Process Validation: Lifecycle Management

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PQRI-FDA Workshop on Process Drift:
Detection, Measurement, and Control
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Agenda

- Process Validation lifecycle as described in FDA's new Guidance for Industry: Process Validation: General Principles and Practice

- Process drift and Stage 3, Continued Process Verification

- Statistics in the CGMPs, the 1978 preamble and other guidelines

- Establishing process variability estimates
    - Basis for routine control strategy and changes to it
    - "statistical procedures where appropriate"
    - SPC and Voice of Process – a tool to reveal variability

- "It met specifications" - how certain?
    - USP disclaimer
    - sample size, desired confidence and probability

GMP Process Validation Requirement

- **Process Validation is an enforceable requirement for _finished drug products_:**
  - 21 CFR 211.100(a) [Foundation for PV]
    - "written **procedures for production and process control designed to assure** that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.
  - 21 CFR 211.110(a)
    - "…procedures that describe in-process controls to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and drug product.

Background on 2008 Draft Guidance for Industry Process Validation: General Principles and Practices

Catalysts for revision of the 1987 PV Guideline

1. Further the goals of the CGMPs for the 21st Century Initiative such as advancing science and technological innovation in pharmaceutical manufacturing.

2. Update Guidance based on regulatory experience since 1987.
   - Need more emphasis on process design elements and maintaining process control during commercialization
   - Communicate that PV is an ongoing program and align process validation activities with product lifecycle
   - Emphasize the role of objective measures and statistical tools and analyses in making science based and risk based decision making.
   - Emphasize knowledge, detection, and control of variability.
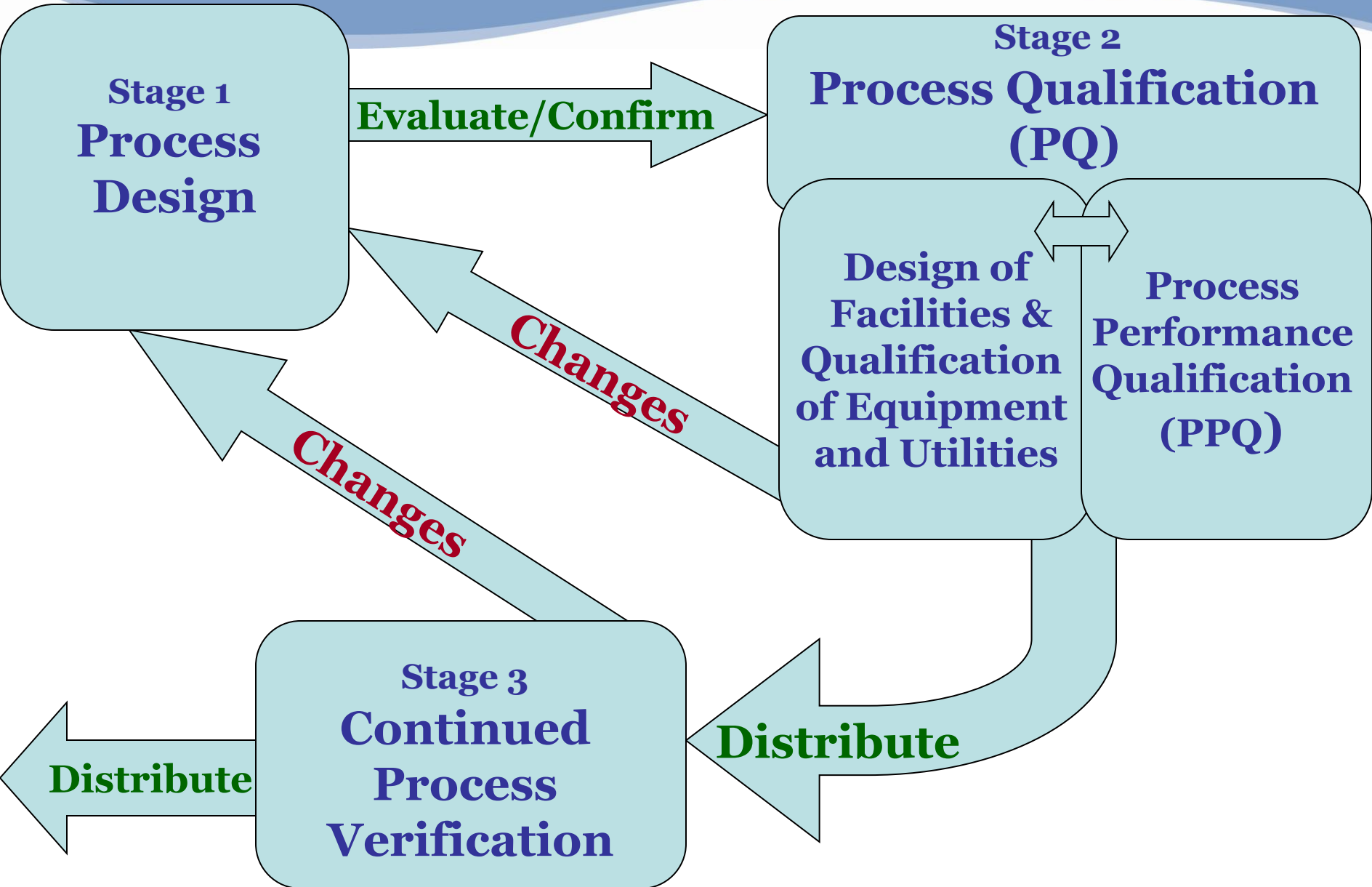
3. More value added and scientific.

