製程確效
Process Validation

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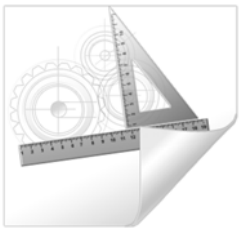
Jun-16



Agenda

1. 製程確效在 Annex 3, Appendix7內容概述
   1) 製程確效背景
   2) 傳統與現代製程確效比較
   3) 如何執行現代製程確效
2. 製程確效案例探討(一般製劑:錠劑、膠囊)

References:

- Annex 3, Appendix 7
- Annex 15, 2001
- Annex 15, 2015
- EMA Guidance on Process Validation, 2001
- EMA Guidance on Process Validation, 2014
- FDA Guidance on Process Validation, 2011
- 設備驗證及製程確效, 林志勇

製程確效在 Annex 3, Appendix7 內容概述

Introduction

- **Process validation is associated with the collection and evaluation of data throughout the life cycle of a product – from the process design stage through to commercial production – and provides scientific evidence that a process is capable of consistently delivering a quality product.**
  - ✓ **Has never been a once-off event**

Introduction

- **A risk assessment approach should be followed to determine the scope and extent to which process(es) and starting material variability may affect product quality. The critical steps and critical process parameters should be identified, justified and documented and based on relevant studies carried out during the design stage and on process knowledge, according to the stages of the product life cycle. During process validation and qualification, the critical process parameters should be monitored.**

Introduction

The objectives of process validation include ensuring that:

— the process design is evaluated to show that the process is reproducible, reliable and robust;

— the commercial manufacturing process is defined, monitored and controlled;

— assurance is gained on a continuous basis to show that the process remains in a state of control.

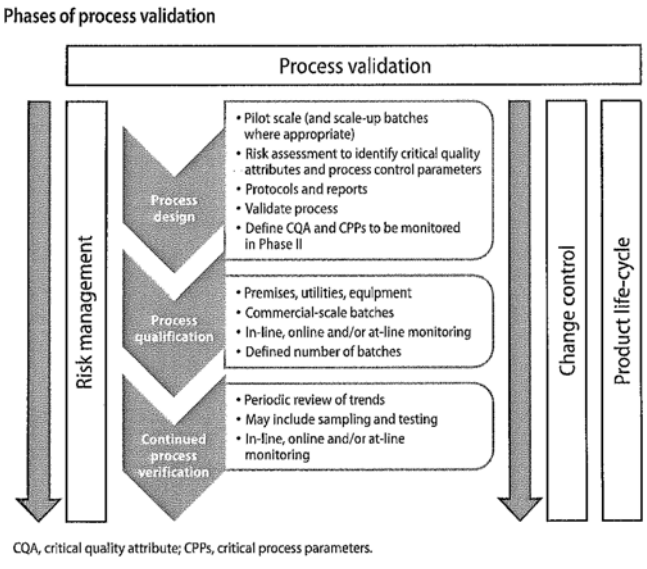
Introduction

- **Process Validation Approaches:**
  a) **Traditional process validation (consisting of prospective and concurrent validation)**
  b) **Process design followed by process qualification and continued process verification**
  c) **A combination of traditional process validation and the new approach described in these guidelines**

Traditional process validation

a. **Quality risk management principles to justify:**
   - **X-number of batches/x-number of samples**
   - **Need sufficient data for evaluation**
   - **Demonstrate a high level of assurance that the process is capable of consistently delivering quality product**
b. **Without a, minimum 3 batches**
c. **Need ongoing process verification**
d. **Protocol: defines critical process parameter(s) (CPP(s)) and critical quality attributes (CQAs)**

Phases in the new approach to process validation



Process Design

- Should normally cover design of experiments, process development, the manufacture of products for use in clinical trials, pilot-scale batches and technology transfer. Process design should be verified during product development.
- Should cover aspects for the selection of materials, expected production variation, selection of production technology/process and qualification of the unitary processes that form the manufacturing process as a whole, selection of in-process controls, tests, inspection and its suitability for the control strategy.

Process Design

- As part of the process validation life cycle some process validation studies may be conducted on pilot-scale batches (corresponding to at least 10% or 100 000 units, whichever is the greater) of the production scale. Where the batch size is smaller and/or where the process is tailored to the geometry and capacity of specific equipment, it may be necessary to provide production-scale validation data.

Process Design

- Process qualification and continued process verification should always be linked to process design and be referenced to those specific batches used in studies critical to the development of the product.
- The number of batches included in the process design stage of validation should be appropriate and sufficient to include (but not be limited to) the expected variations in starting materials, and confirm the suitability of the equipment and manufacturing technology. A statistically-based design of experiment approach can be helpful during this stage.

Process Design

- Development Reports

  QTPP, desired clinical performance, bills of materials, approved suppliers, finished product specifications and test methods, in-process testing specifications, equipment recommendations, master batch production records, master batch packaging records, stability reports, critical quality attributes, critical process parameters, batch comparisons, data on formulation batches, stability batches, clinical/biobatches and scale-up batches.

Process Qualification

- Personnel, premises, utilities, support systems and equipment should be appropriately qualified before manufacturing processes are validated. Materials, environmental controls, measuring systems, apparatus and methods should be considered during validation. The stages of qualification of equipment may include design, installation, operation and performance of equipment (for more details see (WHO Technical Report Series, No. 937, Annex 4 (1)).

Process Qualification

- The number of batches should be justified and based on a risk assessment that includes, for example, variability of results from the process design stage, variability of materials, product history, where the product is being transferred from and where it will be produced.
- The decision should include a justification for the number of batches used based on the complexity and expected variability of the process and critical quality attributes (CQAs). Successful completion of process performance qualification stage of the life cycle is required for commercial distribution.

Process Qualification

- Extensive in-line and/or online and/or at-line controls may be used to monitor process performance and product quality in a timely manner.
- A combination of elements of the traditional process validation approach and the new continuous process verification approach may be considered appropriate, subject to appropriate controls being in place, based on scientific justification and risk management principles.

