to draw meaningful conclusions
- Potential Pitfalls
  - Not utilizing development and qualification knowledge
  - Missed opportunities to customize the protocol
  - Insufficient sampling and/or acceptance criteria
- The completed study should enable manufacturers to determine if the process is within a state of control*

State of Control: A condition in which the set of controls *consistently* provides *assurance* of *continued* process performance and product quality. (FDA Guidance Q10)

FDA Guidance for Industry, Q10 Pharmaceutical Quality System (2009)

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Concurrent Release

- "Concurrent release" is meant exclusively in terms of the process performance qualification (PPQ) study protocol
  - Releasing for distribution a lot of finished product, manufactured following a qualification protocol, that meets the lot release criteria established in the protocol, but before the entire study protocol has been executed.

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Concurrent Release

- Why does this matter?
- Under normal circumstances, a firm's decision to begin to commercially distribute product from a particular process is based on having achieved that high degree of assurance threshold.
- Unless there are special circumstances (e.g., orphan drugs, short shelf-life radiopharmaceuticals, medically necessary drugs to alleviate short supply) there is no reason to distribute products before that threshold has been reached.
  - For these special circumstances, the process should still be evaluated after the product is distributed.
  - In these special circumstances, the benefit of having these drugs available to patients is judged to be greater than the risk of a lower degree of assurance.

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

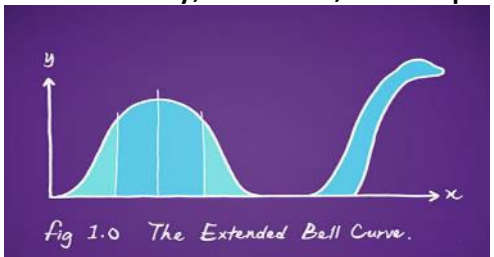
Process Validation: Lifecycle Stages

Description of Activities	*Goals*
Stage 1: Process Design	
Lab, pilot, small scale and commercial scale studies to establish process based on knowledge	Functional understanding between parameters (material and process) and quality attributes
Stage 2: Process Qualification	
▪ Facility, utilities and equipment ▪ Performance Qualification (Confirm commercial process design)	Scientific measurable evidence that ▪ product meets specifications consistently and ▪ process performance meets acceptance criteria; reproducible
Stage 3: Continued Process Verification	
▪ Monitor, collect information, assess during commercialization **▪ Maintenance, continuous verification, process improvement**	**Maintain or improve control and reduction in product and process variability**

FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

Stage 3: Continued Process Verification

- Establish a system or systems for detecting unplanned departures from the process as designed (re-examine criteria periodically)
- Confirmation that the control strategy remains valid
- Continual assurance that the process remains in a state of control
- Identify and implement process and systemic improvements with new knowledge and process experience (e.g., corrective action, preventive action)
- Regular examination for identification and implementation of process improvements with new knowledge and experience
  - "Annual" product quality reviews may not be sufficient to identify, correct, anticipate, and prevent problems
  - Robust change management is important