New PV Guidance

For purposes of this guidance, ***process validation* is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.**

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

- <u>Stage 1 – Process Design</u>: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- <u>Stage 2 – Process Qualification</u>: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- <u>Stage 3 – Continued Process Verification</u>: Ongoing assurance is gained during routine production that the process remains in a state of control.

This guidance describes activities typical in each stage, but in practice, some activities in different stages might overlap.

Stage 1
Process Design

Evaluate/Confirm

Stage 2
Process Qualification (PQ)

Design of Facilities & Qualification of Equipment and Utilities

Process Performance Qualification (PPQ)

Changes

Changes

Stage 3
Continued Process Verification

Distribute

Distribute

Stage 3 and process drift

- The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or **systems for detecting unplanned departures from the process as designed** is essential to accomplish this goal.

Process Drift in the 2008 Draft PV GFI

- **Stage 3 –**

"Adherence to the CGMP requirements, specifically including the collection and evaluation of information and data about the performance of the process (see below), will allow detection of **process *drift***. The evaluation should determine whether action must be taken to prevent the process from **drifting out of control (§ 211.180(e))."**

Replaced "drift" with variability in the PV Guidance to be finalized

- **Stage 3 – Continued Process Verification**
  - CGMP requirements, specifically, 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)).

- Drift is one of five statistical changes:
  1. A gradual change to or away from a target.
  2. Sudden change in the average
  3. Outliers
  4. Increase or decrease in the variability
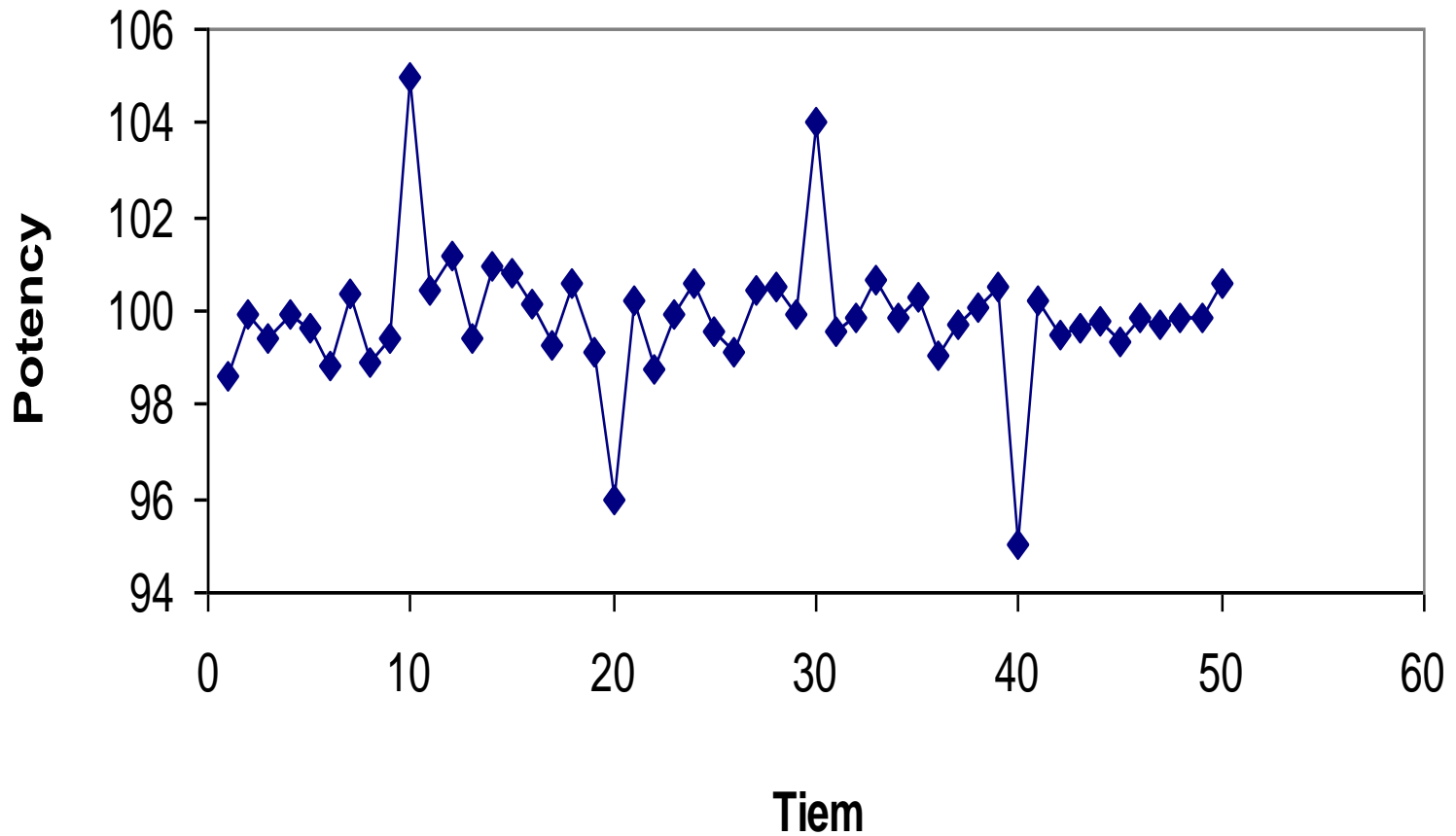 5. Reoccurring cycles