Process Qualification

- Validation should be done in accordance with process validation protocols. The protocol should include or reference at least the following elements:
  1. the manufacturing conditions including operating parameters, processing limits and component (raw material) inputs;
  2. the data to be collected and when and how they will be evaluated
  3. the type of testing or monitoring to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step;

Process Qualification

- Validation should be done in accordance with process validation protocols. The protocol should include or reference at least the following elements:
  4. the scientifically justified sampling plan, including sampling points, number of samples and the frequency of sampling for each unit operation and attribute;
  5. the number of batches for which additional monitoring is proposed;
  6. status of the validation of analytical methods used in measuring the process, in-process materials and the product;

Process Qualification

- Validation should be done in accordance with process validation protocols. The protocol should include or reference at least the following elements:
  7. a description of the statistical models or tools used;
  8. review and approval of the protocol by appropriate departments and the quality unit;
  9. a description of the process;
  10. details of the equipment and/or facilities to be used (including measuring or recording equipment) together with its calibration status;
  11. the variables to be monitored with appropriate justification;

Process Qualification

- Validation should be done in accordance with process validation protocols. The protocol should include or reference at least the following elements:
  12. the samples to be taken – who, where, when, how, how many and how much (sample size);
  13. the product performance characteristics or attributes to be monitored, together with the test methods;
  14. the acceptable limits;
  15. personnel responsibilities;
  16. details of methods for recording and evaluating results, including statistical analysis.

Process Qualification

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  13. the product performance characteristics or attributes to be monitored, together with the test methods;
  14. the acceptable limits;
  15. personnel responsibilities;
  16. details of methods for recording and evaluating results, including statistical analysis.

Process Qualification

- Data should be collected and reviewed against predetermined acceptance criteria and fully documented in process validation reports.
- The outcome should confirm that the acceptance criteria have been met. Any deviations (including abandoned studies) should be explained and justified.
- The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next phase for confirmation.

Continued process verification

- Manufacturers should monitor product quality of commercial batches after completion of process design and process qualification. This will provide evidence that a state of control is maintained throughout the product life cycle.
- The scope and extent of process verification will be influenced by a number of factors including:

Continued process verification

- The scope and extent of process verification will be influenced by a number of factors including:
  - ✓ prior development and knowledge of the manufacturing of similar products and/or processes;
  - ✓ the extent of process understanding gained from development studies and commercial manufacturing experience;
  - ✓ the complexity of the product and/or manufacturing process;
  - ✓ the level of process automation and analytical technologies used;
  - ✓ for legacy products, with reference to the product life-cycle
  - ✓ process robustness and manufacturing history since the point of commercialization, as appropriate.

Continued process verification

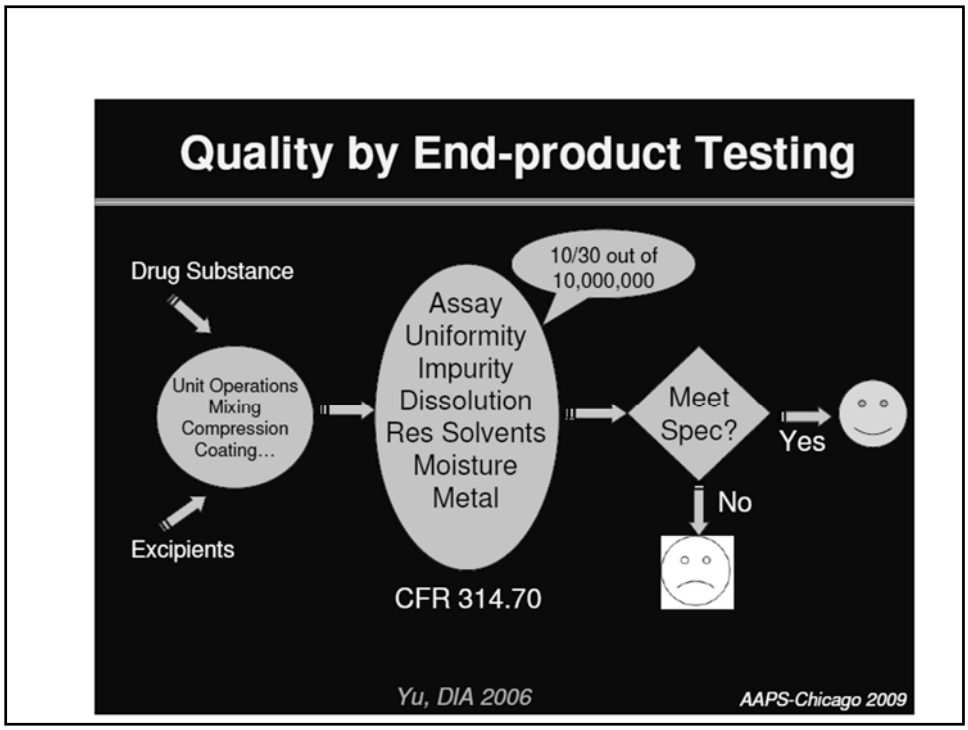
- Manufacturers should describe the appropriateness and feasibility of the verification strategy (in the protocol) including the process parameters and material attributes that will be monitored as well as the validated analytical methods that will be employed. Manufacturers should define:
  - ✓ the type of testing or monitoring to be performed;
  - ✓ the acceptance criteria to be applied;
  - ✓ how the data will be evaluated and the actions to be taken.
  - ✓ Any statistical models or tools used should be described.