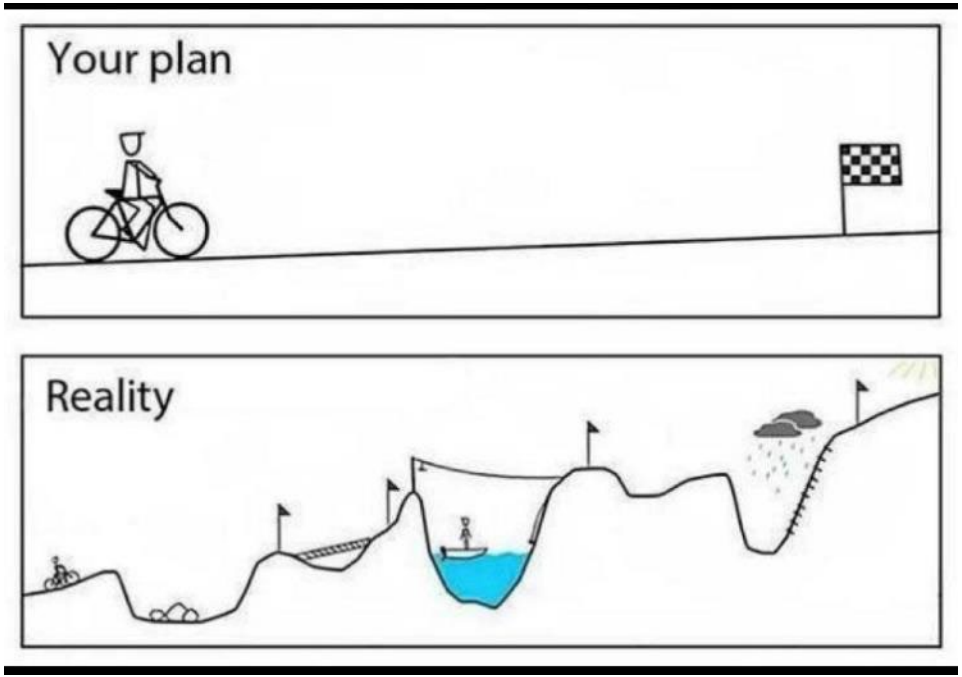


http://media2.smashingmagazine.com/images/science-posters-illustrations/extended%20bell%20curve.jpg

FDA Guidance for Industry, Q10 Pharmaceutical Quality System (2009)
FDA Guidance for Industry, Process Validation: General Principles and Practices (2011)