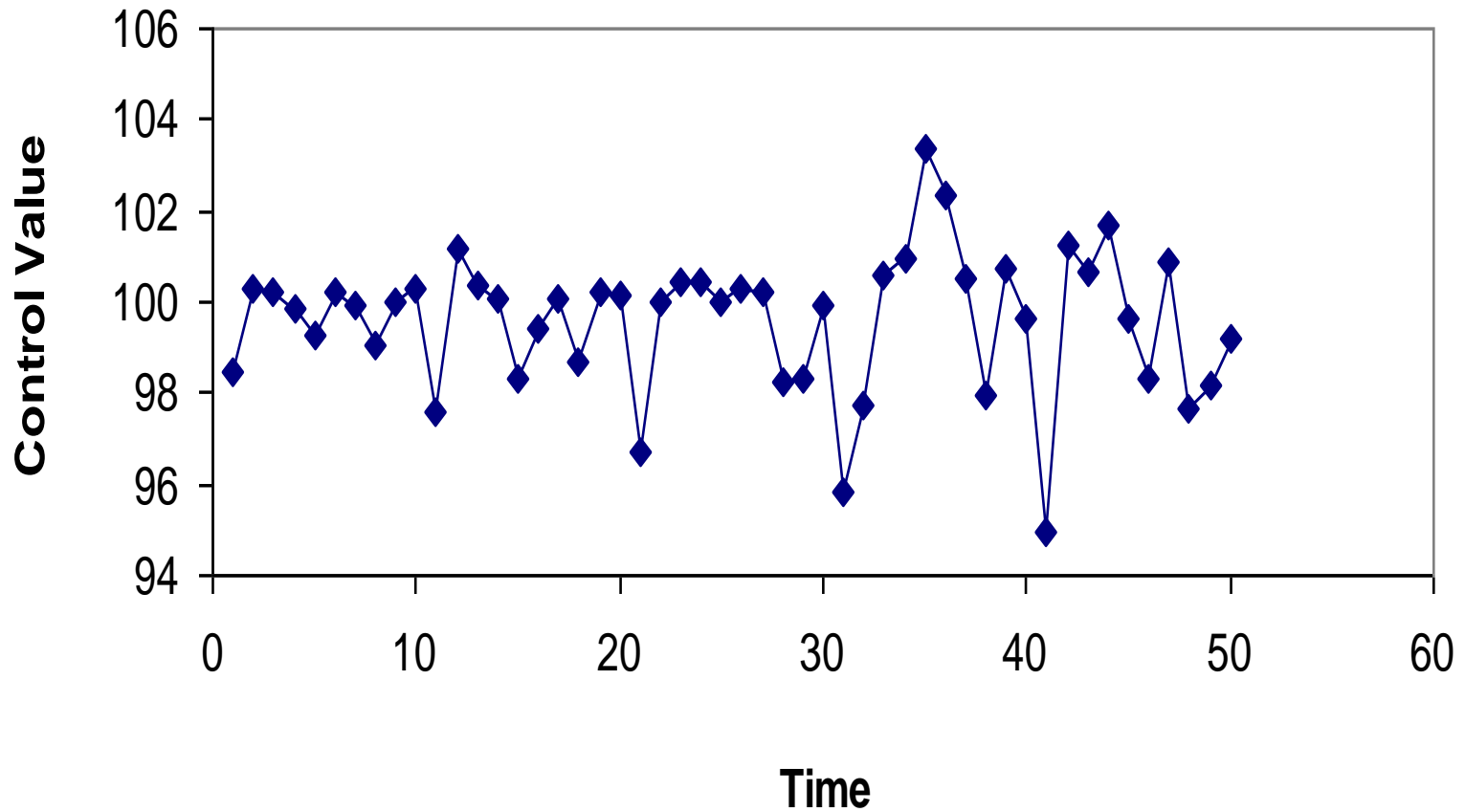Process Drift Away from the Target of 100%