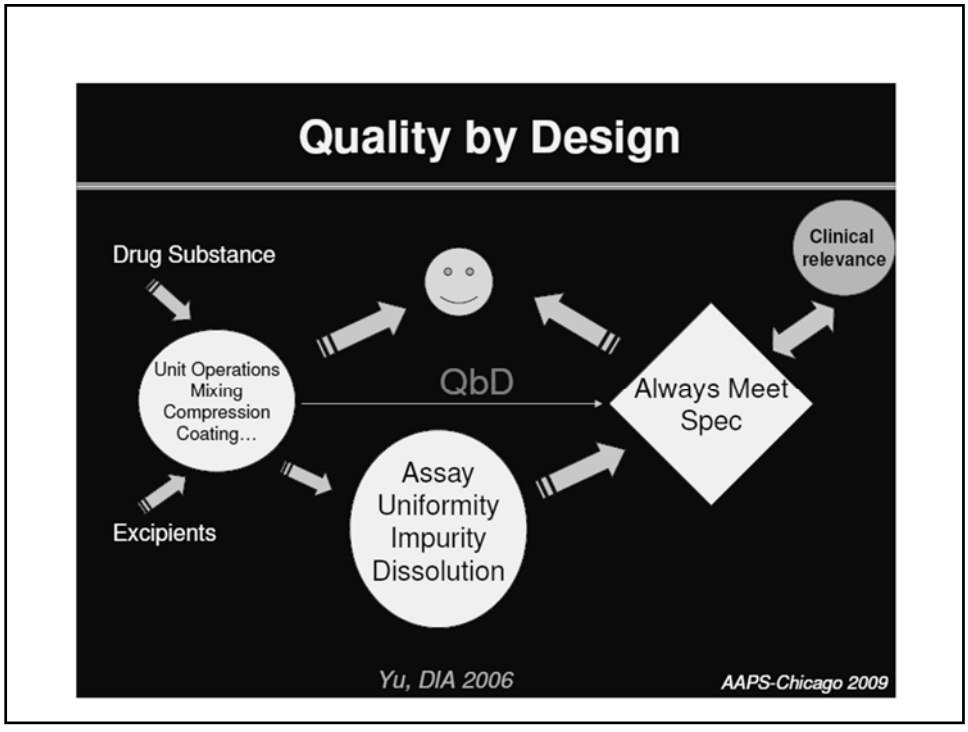
Continued process verification

- Periods of enhanced sampling and monitoring may help to increase process understanding as part of continuous improvement.
- Information on process trends, such as the quality of incoming materials or components, in-process and finished product results and non-conformances should be collected and assessed to verify the validity of the original process validation or to identify changes required to the control strategy.
- The scope of continued process verification should be reviewed periodically and modified if appropriate throughout the product life cycle.

Comparison of Process Validation (PV) Approaches

FDA, 2011	Annex,2001 EMA PV Guidance, 2001 (Traditional PV)	Annex, 2015 EMA PV Guidance. 2014
Stage I: Process Design	Yes	Yes
Stage II: Process Qualification (PPQ)	Three batches	1. Traditional process validation (3 batches) 2. Continuous process verification 3. Hybrid approach
Stage III Continued Process Verification (CPV)	Not specified	Ongoing Process Verification during Lifecycle


Quality by End-product Testing
Drug Substance
Unit Operations
Mixing
Compression
Coating…
Excipients
Assay
Uniformity
Impurity
Dissolution
Res Solvents
Moisture
Metal
10/30 out of
10,000,000
CFR 314.70
Meet
Spec?
Yes
No
Yu, DIA 2006
AAPS-Chicago 2009


Quality by Design
Drug Substance
Unit Operations
Mixing
Compression
Coating…
Excipients
QbD
Assay
Uniformity
Impurity
Dissolution
Always Meet
Spec
Clinical
relevance
Yu, DIA 2006
AAPS-Chicago 2009

PV Approach

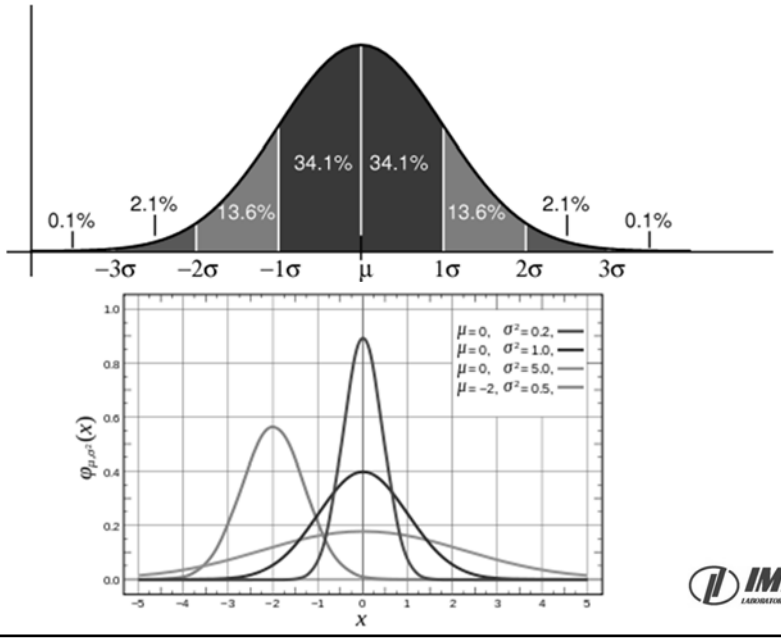
- **Approach should be defined in Process Validation Master Plan and Process Validation SOP**
  - ✓ **FDA emphasize statistical requirement: need to establish number of batches and sampling plan by statistical analysis. In addition, the results need to conduct statistical analysis to evaluate potential variation (within lot and lot to lot)**
  - ✓ **At least 3 batches to satisfy both FDA and EMA**

Statistical Analysis

Process Capability Indices

- **For Measuring and Reducing Process Risk**
  - ✓**Short-Term (Cp and Cpk)**
  - ✓**Long-Term (Pp and Ppk)**

