Process Validation of Solid Oral Dosage Forms, Part I

General Principles

İKEV Meeting

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European definition

European Commission:

1991 - "Validation - Act of proving, in accordance of GMPs that any… Process… actually leads to expected results.

2000 - (Annex 15) - Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

US Definition

- US Food and Drug Administration, 1987

"Process Validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

Note: Definition is now close to harmonization

Definition - additional comments

- Specific process/product consistently meets predetermined specifications
- Proven to do what it is represented to do
- Proof-through collection of data
- Includes process qualifications

Reference: USA Food and Drug Administration Guidance, Federal Register Nov. 30, 1995

Process Validation

- A study based on intensive testing and monitoring
  - More than routine testing
  - Sample sizes are larger and/or more frequent sampling
- At least 3 successive batches
- The product is shown to be uniform within a lot, consistent between lots, and meeting the criteria
- The quality of the full-scale production batch is comparable to that of the biobatch

WHAT VALIDATION IS NOT

- An exercise to create as much paper as possible
- Another unnecessarily burdensome regulatory requirement

Types of Validation

Prospective - At least three successive production-size (US view) batches, all batches made, tested, and report approved before distribution, facilities and equipment qualified

Concurrent - Generation of validation data concurrent or simultaneously with normal production schedules. Used in exceptional cases (low volume products); interim reports required.

Retrospective - based upon accumulated manufacturing, testing, and control batch data (EU Annex 15); least preferred approach (used typically for mature products), no changes during period, assess critical test results of at least 20 batches

References: FDA Guide on APIs, March 1998, page 48; PIC Guide, March 1999, page 32; Gold Sheet, Feb 1999, page 6.

Validation Responsibilities

Colleagues to administer program - e.g. Technical Services or Site Validation Committee (SVC)*

- Develop site master validation plan.
- Prepare/execute/approve validation studies.

Manufacturing Operations prepares the batches as though they are routine production batches.

QA ensures compliance and that documentation and procedures are in place. Approves protocols and reports.

QC Laboratories - performs testing or contracts validation testing. Reviews protocols and reports as needed.

*SVC - Technology Group (lead), Manufacturing Operations, QA/QC, Engineering, Computer Systems

Validation Checklist

Validated analytical methods for registered in-process and final product testing

Raw materials meet specifications; Drug substance is validated and fully characterized; at least 2 separate lots from vendor

Facilities and equipment are qualified and calibration and PM programs are in place

Key process variables are identified and their operating ranges have been established

Finalized master batch record

Relevant SOPs are in place and training is completed on equipment operation, manufacturing instructions, and sampling strategy.

Quality Systems such as deviations, change control, site Quality Review Committee are in place

Validation Protocol

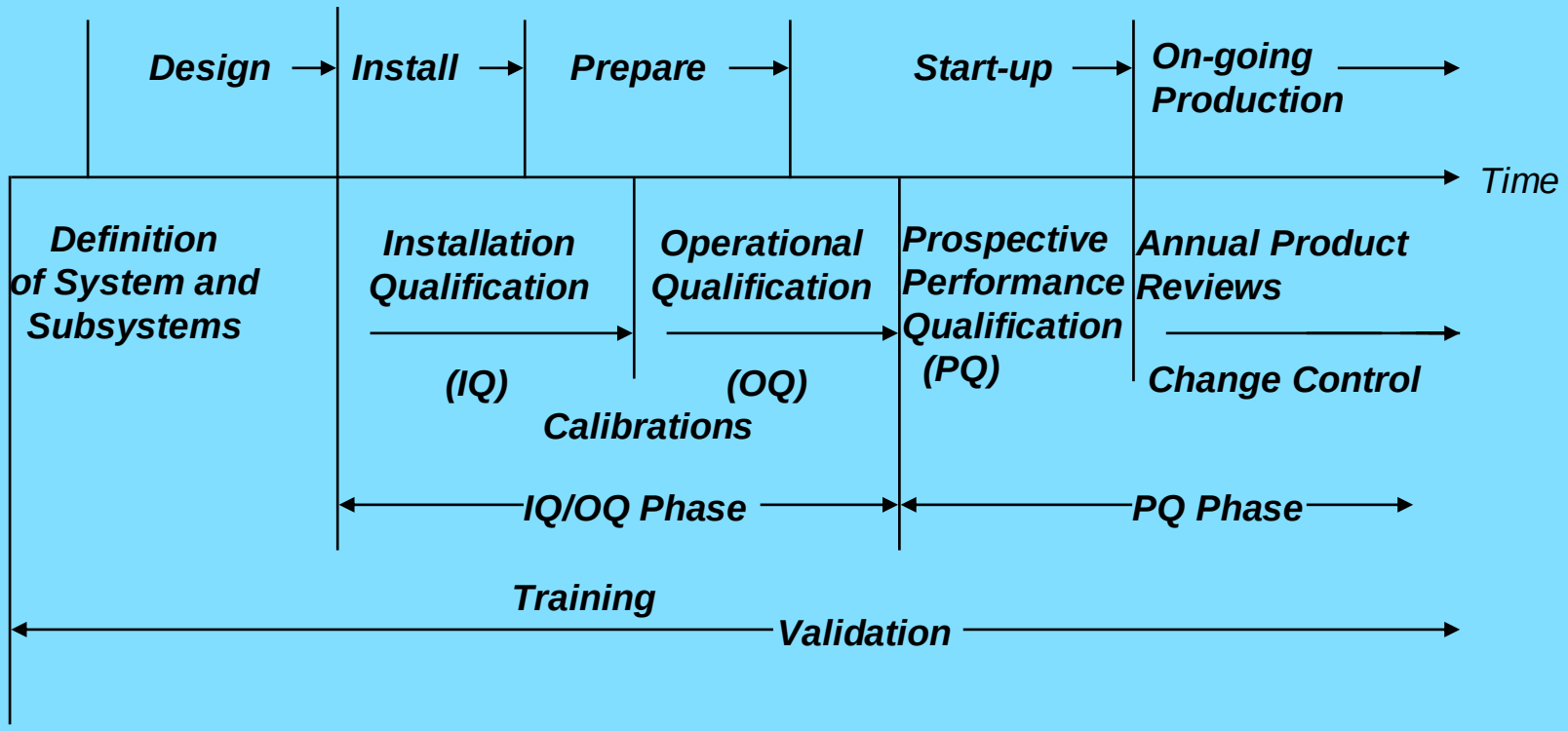
1. General information
2. Objective
3. Background/Prevalidation Activities

   Summary of development and tech transfer (from R&D or another site) activities to justify in-process testing and controls; any previous validations.
4. List of equipment and their qualification status
5. Facilities qualification
6. Process flow chart
7. Manufacturing procedure narrative
8. List of critical processing parameters and critical excipients
9. Sampling, tests and specifications
10. Acceptance criteria

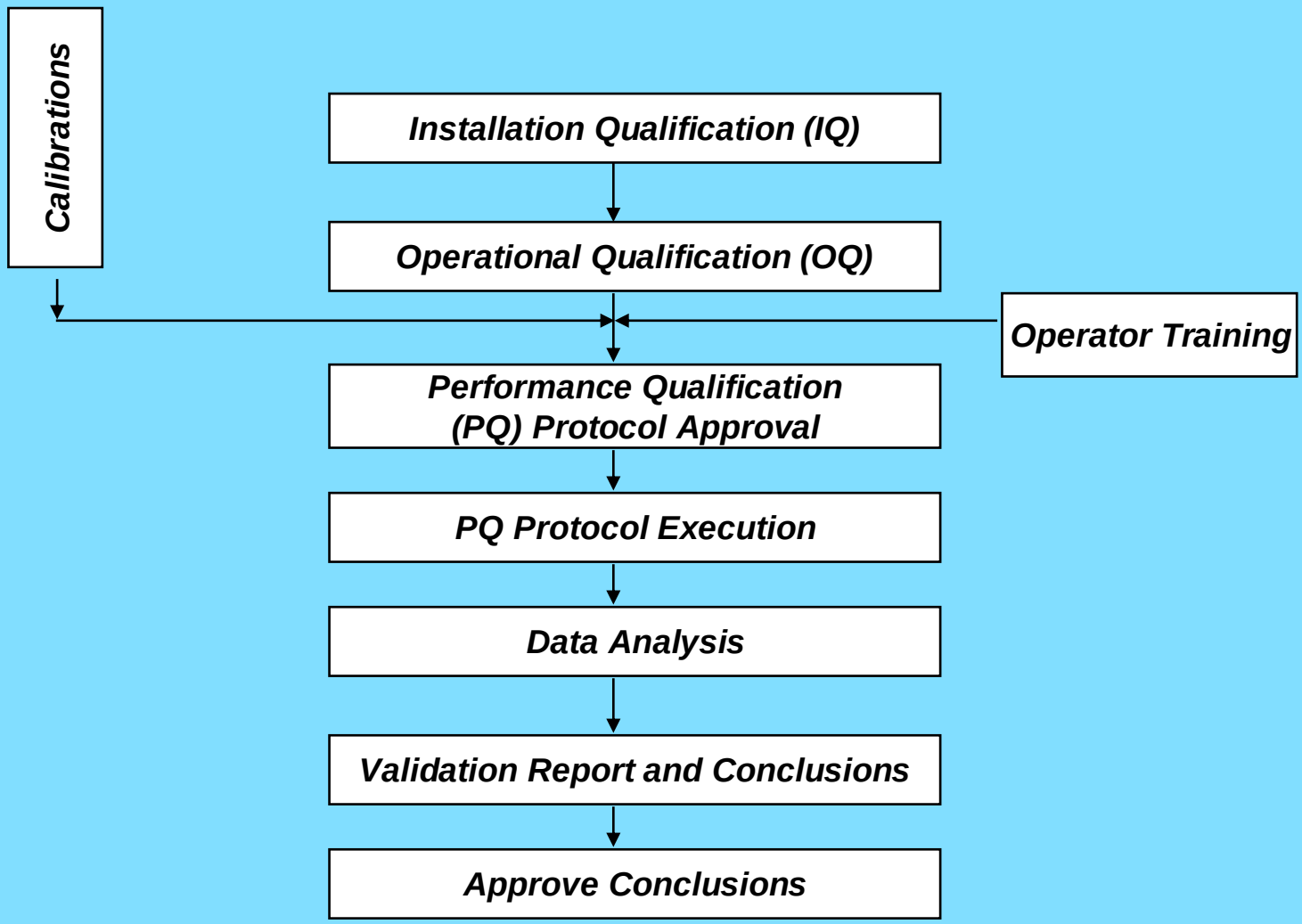
Reference to: Stability protocol/packages, protocol change provisions (i.e., procedures to handle any deviations), plans for a biobatch comparison (formula, process, specifications)