U.S. Food and Drug Administration
Protecting and Promoting Public Health
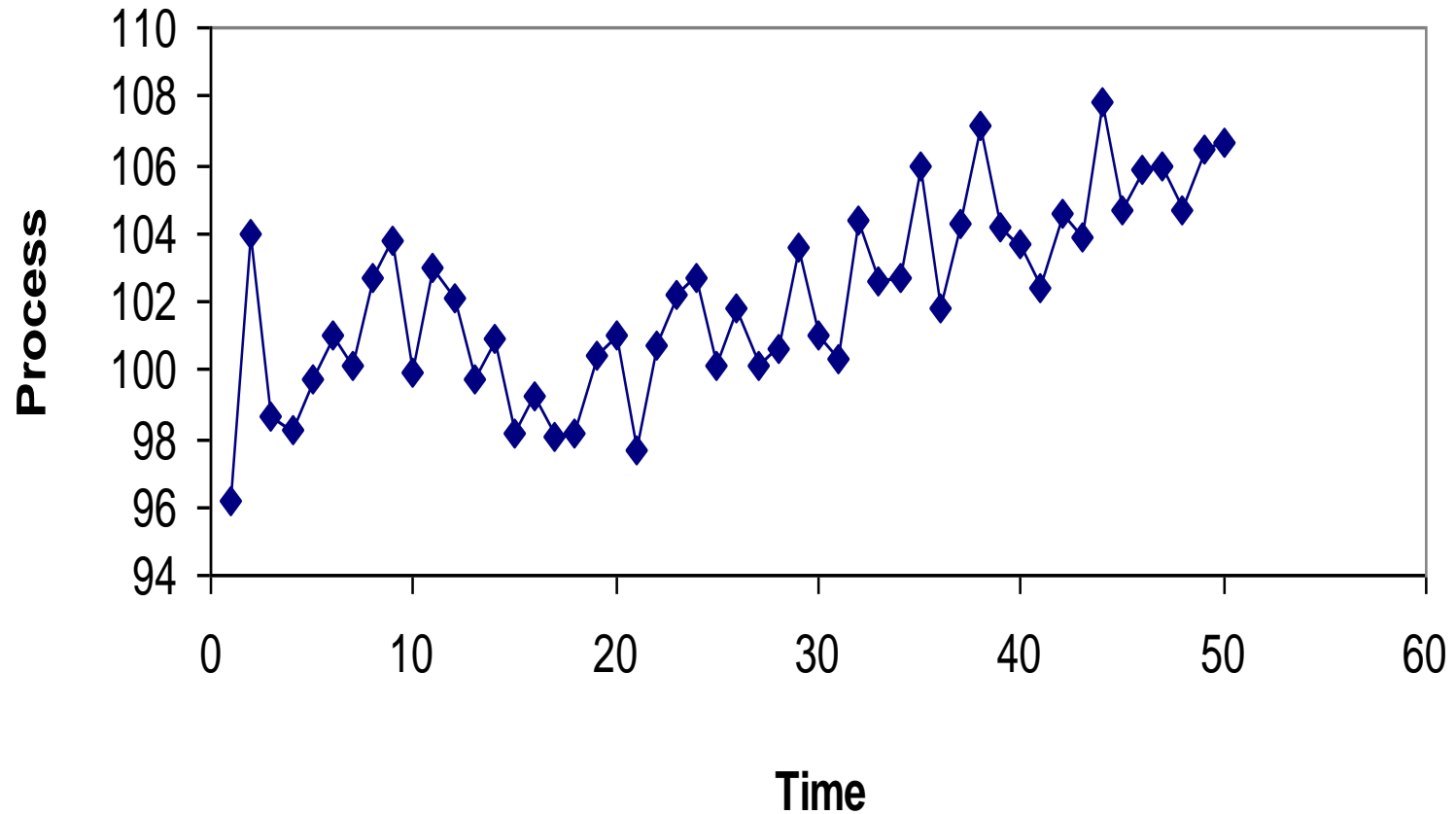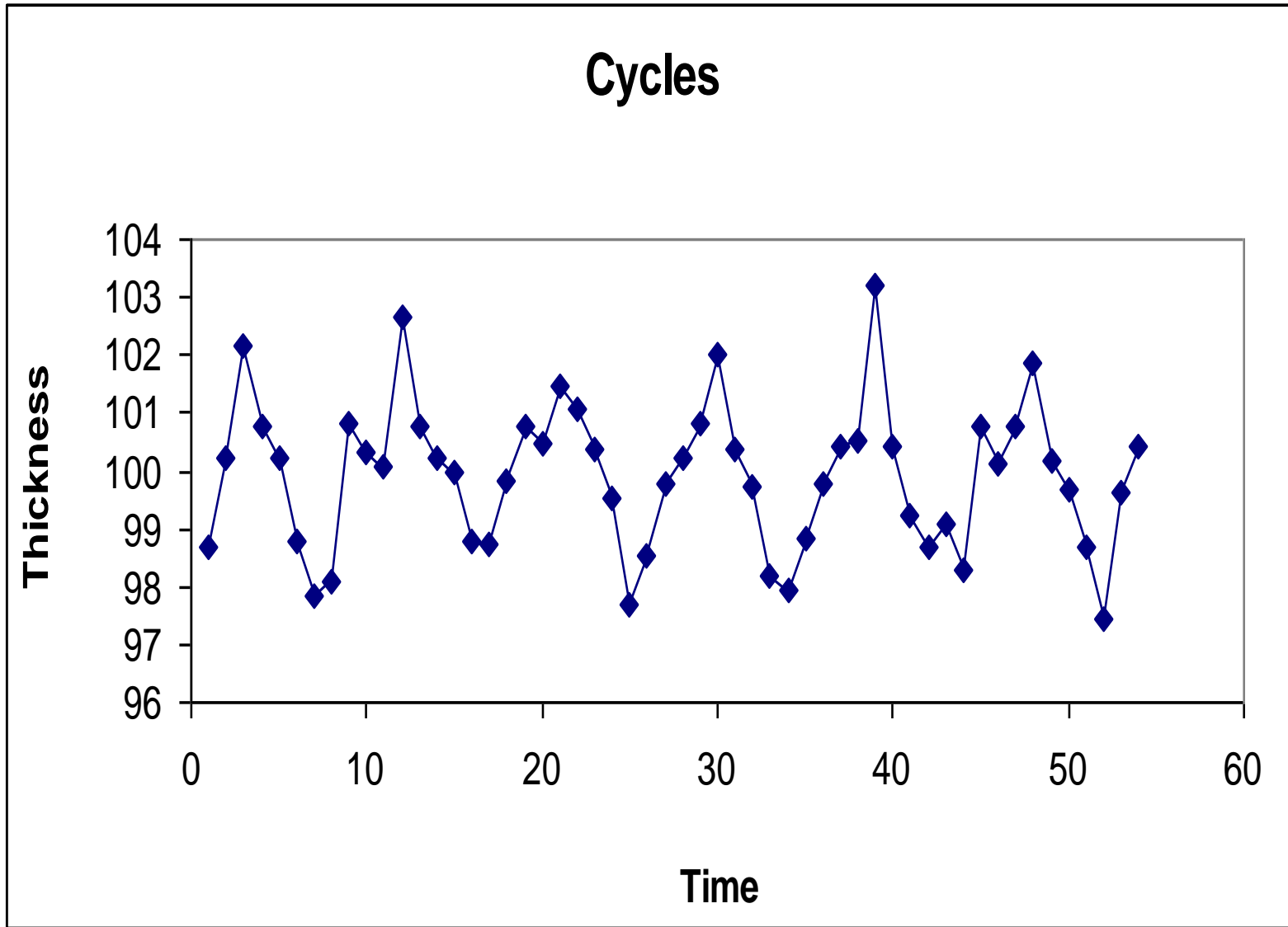