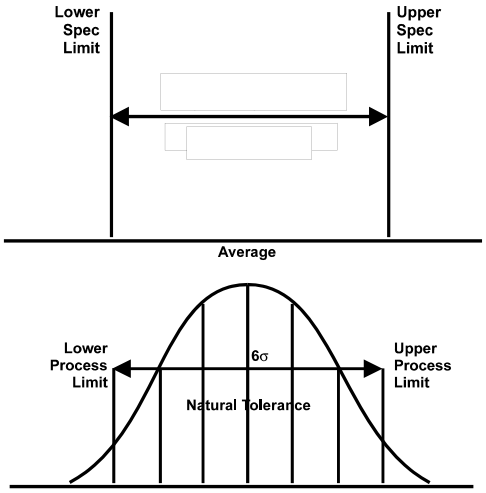
Normal Distribution



Measuring Process Capability

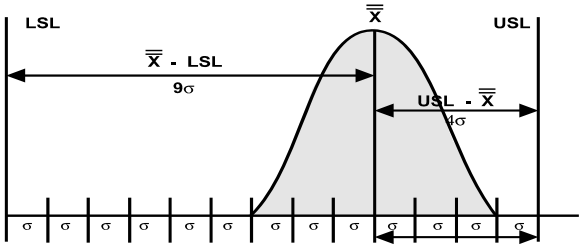
Cp Index

Compares Process Variation to Spec Limits



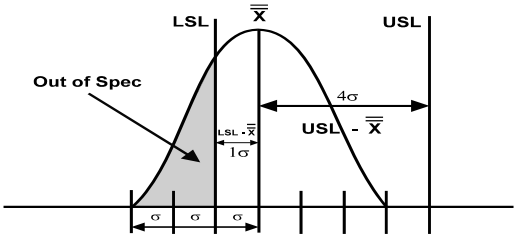
$$Cp = \frac{USL - LSL}{6\ (\textit{Short-term}\ \text{Standard Deviation})}$$

C_{pk} Index Compares Process Variation to Difference Between Process Average and Specs



$$Cpk = \frac{USL - Average}{3\ (\textit{Short-term}\ \text{Standard Deviation})} = 1.33 \text{ Good!!}$$

C_{pk} Index Compares Process Variation to Difference Between Process Average and Specs



$$Cpk = \frac{\text{Average} - \text{LSL}}{3\ (\textit{Short-term}\ \text{Standard Deviation})} = 0.33\ \text{Poor}$$

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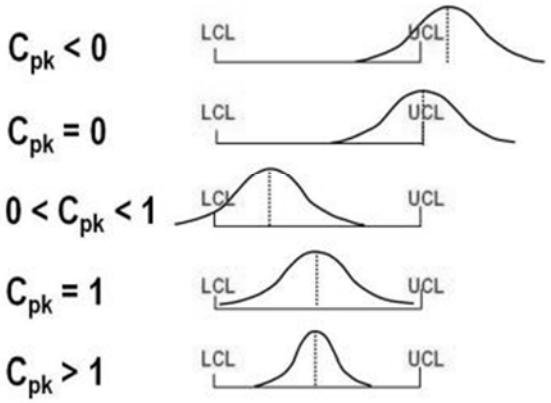

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Process Capability and Defect Rate

Cpk Value	Sigma Value	Non Conforming ppm
0.5	1.5	133614
0.7	2.1	35729
1.0	3.0	2700
1.33	4.0	65
1.67	5.0	0.58
2.0	6.0	0.002

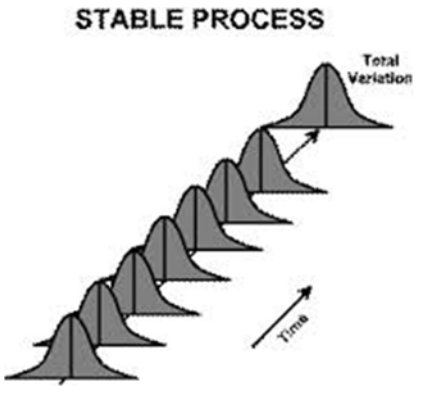
Common Causes of Variation (Cp, CpK)

If only common causes of variation are present, the process output is stable over time and is predictable

Common Causes:

- Present all the time
- Influences all process outputs
- Require process changes to reduce
- Minimum possible process variation

Example:
Variation Between Back-to-Back Samples Taken from a Vial Production Process



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Special Causes of Variation (Pp, PpK)

If special causes of variation are present, the process output is not stable and is **not predictable**

Special Causes:

- *Due to outside influences*
- *Affect some of the process outputs*
- *Can cause data to form non-normal patterns*

Examples

Ambient Temperature
Raw Material Lot
Equipment

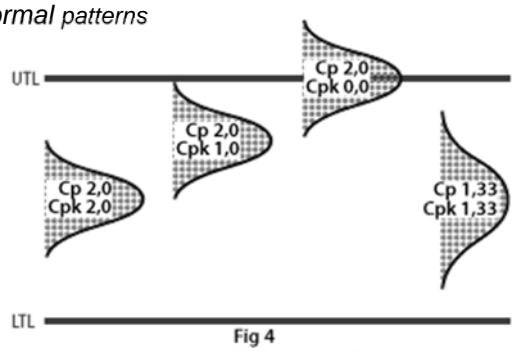

Fig 4

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Traditional Performance Indices

Long-Term Variation – What Customers Experience

Two traditional measures of process performance:

$$Pp = \frac{USL - LSL}{6\ (\textit{Long-term}\ \text{Standard Deviation})}$$

Where:

LSL = Lower Specification Limit
USL = Upper Specification Limit

$$Ppk = \frac{\text{Min}\ (USL - \text{Average},\ \text{Average} - LSL)}{3\ (\textit{Long-term}\ \text{Standard Deviation})}$$