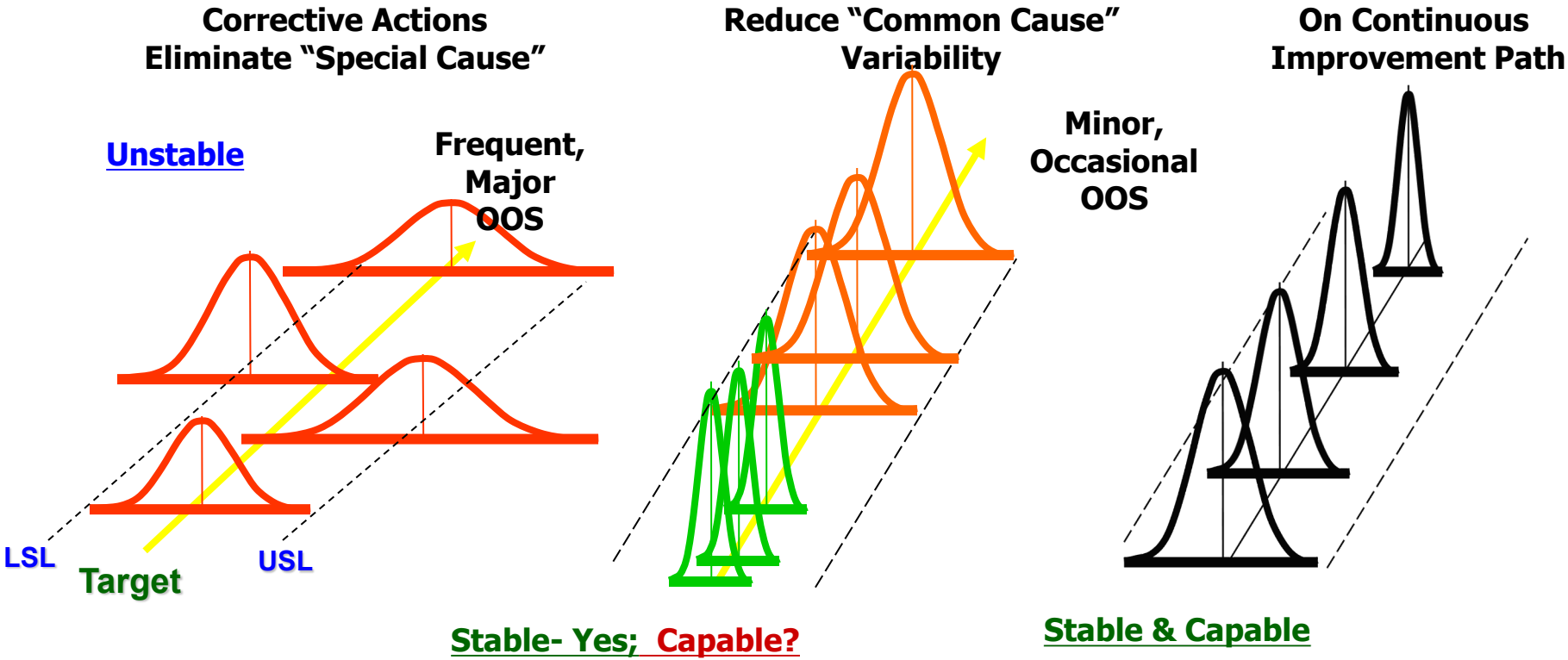
Q10: Facilitate Continual Improvement

To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill quality needs consistently.



FDA Guidance for Industry, Q10 Pharmaceutical Quality System (2009)

Is Your Process Stable and Capable?



Case Studies

Case Study: Manual Scooping

- What happened
  - Prompt release tablet, low dose, two actives, narrow therapeutic
  - Inspection identified significant process-related issues:
    - Manual scooping of partial drums potentially causing segregation
    - Compositing of blend uniformity samples masking variability
  - Inspection also identified other issues, including: (1) investigations of out-of-specification results with inadequate root cause determination and Corrective Action and Preventive Action (CAPA), (2) complaints involving PPQ batches, (3) use of failing components
  - Samples were collected by FDA and failed for potency and content uniformity
- Outcome
  - Warning Letter
  - Recalled all of this product from the market (multiple strengths)
  - Out-of-business at follow-up

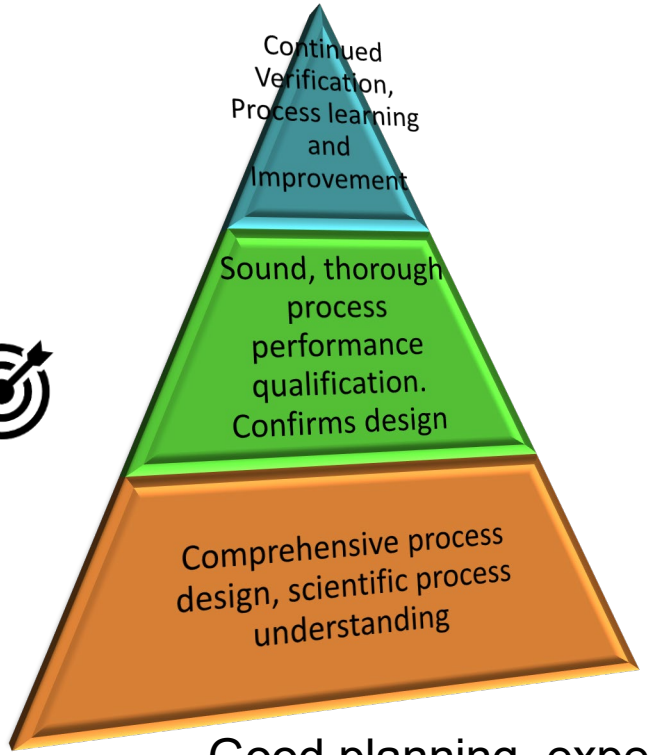
Case Study: Manual Scooping

- Key Takeaways
  - Important to have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality
  - Important to demonstrate that the manufacturing process is reproducible and controlled
  - Important to have a data-driven and scientifically sound analysis that identifies all sources of variability including, but not limited to, raw materials and manual steps
  - Important to determine the capability of each manufacturing process step and implement appropriate CAPA
  - Important to determine any process improvements needed

Case Study: Patches

- What Happened
  - After approval of an opioid patch, manufacturer had a problem with the process at commercial scale (e.g., several non-consecutive PPQ batches did not pass release testing). The manufacturer implemented many “small” changes to the process; it was unclear that the manufacturer identified the root cause of the failures.
- Outcome
  - Manufacturer was unable to demonstrate a reproducible and controlled process and distribute product
- Key Take-Aways
  - Investigation into PPQ batch failures was incomplete; the root cause analysis was inadequate
  - PPQ is not the time to find out the process is under-developed