Note: Resolve deficiencies in any of the above prior to executing the protocol.

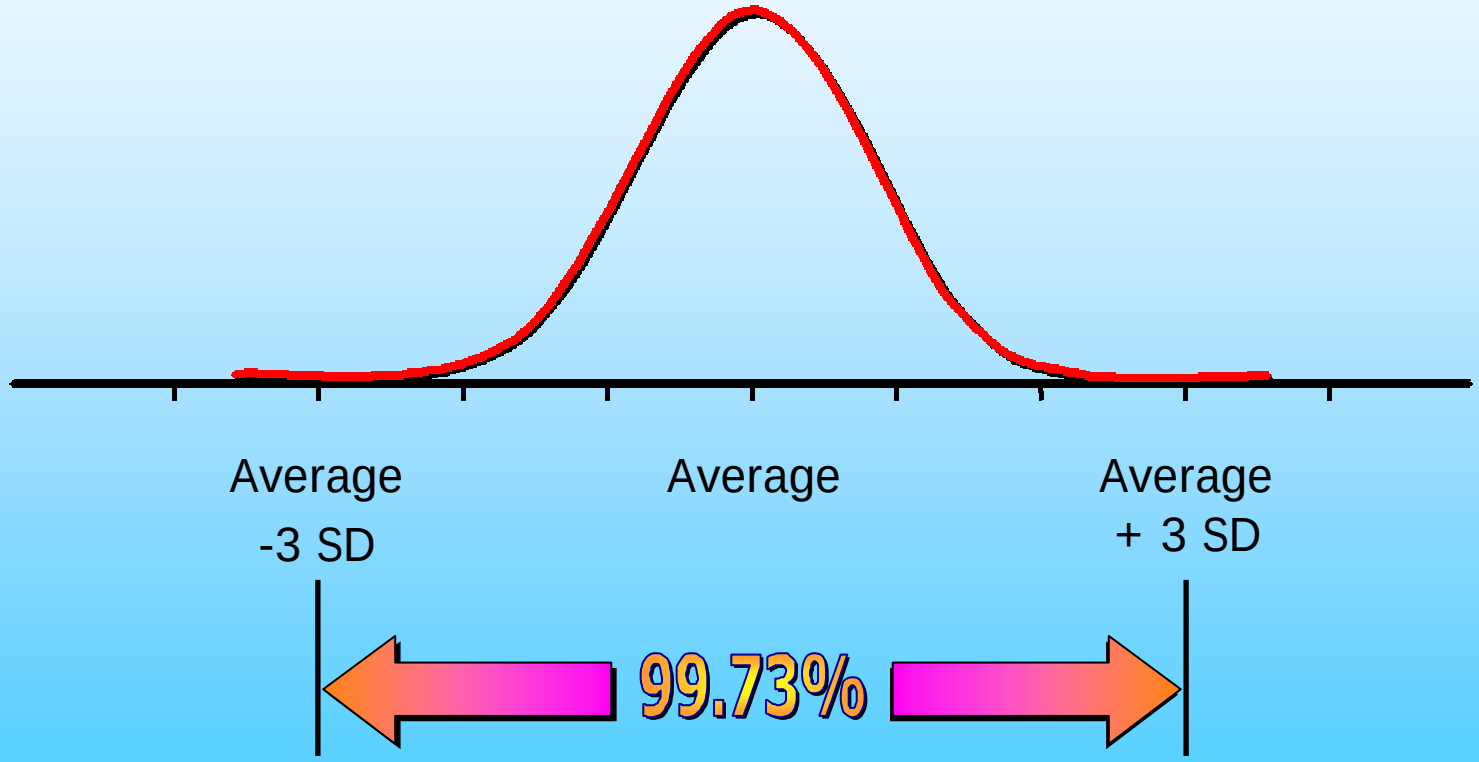
Phases Of Validation



Prospective Process Validation



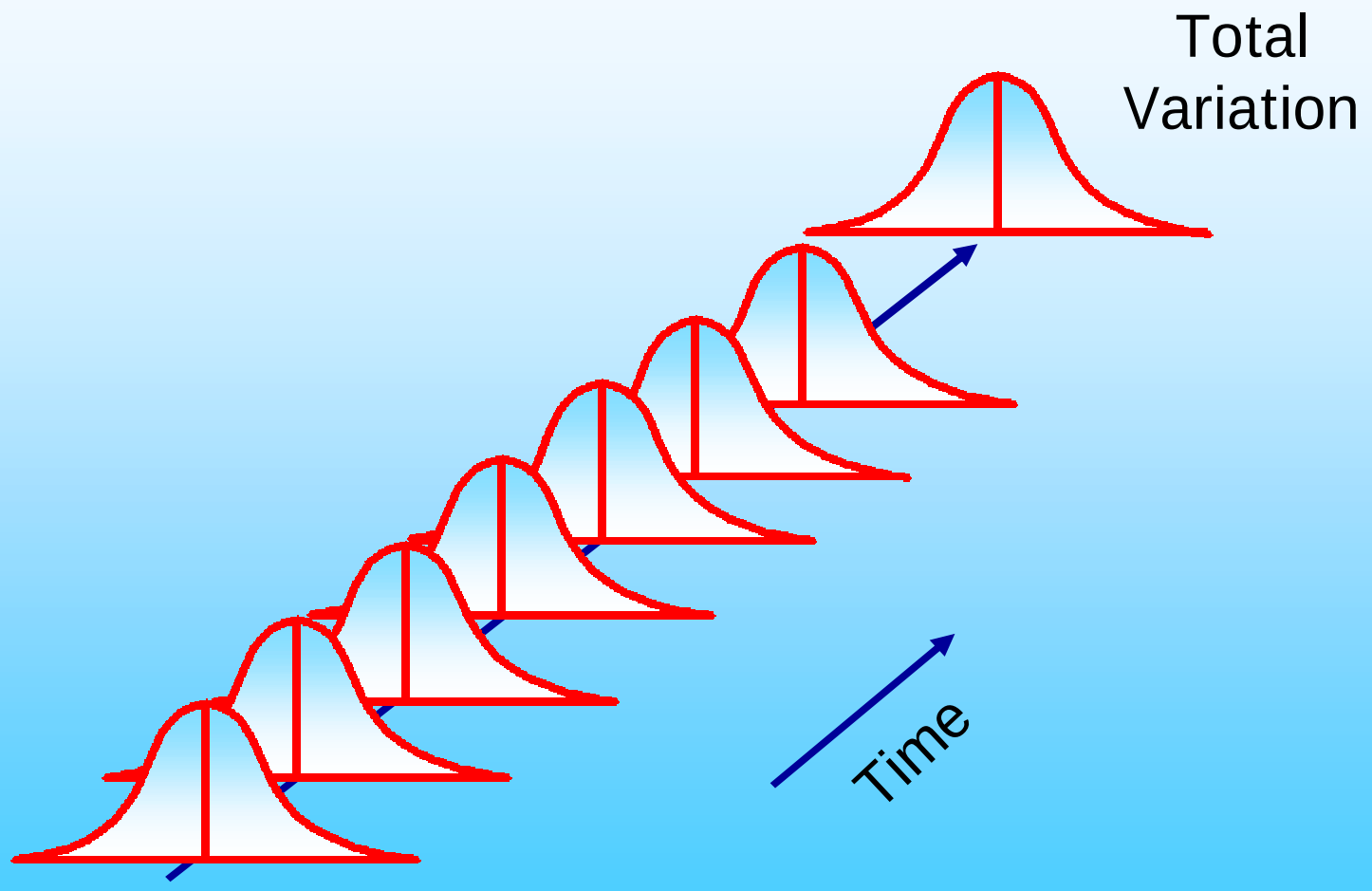
Normal Curve Showing % Of Values Within 3 SD Units