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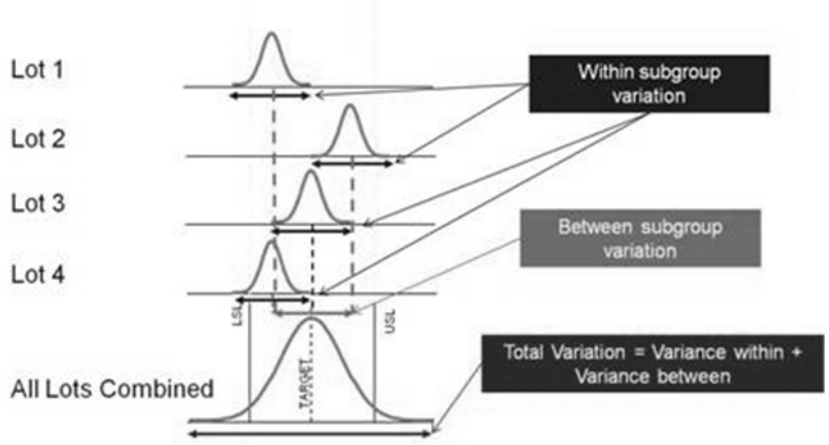
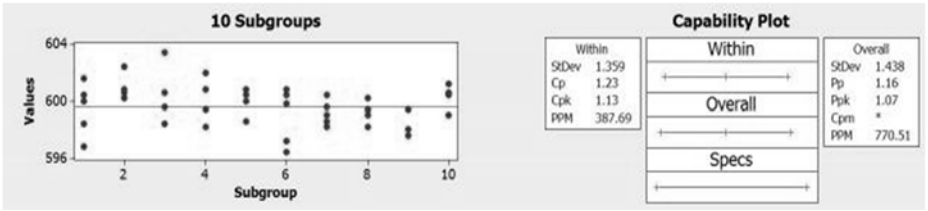
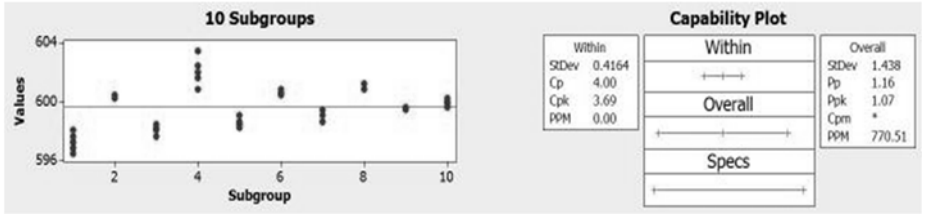
Process Performance Index (lot to lot variation)



PpK vs CpK

$$PpK = \text{Minimum of} \left(\frac{USL-\bar{\bar{X}}}{3\sigma}, \frac{\bar{\bar{X}}-LSL}{3\sigma} \right)$$

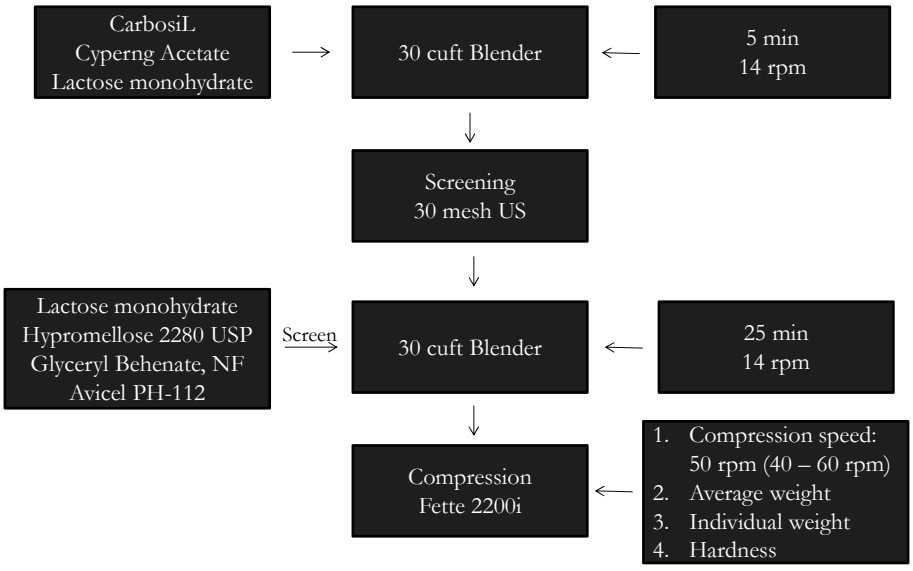




Example

It does not represent TFDA policy or guidance, and it does not create any obligation on TFDA or any other person or entity.

Case Study: FDA/Traditional



Critical Quality Attributes (CQAs)

CQA	Specification
Assay	93.0% - 107.0%
Dissolution	1. 1 hr: ≦25% 2. 4 hrs: 45 % – 65% 3. 8 hrs: 65% – 85% 4. 12 hrs: ≥85%
Impurities	USP/EP
Content Uniformity	USP/EP

Table 1. Severity Risk Ranking

1	2	3		
Product Type- route of administration				
Topical; Cosmetic	Oral	Inhalation; Vaginal, or non-sterile biologic drug substance	(sterile) ophathalmic	Parenterally administered products, sterile API/Biologic drug substence
Patient effect if product is unavailable				
No harm/patient complaints expected but no adverse effect	Patient discomfort possible	Temporary harm to patient possible	Permanent injury to patient possible	Fatality possible

Table 2. Probability Risk Ranking

1	2	3
Process Adjustability		
On-lined monitoring with real-time process control	Some control strategy in equipment	Traditional process monitoring
Process performance during clinical and/or development studies, or previous manufacturing history		
No significant process issues, consistent quality, Process Capability index (Cpk ≥ 1.69)	Some changes observed during development but consistent quality results (1.33 ≤ Cpk < 1.69)	Weak process capability results (1 <Cpk <1.33)

Table 3. Suggested Number of Validation Batches and Other Action Plans for Validation

Risk Priority Number (RPN)	
1 – 6	At least 3 batches are sufficient, given the low risk ranking that supports a conclusion that it should not be difficult to establish process consistency. The rationale should include why potential risks are considered to be mitigated(e.g. similar to another validated process, operating within same design space, few easily achieved CPPs, etc.)
7 – 9	A moderate number of batches (e.g. at least 4) should be prepared to confidently show process consistency.
> 10	Several (e.g. at least 5) batches should be prepared to show process consistency, as the risk assessment shows sufficient factors to indicate that there is an increased risk of success in confidently demonstrating process consistency with just a few batches.