A Suddden Change in the Average
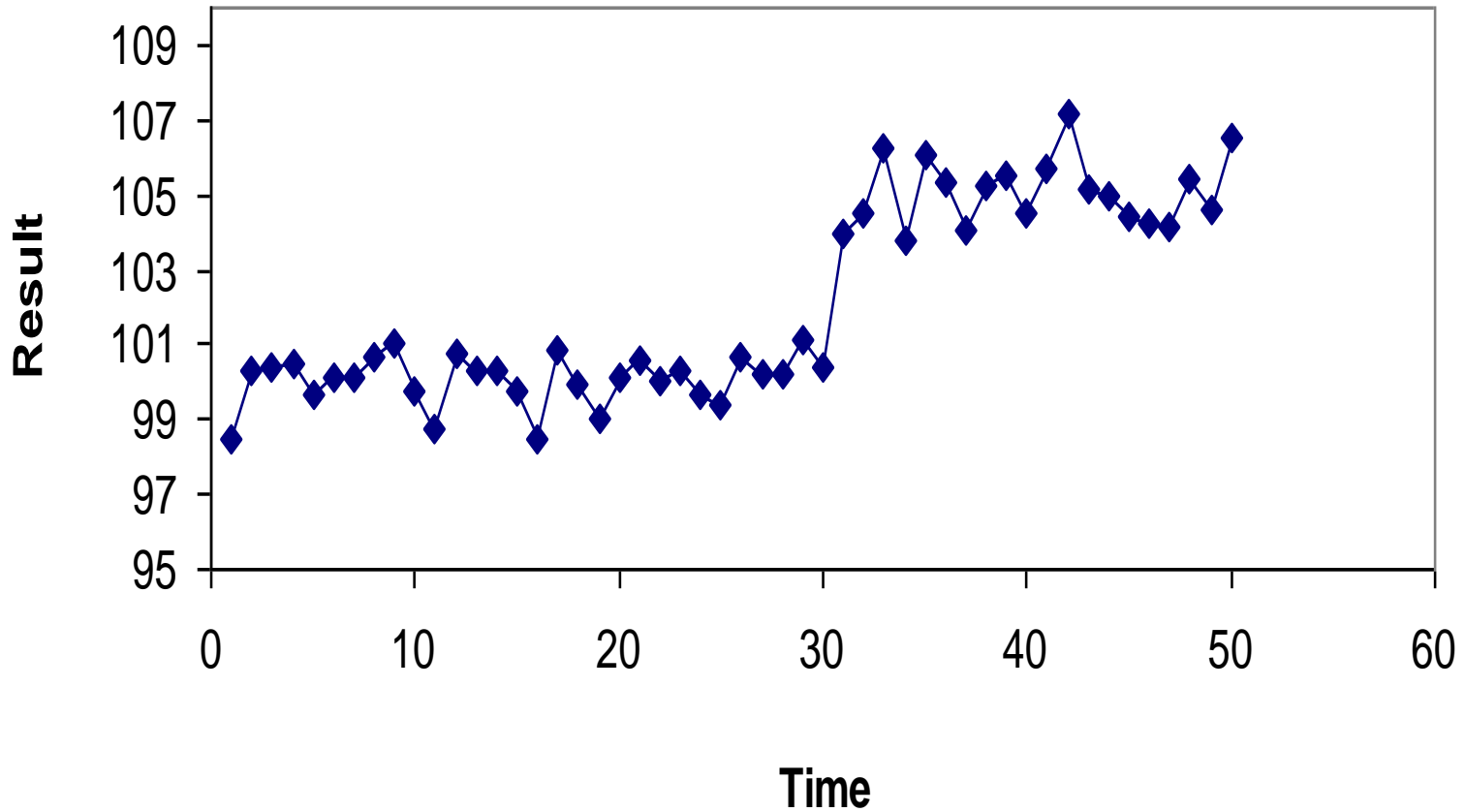
Systematic Outliers