Two approaches to learning

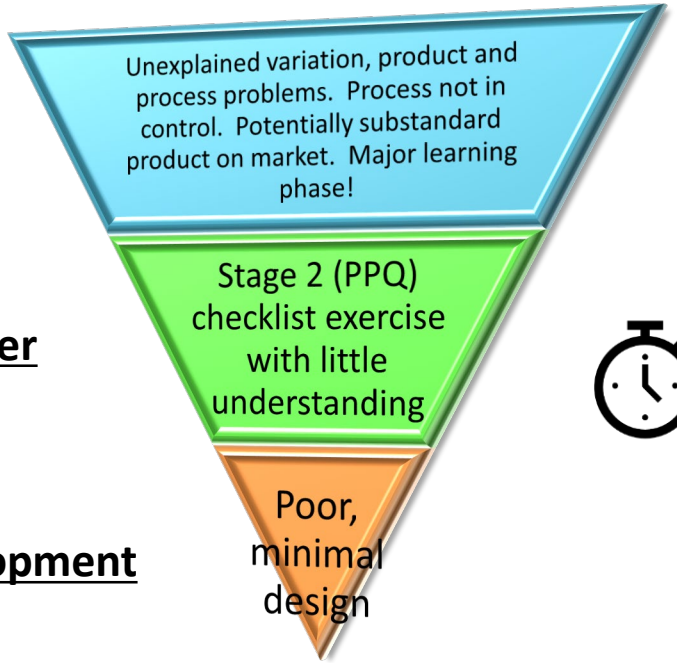


Good planning, expected path

Commercial

Tech Transfer

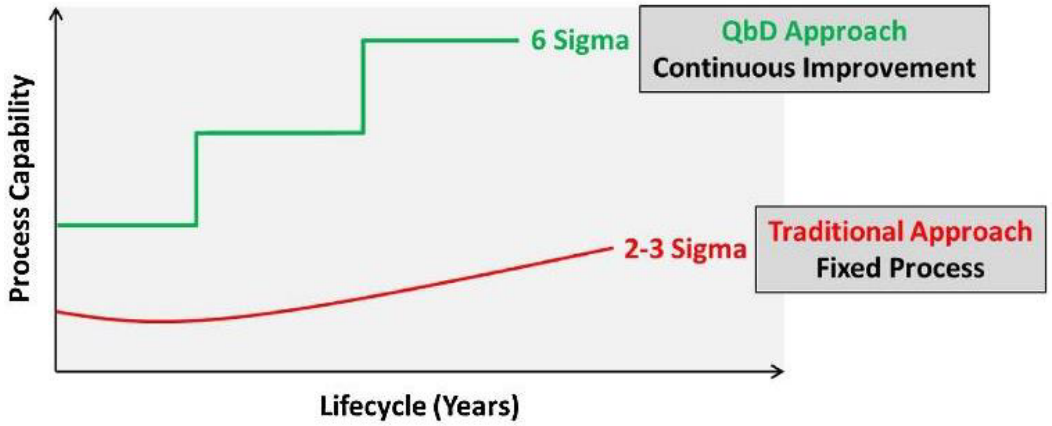
Development



Poor design, planning, process understanding

Future of Pharmaceutical Quality

- Six sigma manufacturing for higher process capability and product quality assurance
- Robust process validation is a data-rich tool for achieving high quality manufacturing



Yu., L. X.; Kopcha, M. Int. J Pharm. (2017) 528, 354-359

Summary: Process Validation

Key Focus - Variation

- Understand
  - Detect
  - Respond
- Control from input through output
- Throughout Lifecycle of Product

"Uncontrolled variation is the enemy of quality."
Dr. W. Edwards Deming


FDA
U.S. FOOD & DRUG
ADMINISTRATION