Determination of Number of Batches for Process Validation

Ppk of CQAs from Development Batches

CQA	Specification	Ppk	Ppk
Weight	186mg – 214 mg	2.81	2.81
Hardness	7 – 13 kp	1.60	1.60
Assay	93.0% - 107.0%	2.12	2.12
Dissolution	1. 1 hr: ≦25% 2. 4 hrs: 45 % – 65% 3. 8 hrs: 65% – 85% 4. 12 hrs: ≥85%	1. 1.67 2. 2.67 3. 1.89 4. 3.13	1. 1.67 2. 1.13 3. 1.89 4. 3.13
Impurities	USP/EP		
Content Uniformity	USP/EP		

Number of Batches

- Oral: 1
- Patient effect if product is unavailable: 1
- Process Adjustability: 2
  - ✓ Fette automatic weight control during compression
- Process performance during clinical and/or development studies, or previous manufacturing history: 3
- Total score: 1+1+2+2=6
  - ✓ 3 batches for PPQ

Sampling Plan?

Stage II PPQ

- Sampling Plan
  - Number of batches and samples
    - ✓Traditional: 3 batches
    - ✓New Guidance:
      - Risk assessment + Statistical analysis
      - Risk assessment or Statistical justification for number of samples and batches
      - Defined in SOP

Sampling Plan

- **Sampling Plan**
  - **Attribute**
    - ✓**Pass or fail criteria (CU, Assay, AQL)**
    - ✓**Large sampling size if we need to include in PPQ protocol, such as assay**
  - **Variable Sampling plan**
    - ✓**Based on statistical calculation**
    - ✓**Normality, lot to lot variation may cause headache**

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ATTRIBUTE SAMPLING PLAN

Table B1: 95/95 Attribute Sampling Plans ($\mathbf{RQL_{0.05}}$ = 5%)

Type	Parameters	AQL*
Single	n=59, a=0	0.087%
Double	n_1=63, a_1=0, r_1=2, n_2=50, a_2=1	0.35%
Single	n=93, a=1	0.38%
Double	n_1=64, a_1=0, r_1=2, n_2=77, a_2=2	0.48%
Single	n=124, a=2	0.66%
Double	n_1=64, a_1=0, r_1=3, n_2=116, a_2=3	0.78%
Single	n=153, a=3	0.90%
Double	n_1=65, a_1=0, r_1=3, n_2=141, a_2=4	0.92%
Single	n=181, a=4	1.00%
Single	n=208, a=5	1.26%
Single	n=234, a=6	1.41%
Single	n=260, a=7	1.54%
Single	n=286, a=8	1.65%
Single	n=311, a=9	1.75%
Single	n=336, a=10	1.85%
Single	n=386, a=12	2.00%
Single	n=434, a=14	2.14%
Single	n=482, a=16	2.26%
Single	n=530, a=18	2.36%

*Historical defect rate.

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CU Strategy

Demonstrating Statistical Confidence

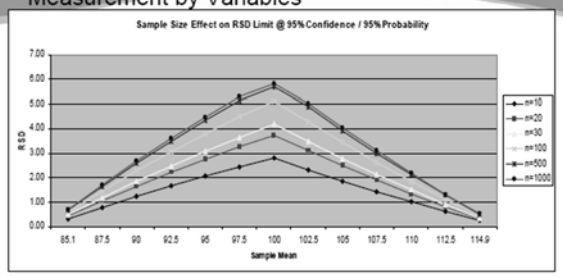
Measurement by Variables

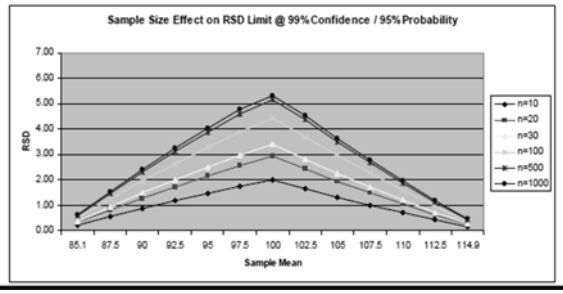
U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

ASTM **E2709**

Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure

One tool to analyze Uniformity of Dosage Units





Sampling Plan

- **Blend Uniformity (BU):**
  - ✓ **Blender (3 x 10/batch)**
  - ✓ **Drum (3 x 10/batch)**
- **Compression:**
  - ✓ **Stratified sampling: 20 bottles during compression**
    - **BU: 3 (or 7) tablets**
    - **4 dissolution runs**
    - **5 assay**

- **BU:**

Pass Specification

- **Compression:**
  - ✓ **BU/CU: pass criteria**
  - ✓ **Dissolution:**

1. Pass specification

2. Pass 95%/95%

Sampling Plan

	Sampling plan	Acceptance Criteria
Blend Uniformity (Blending)	Blender (3 x 10/batch) Drum (3 x 10/batch)	Pass Specification
Compression	Per Batch: Stratified sampling: 20 bottles BU: 3 (or 7) tablets 4 dissolution runs 5 assays	BU/CU: Pass Specification Dissolution and assay: 1. Pass specification 2. Dissolution: Can claim 95%/95% conformance 3. Assay: Pass 95%/95%, if not, use Stage 3 for monitoring or increase the number of assay samples

PV Results

- Meet release specification
- Extra Sampling:
  - Assay and dissolution meets 95%/95% tolerance interval
  - Ppk

CQA	Specification	Case 1: Ppk	Case 2: Ppk	Case 3: Ppk
Weight	186mg – 214 mg	2.81	2.81	2.81
Hardness	7 – 13 kp	1.60	1.60	1.60
Assay	93.0% - 107.0%	2.12	2.12	2.12
Dissolution	1. 1 hr: ≦25% 2. 4 hrs: 45 % – 65% 3. 8 hrs: 65% – 85% 4. 12 hrs: ≥85%	1. 1.67 2. 2.67 3. 1.89 4. 3.13	1. 1.67 2. 1.13 3. 1.89 4. 3.13	1. 1.67 2. 0.98 3. 1.89 4. 3.13
Impurities	USP/EP			
Content Uniformity	USP/EP			