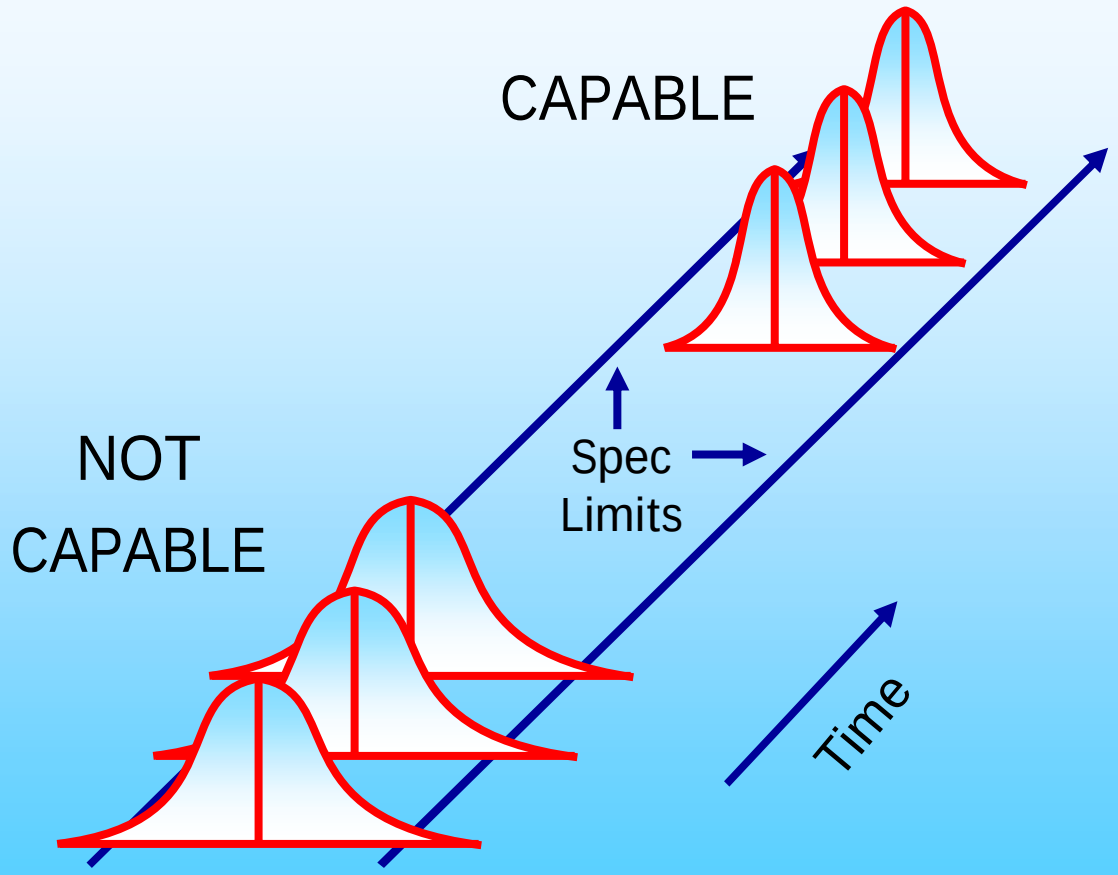
+/- 2 SD = 95% ;

+/- 1 SD = 67%

Stable Process

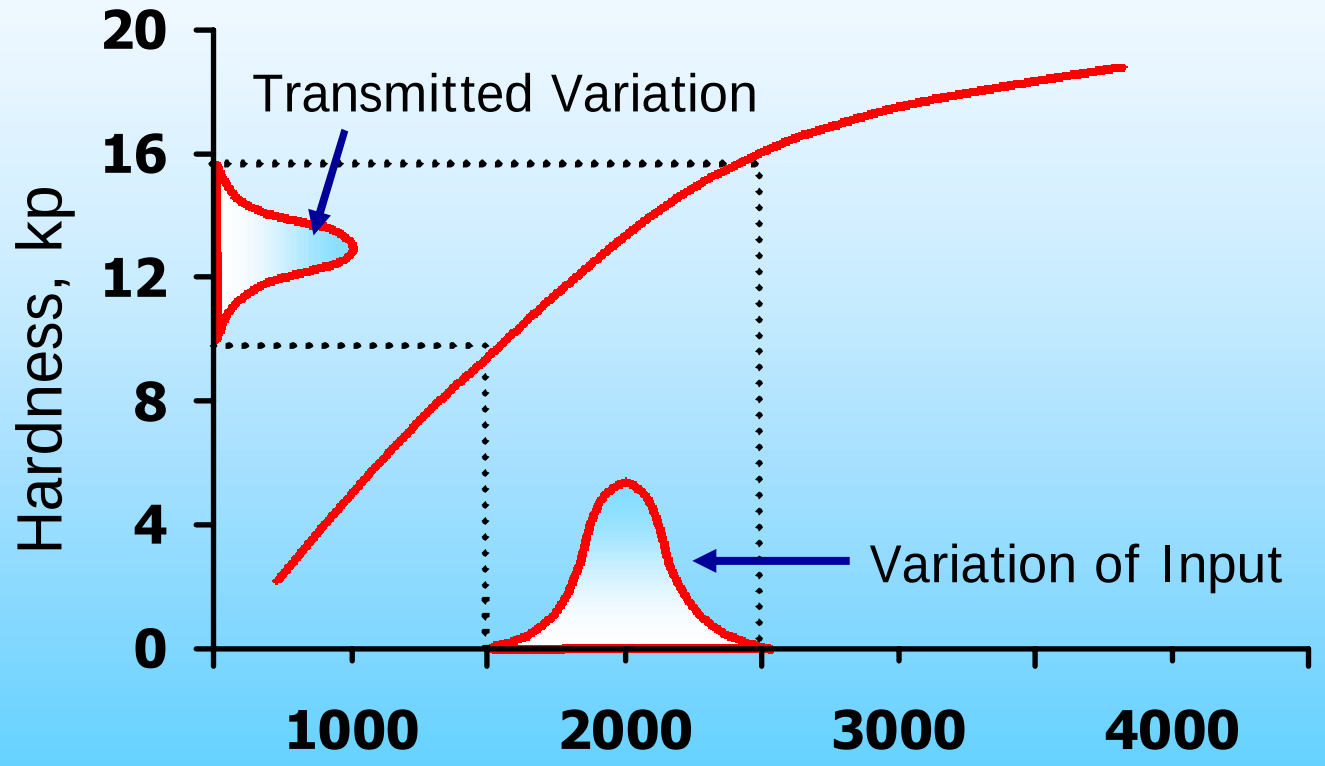


Process Capability



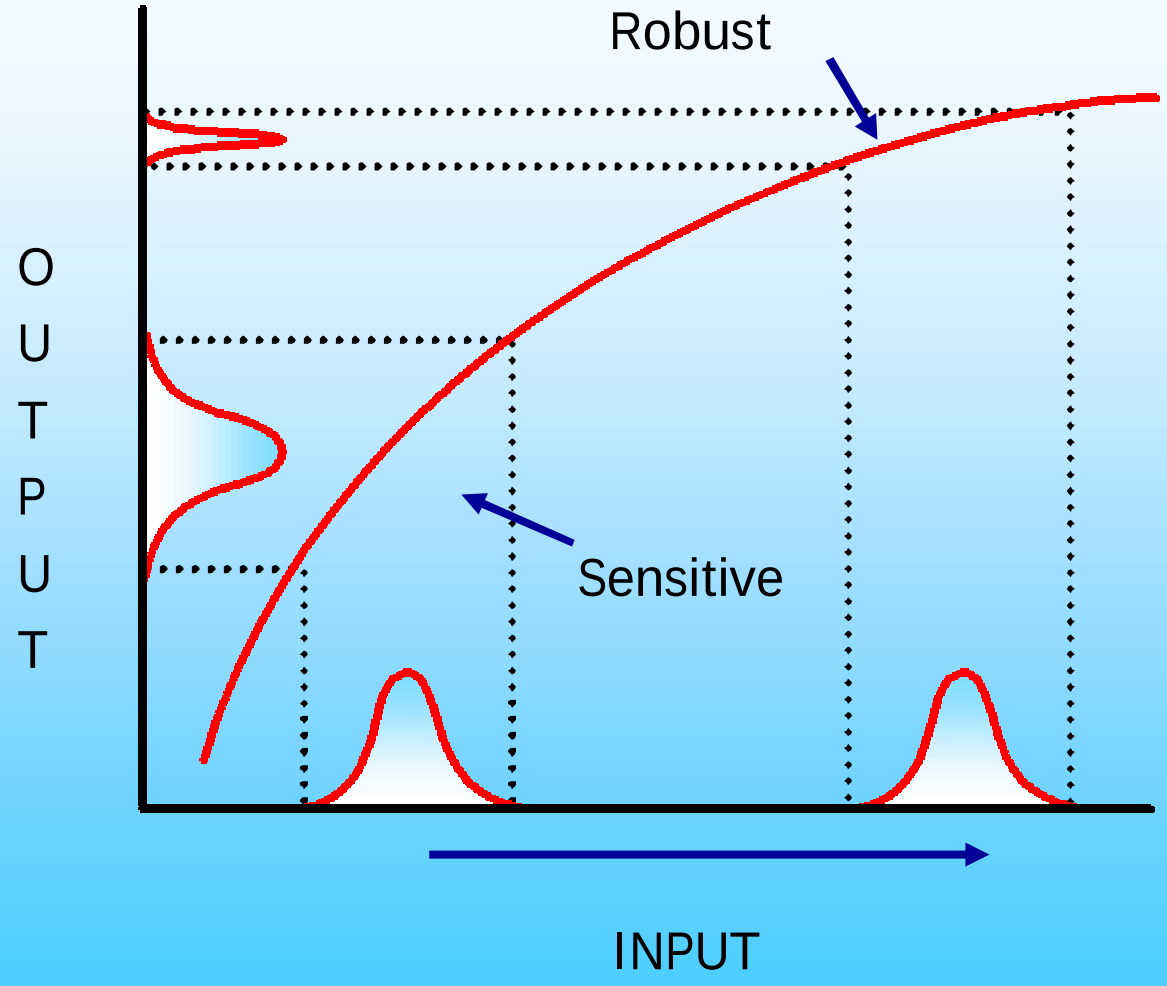
Transmission Of Variation

Example: Tablet Hardness



At Constant Weight

Robustness of Process



Robust: large spread in input variable results in small variation in output

Process Capability

CpK - True measure of capability
- Measure of centeredness

$$\textbf{CpK} = \frac{X - LSL}{3S} \quad \textbf{OR} \quad \frac{USL - X}{3S}$$

LSL - Lower Specification Limit

USL - Upper Specification Limit

X - Mean

S - Standard deviation

Cp - Process capability
- Compares process to entire specification range – 6 sigma

CpK ≥ 1.0 in general
- Process is capable
- Appropriate specifications

$$\textbf{Cp} = \frac{USL - LSL}{6\ S}$$

Example Of Process Capability

Tablet Hardness

X - 110N (n=50 Tablets)

S - 6N

USL - 140N

LSL - 60N

$$\textbf{CpK} = \frac{110-60}{18} \quad \text{OR} \quad \frac{140-110}{18}$$

min. 2.8 OR 1.7

CpK = 1.7

Process is capable and Specification Range is Acceptable

Validation Report

Executive Summary

Background

Presentation and Discussion of All Results.

- **Statistical Summary of IPC data, Control charts**
- **Critical Processing parameters/operating ranges**
- **Evaluate data points outside of in-process limits**
- **Elegance evaluation**

Deviations - impact assessment on validation

Conclusions

Recommendations, Attachments

Reviewed and approved by same colleagues that approved the protocol.

Validation Strategies

- FDA says it is possible, but has not adopted a position
- ***Matrixing*** - different strengths of same product
  - different sizes of same equipment
- ***Family*** - different, but similar products (e.g., oral solutions, OTC line, solubilities, etc.)
- ***Bracketing*** - evaluating extremes (e.g., largest and smallest fill volumes, fastest and slowest operating speeds)

Matrixing - Example

- Formulation A has common granulation (same blend) compressed into 20, 30, and 40 mg strengths.
  - 20 mg is a 150 mg tablet and 30 mg is a 225 mg, etc.
- Three granulation/blend batches are validated and
  - Two batches of each (10, 20, and 30 mg) strength are validated for compression and coating.
    - Comparison of data and assessment of variability within and between strengths is made.
- One single validation report

General Notes on Validation - #1

- Process validation is a cGMP requirement.
- More importantly, it provides documented evidence of consistency from batch to batch.

General Notes on Validation - #2

- Validation batches are saleable and therefore will be used by patients.

  True validation batches mimic routine production in every detail. For example,

  - Material handling methods of feeding a tablet press may affect the processability.
  - Batches should be ‘QC releasable’. We are validating ‘acceptable’ processing and product.

Note: Data from unacceptable batches may in special cases support validation

General Notes on Validation - #3

- Sampling is frequently an issue in validation.
  - Thus, think and plan ahead on specifics of the number of samples, sample size, sampling location, method, and handling and who will perform what activity
  - Also, sample in the same way as development, demonstration or prevalidation batches.
- Sampling strategy can be as important as process development.

General Notes on Validation - #4

- Following protocols and procedures is another frequent issue in validation.
  - Consult the protocol and procedures frequently to be sure they are being followed.
- Know your equipment, process parameters, materials, tests and expected results.
- A robust process will allow some normal variation in equipment operation, raw materials, and other variables (e.g. environmental)

General Notes on Validation - #5

- Deviations and OOS (out-of-specification) results can jeopardize a successful process validation.
- The development and production history can be helpful in investigations.
- Conduct scientific and thorough investigations. Write clearly. Implement corrective actions.
- Quality cannot be inspected or tested into the product; i.e. repeat testing and resampling will not improve the quality.
- Quality comes through designing and proper controls of manufacturing parameters (build quality into product).

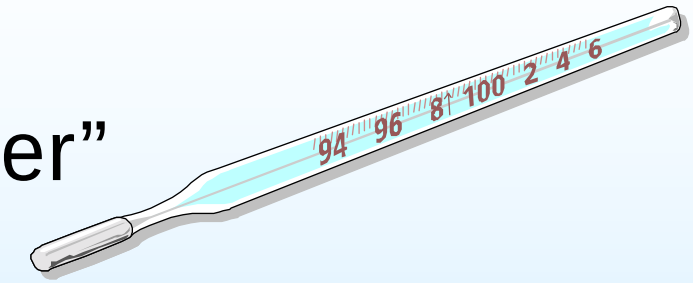
Process Revalidation

Repetition of a portion or all of validation* based on

- Proposed change in physical characteristics of the drug substance or excipients, change in processing steps/ equipment, manufacturing site or in specifications
- Annual reviews: Trends (lab and process data), Stability, Complaints, Batch rejections, deviations
- US FDA guidance on classifying changes
  - Tied to change control system, assessment of change (impact analysis performed by the technical unit or SVC) to determine need and extent of validation.

*Reference: FDA Guide, Process Validation, 1987

“Validation Fever”



Process Validation can bring about hot fevers.

It rarely goes perfectly.

Proper design and development of robust processes and tests with appropriate quality control checks will lead to a high quality product. Manufacturing quality into the product is essential and validation data will be indicative of the tendency to meet the specifications.

Validation-related Issues

- Approach to validation
- SOPs
- Calibration
- Environmental monitoring
- Preventive maintenance
- Training
- Raw material sampling and qualification programs
- Change control
  - Facilities/systems
  - Manufacturing/packaging methods
  - Formulations
  - Raw materials & Suppliers
  - Cleaning Procedures
  - Computer and control systems

Validation Issues As Reported by FDA

- Problems seen recently are similar to ones in past
- Validation issues - one of top two reasons for deficiency notices
  - Protocols are not followed
  - Inadequate (insufficient testing, lack of specs, etc.)
  - Retrospective validation - changes occurred within sequence
  - Inadequate change control, revalidation program
  - Older products - bringing up-to-date is difficult