PV Results to Define Ongoing Process Verification

- Case 1: All Ppks ≧ 1.33
  - Monitor 15 batches or every 6 months
- Case 2: one Ppk is 1.00 ≦ Ppk < 1.33
  - Monitor 5 batches or every 3 months
- Case 3: Ppk < 1.00
  - The first 3 batches will follow the PV sampling plan for dissolution

Ongoing Process Verification Protocol Preparation

- Ppk ≧ 1.33
  - Monitor 15 batches or every 6 months
- 1.00 ≦ Ppk < 1.33
  - Monitor 5 batches or every 3 months
- Ppk < 1.00
  - The first 3 batches will follow the PV sampling plan for dissolution

Ongoing Process Verification Protocol Preparation

- **Monitor CQAs**
  - ✓ **Raw materials impact?**
  - ✓ **Process parameters and CPPs impact?**
  - ✓ **Define next verification frequency**
    - **All Ppk ≧ 1.33**

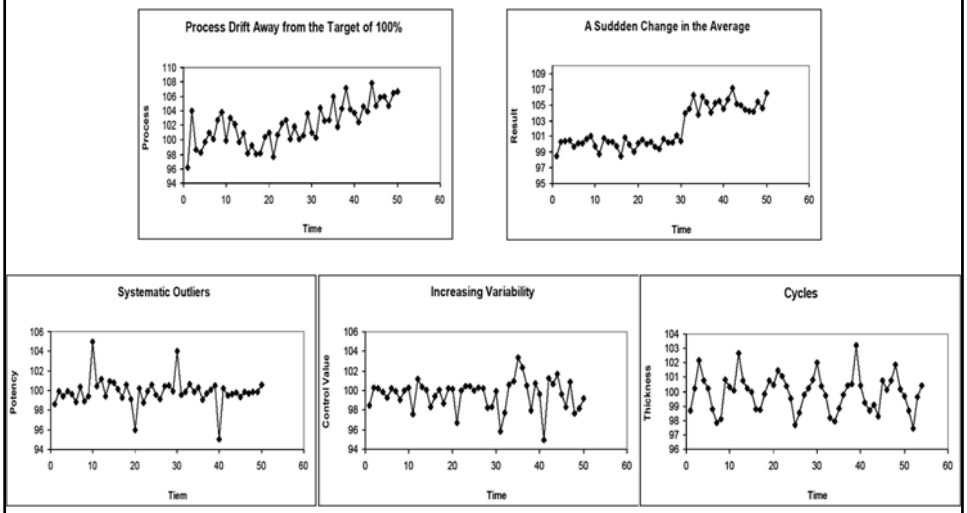
      Monitor in annual product review
    - **Ppk ≧ 1.33 (85%)**

      1.00 ≦ Ppk < 1.33 (15%)

      Monitor every 6 months, otherwise every 3 months
    - **Ppk < 1.00**

      Should initiate an improvement project to increase the capability.

Variability??