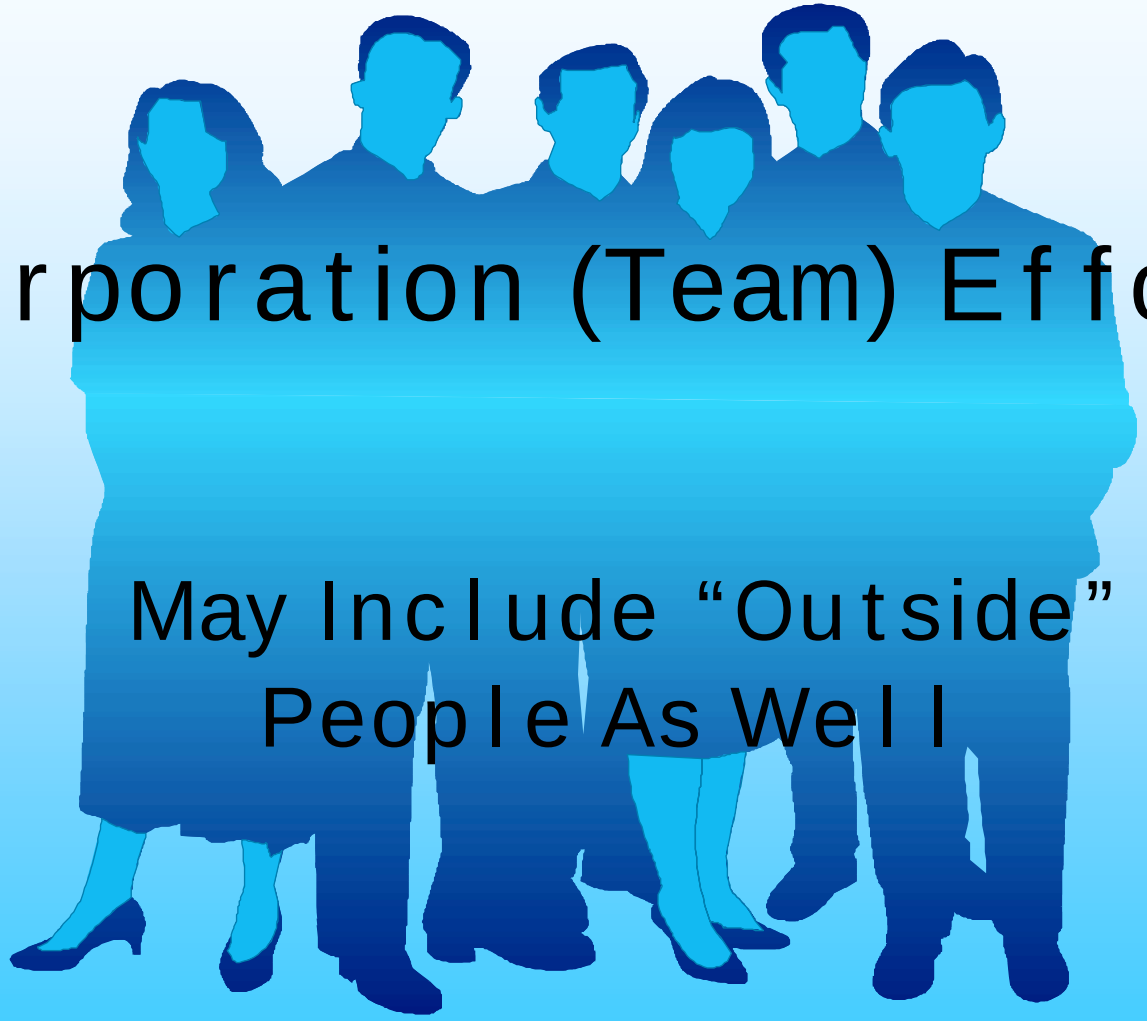
Areas of Focus During FDA Inspection

- Relationship between validation batches and biobatch
- Raw material controls
- Manufacturing procedure and equipment
- In-process controls including granulation analysis
- Use of validated methods
- Investigation of product failures

Validation

Corporation (Team) Effort

〈 May Include “Outside” People As Well 〉



Thank You!

Questions?

Process Validation of Solid Oral Dosage Forms, Part II - Unit Operations

Turkish Pharmaceutical Society Meeting

31 May, 2001

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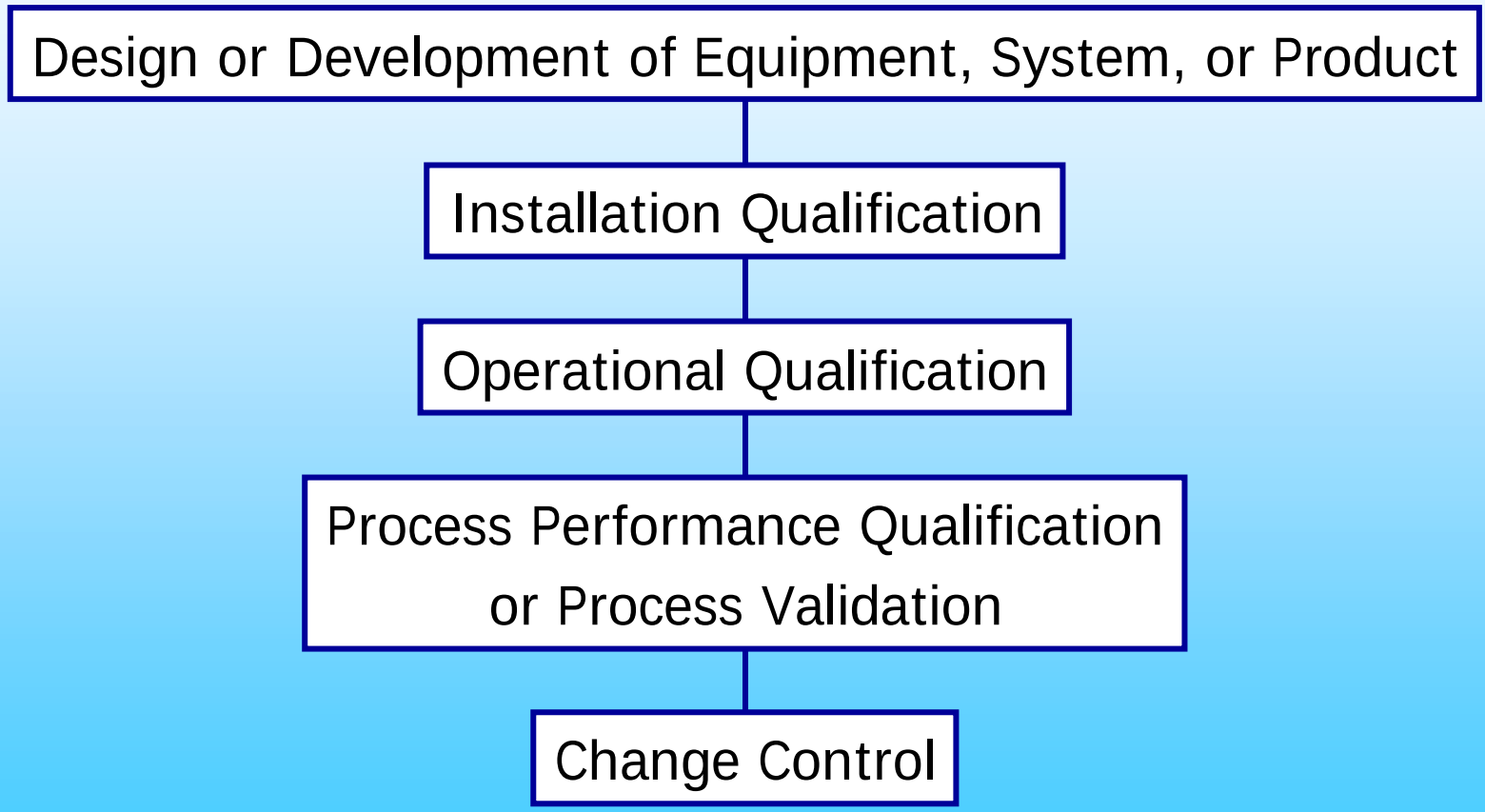
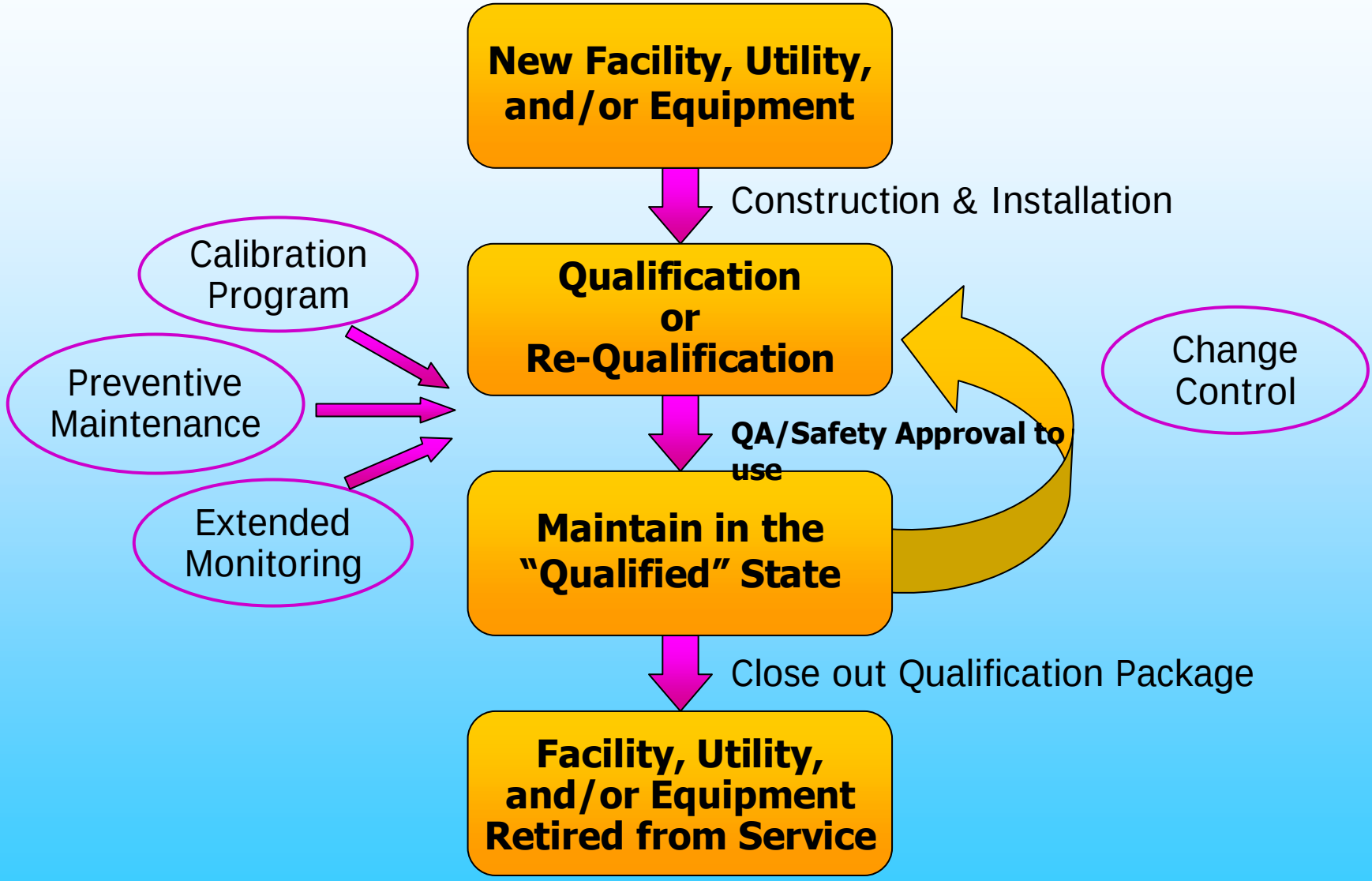
Qualification And Process Validation



Qualification Life Cycle



Qualification

Equipment/Facility Qualification

- IQ (installation)
  - Facility and site acceptance testing, if applicable
  - Per Piping and Instrument Drawings (P&ID)
  - Calibration
  - Materials of construction
- OQ (operational)
  - Tests based on knowledge
  - Upper/lower limits (worst case) of critical parameters
  - Training completed
  - SOPs, “Release” of equipment by QA, Safety
- PQ (performance)- system
  - Test with materials- e.g. placebo
  - Include upper/lower settings of critical parameters

Examples: Milling Qualification

OQ tests

- Mill without material
- Operating extremes
  - Mill speed (±10%)
  - Auger speed (±10%)
  - Proper Direction
  - Other (Nitrogen flow)
  - Safety, calibration, etc.

PQ tests

- Placebo powder (if feasible)
  - pass abut 1 kg material and demonstrate size reduction took place to desired range.

Examples: Compression Qualification

OQ tests

- Press without material
- Operating extremes
  - Press speed (±30%)
  - Alarms, sensors, etc.
  - Security and recipe access

PQ tests

- Placebo tablets (if feasible)
  - Press speed - 1 hr, ±10% target
  - Weight (Volume), ±10% target
  - Compression force, ±25 % CF
  - Measure attributes affected by above: e.g., thickness, hardness, friability
- Start-up/shut down and alarm evaluations.

Examples: Coating Qualification

OQ tests
(Pan is empty)

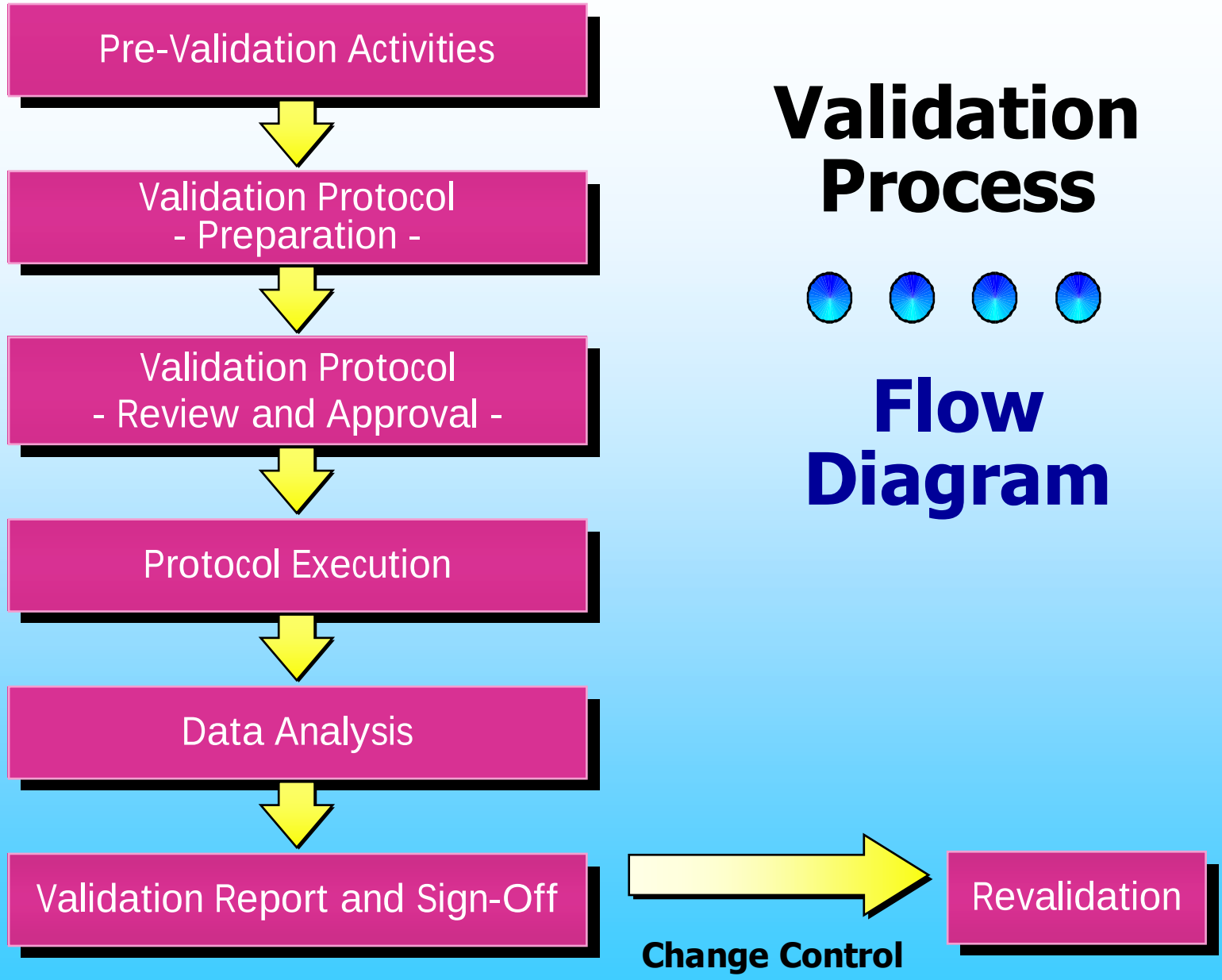
- Operating extremes
  - Pan speed
  - Air volume, temperature
  - Air humidity
  - Spray conditions
  - Alarms, sensors, etc.
  - Security and recipe controls

PQ tests
(Placebo or active tablets)

- Conditions are challenged
  - Spray rate extremes
    e.g. ±25% target
  - Load extremes
    e.g. ±20% target
  - Other variables affected by above parameters
    e.g. Spray angle-90 or lower.