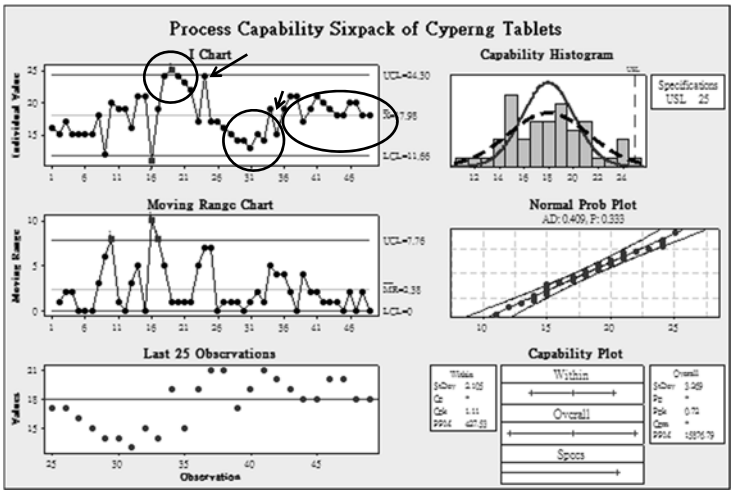


Example

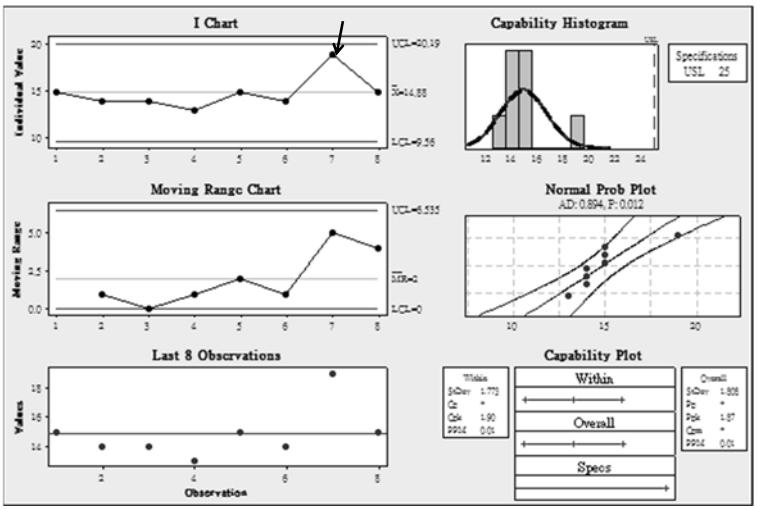
FDA: Continued Process Verification

EMA: Ongoing Process Verification

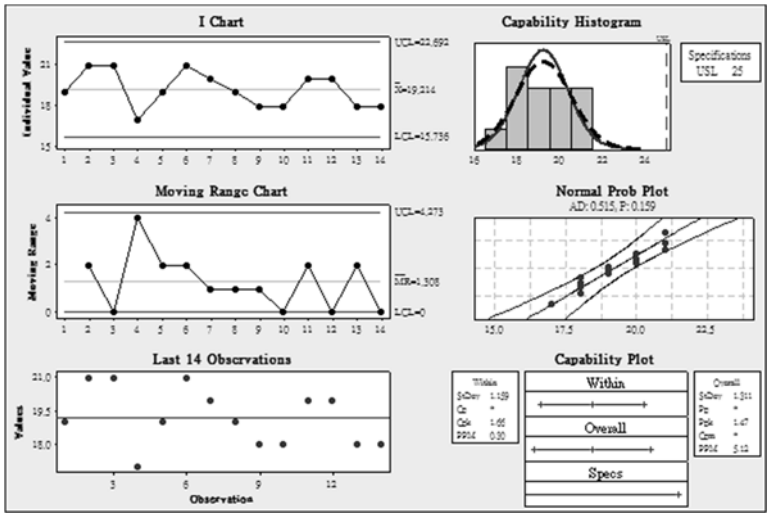
Dissolution of Cyperng Tablets @ 1 hr



Dissolution of Cyperng Tablets @ 1 hr



Dissolution of Cyperng Tablets @ 1 hr



Dissolution of Cyperng Tablets @ 1 hr

- **API impacts the dissolution**
  - ✓ **Particle size variation**
- **Operator's operation variation**
- **Equipment issue**

Ongoing Process Verification

- Will allow detection of **undesired process variability**
- An **ongoing program** to collect and analyze product and process data that relate to product quality must be established
- The data collected should include relevant **process trends** and **quality of incoming materials or components, in-process material, and finished products**.

Ongoing Process Verification

- The data should be statistically trended and reviewed by trained personnel (**statistician)**
- Production data should be collected to evaluate **process stability and capability**.

- guard against overreaction
- against failure to detect unintended process variability

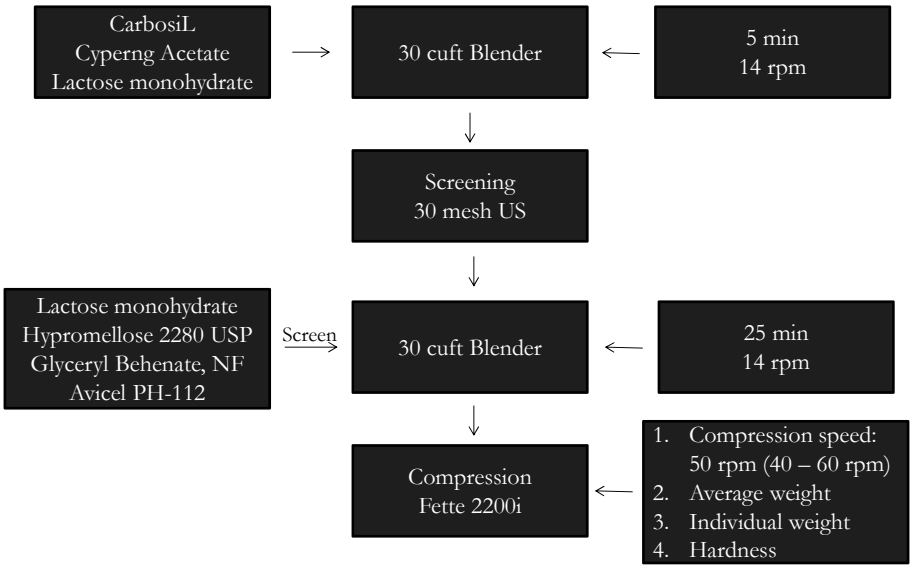
- Can identify variability in the process and/or signal potential **process improvements**.

Example

EMA: Continuous Process Verification

- **Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.**
  - **Demonstration that the process is validated (under specified control)**
  - **Based on control strategy and process knowledge**
  - **Applied at various scales and stages**
  - **Composite of data from lab and various scale manufacturing**
  - **Can include multiple data sources (IPC, batch, in-line at line off-line)**

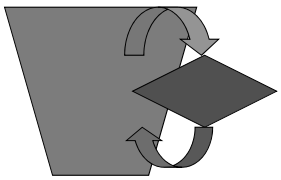
Case Study: Continuous Process Verification



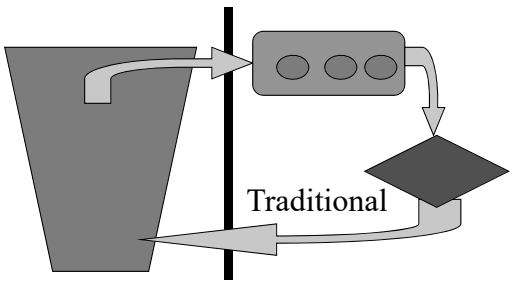
Convention vs. PAT

- Conventional
  - Compendial tests for excipients
  - Blending
    - BUA Testing (drug only)
  - Compaction
    - Hardness, thickness, weight, friability
    - Content uniformity
    - Dissolution
- NIR
  - Identification and characterization (moisture, particle size,….)
  - On-line control of adequacy of mix with respect to all components
  - At-line assurance of acceptable hardness and friability
  - At-line assurance or control of content uniformity
  - At-line assurance of dissolution rate

PAT - Blending

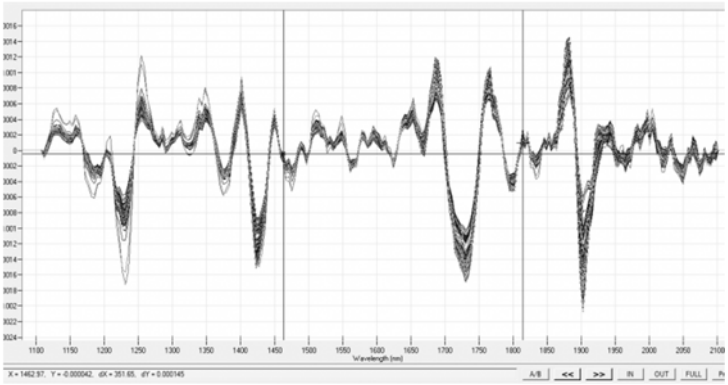


Many technologies
- “real-time”
- without “sampling”
- multivariate
- e.g., Near IR, Raman,.



PAT - Tableting

PAT




Thanks for Your Attention
Questions / Comments ?