Validation Process

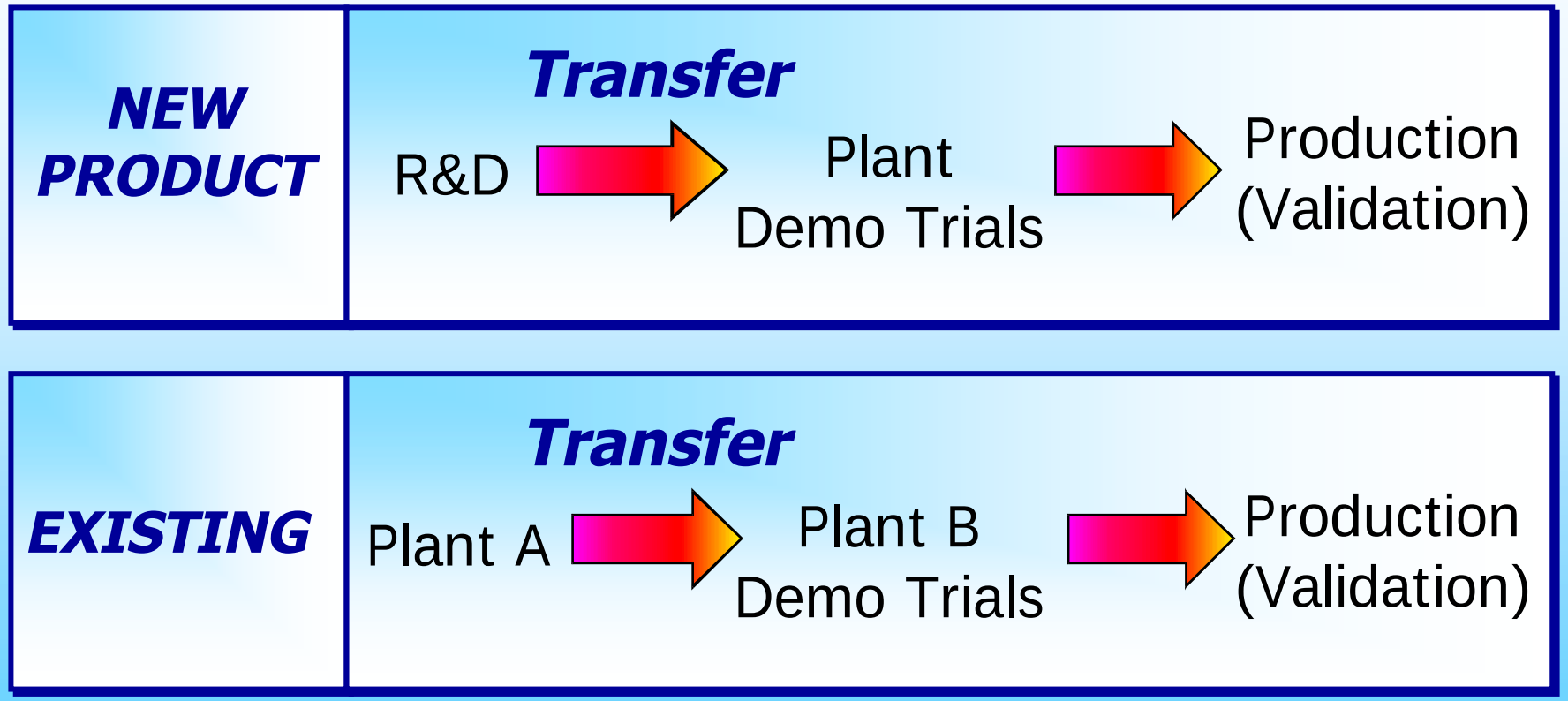
Flow Diagram



When To Validate

- After finalizing formula, process, and specifications
- Either before or after new drug application (NDA) approval
- Prefer to start during process development phase
- More frequently being done before NDA approval/filing

Solid Dosage Form Transfer Locations



- Plants may be third-party contractors

Some Common Variables In The Manufacture Of Tablet Products

- Particle size of drug substance
- Bulk density of drug substance/excipients
- Powder load in granulator
- Amount and concentration of binder
- Mixer speed and mixing times
- Granulation moisture content
- Milling conditions
- Lubricant blending times
- Tablet hardness
- Coating solution spray rate

Granulation

Control Parameters

Fixed	Variable (Monitor)	Response (Test)
Equipment	Mixing speeds	Drug distribution
Batch size	Amount of granulation fluid	Water/solvent content
	Feed rate	Appearance (size)
	Granulation time	Power consumption (amp/torque)
	Load	

Reference: Nash, R. DDIP 22:25-34 (1996)

Fluid Bed Drying

Fixed	Variable (Monitor)	Response (Test)
Bowl charge	Inlet/exhaust air temperature	Particle size distribution
Porosity of filter bags	Product temperature	Densities
Bowl sieve	Drying time	Loss on drying
	Air volume	Assay (for heat sensitive materials)
	Humidity of incoming air (dew point)	
	Humidity of exhaust air	

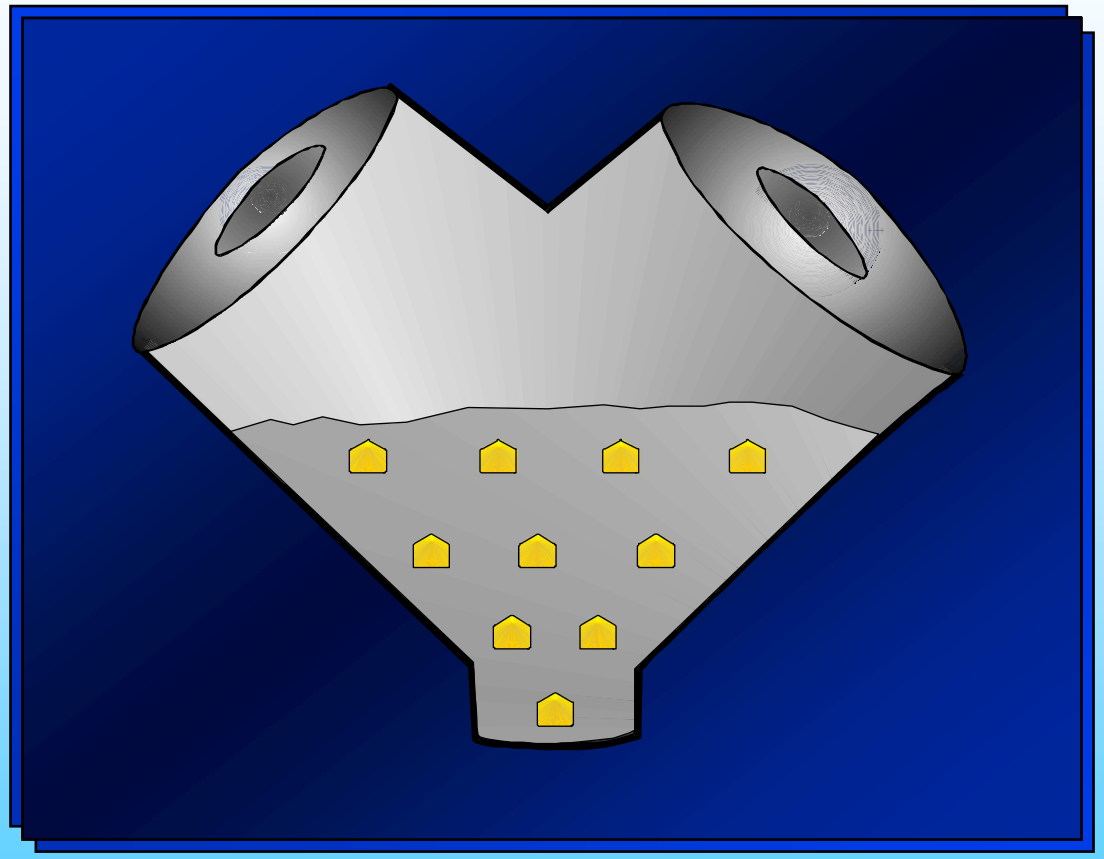
Milling

Variable	Response
Screen size	Particle size distribution/shape
Milling speed	Loose/tapped densities
Feed rate	

Powder Blending

Variable	Response
Blending time	Content uniformity
Blender speed	Assay
Intensifier bar	Particle size distribution
	Powder flow
	Densification/Aeration

PK Blender Sampling Locations



10 locations in blender
Discharge sample in motion also

Lubrication

Variable	Response
Blender speed	Particle size distribution
Blending time	Loose/tapped densities
Method of addition	Flow properties
	Tabletting characteristics (friability, hardness)

Compression

Variable	Response
Speed of press	Appearance
Pre-compression	Weight variation
Compression force	Hardness/friability
Feed frame (open/forced)	Thickness
Feeder speed	Moisture content
	Disintegration/dissolution
	Assay/dose uniformity

Pan Coating

Variable	Response
Pan load	Percent weight gain
Inlet/exhaust temperatures	Thickness
Inlet/exhaust humidities	Elegance
Pan speed	Dissolution
Spray nozzle size	Assay
Atomizing pressure	Degradation level
Spray rate	Residual solvent
Spray angle	
Gun to bed distance	
Tablet core characteristics	

Tablet Appearance /Elegance Evaluation

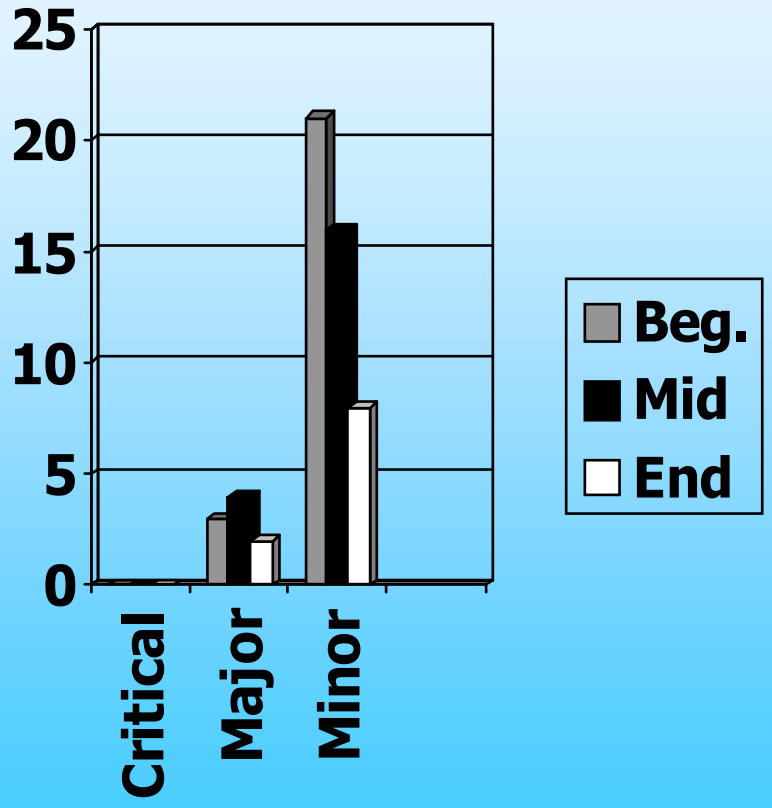
Critical A (e.g. missing logo)

Critical B (e.g. >15% broken, capped or chipped)

Major A (e.g. foreign matter)

Major B (e.g. 5-15% broken, capped or chipped; discolored, cracks, spots (>1 mm))

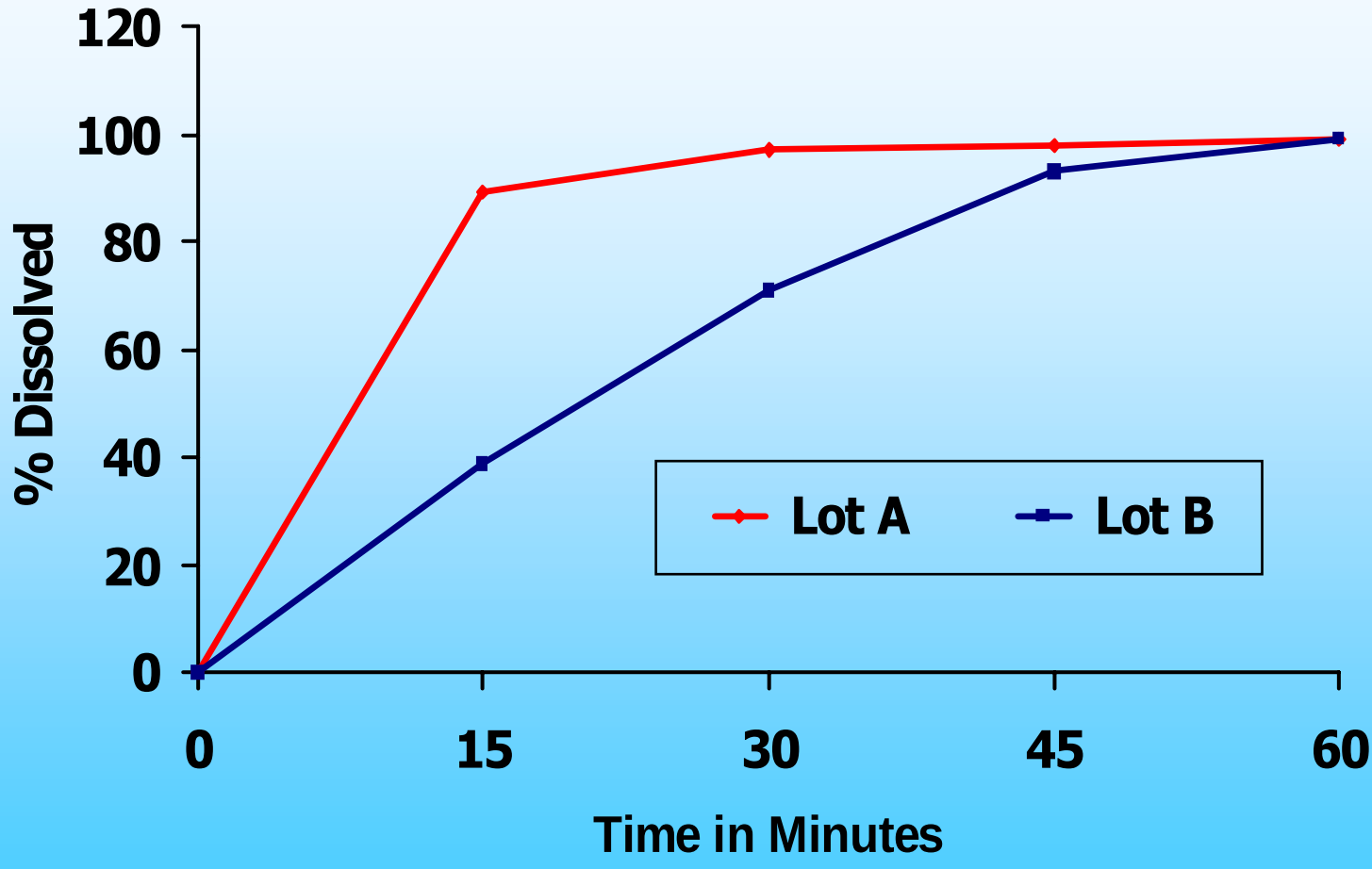
Minor (e.g.< 5% broken, capped or chipped, spots, film caking (<1 mm), rough coating 'orange peel')



Encapsulation Parameters

Variable	Response
Machine speed	Dose uniformity
Bed height	Weight variation
Compaction pressure	Appearance/length
Dosing volume	Content uniformity
Closing pressure	Dissolution
	Microbial count
	Moisture content (brittleness)

Effect of Raw Material Change on Dissolution



Use Multiple Lots of Critical Components in Validation

Soft Gel Capsules

Variable	Response
Speed of die rotation	Elegance/color
Temperature of gelatin	Capsule fill weight
Ribbon thickness	Capsule shell weight
Temperature and humidity of processing area	Capsule wall thickness
	Assay and content uniformity
	Dissolution (where appropriate)
	Moisture content
	Leak test

Manufacturing Equipment Change

Change Level	Class	Subclass	Nature of Change	Example
I	Same	Same	Same design and operating principle	Vector FBG to Glatt FBG
Intermediate	Same	Different	Carefully evaluate degree of similarity	V-Blender to Bin blender
II	Different	Different	Different design and operating principle	Oven to Fluid Bed Dryer

Examples of Validation Requirements for Manufacturing Equipment Change

Class	Subclass	Example	Validation Requirement
Same	Same	Vector FBG to Glatt FBG	Granulation parameters, characteristics LOD, Particle size
Same	Same	Tablet Press (Open Feed to Auger)	Tablet Properties (hardness, weight) Tabletting parameters
Same	Different	V-Blender to Bin blender	Blend Uniformity Blend characteristics
Different	Different	Oven to Fluid Bed Dryer	Granulator parameters (inlet temp, air volume) Granulation characteristics (LOD, Particle size) Final dosage form properties

- All changes are to be validated
- Validation data- reviewed by Field Investigators

Approaches to Improve Process Validation #1

- Definition of in-process specifications (e.g. LOD, particle size)
  - Capability of process
    - Adequate operating parameters or specifications
    - C_P and C_PK statistical indices
    - Probability of OOS (Out of Specification Results)
  - Criticalness, necessity
  - Challenges - “worst case”
- Sampling methods
  - Defined in protocol
  - Evaluated before validation
- Equipment OQ
  - Simulate production conditions (e.g., drying time)
  - Review equipment history (deviations, corrections)
  - Review set-up procedures

Approaches to Improve Process Validation #2

- Focus on “newness” - anything new: components or raw materials, equipment, process or package steps, dosage form
    - Adequate trials at full-size for new item
    - Assure raw material/component is from vendor’s routine production
- Complete review of pre-validation documentation
- Adequately identify cause and correct problems
- Data used in establishing operating ranges and specifications
- Data submitted to regulatory agencies

Approaches to Improve Process Validation #3

- Handling out-of specification (OOS) results
  - Identify if caused by equipment, product, normal process variation, or error or combination
  - May require additional experimentation
  - Pursue conservative approach, if unsure of cause
- Mechanism to bring development/validation issues to team management for resolution
  - Review meetings
  - Team approach
  - Open, honest interactions

Thank You!

Questions?