Increasing Variability

Cycles

Process drift and process variability

- In order to detect process drift, **normal (common cause) variability** has to be understood and measured where possible.

- Range of input variability a process may encounter in commercial production may not be fully known during the process design stage.
  - E.g., excipients–
  - Laboratory or pilot-scale models that are representative of the commercial process can be used to estimate variability but need to obtain data from commercial manufacturing experience to confirm predictions.

Uniformity
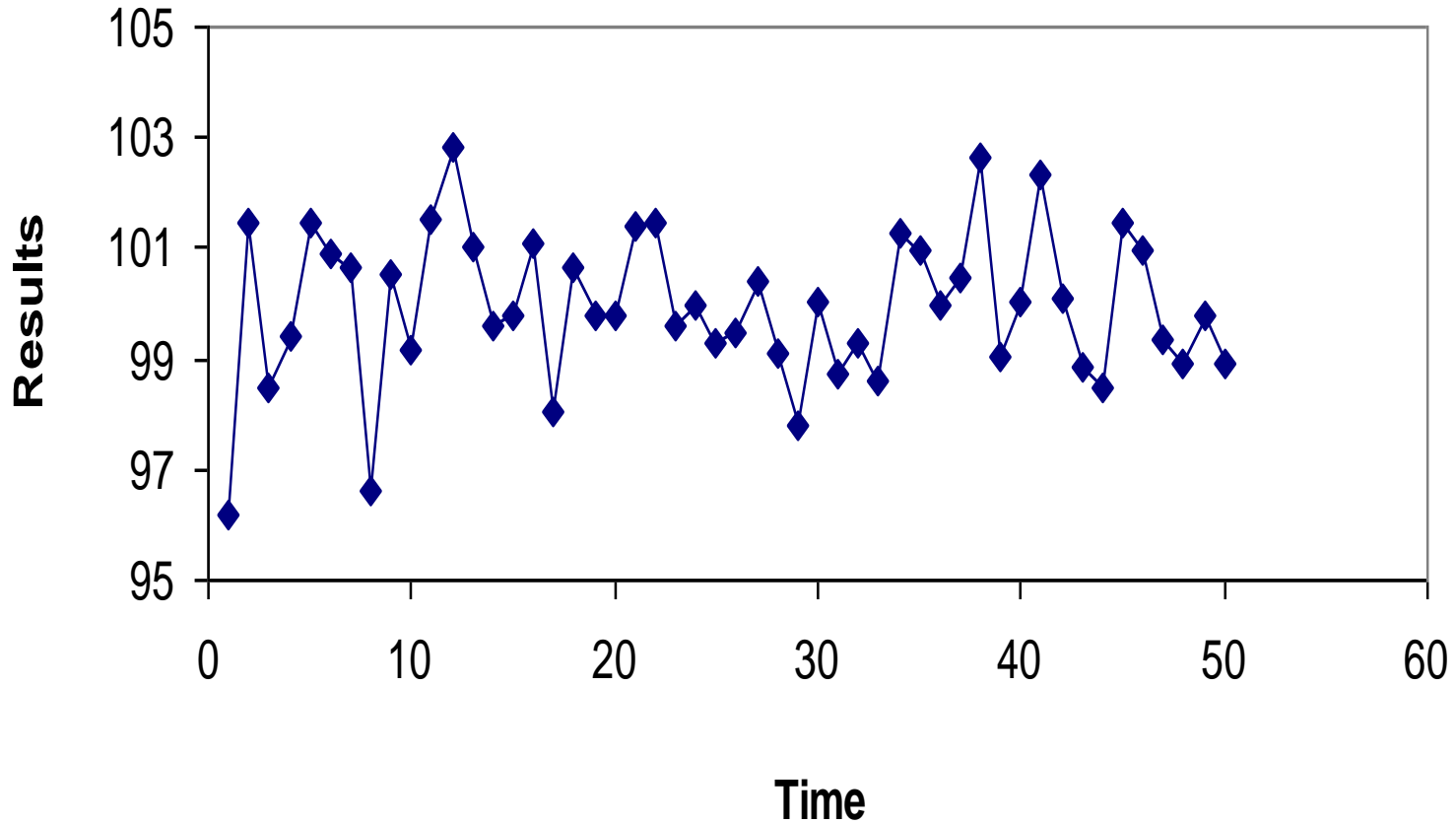
PV Stage 3

- An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

Changes - 211.180(e)

- (e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product **to determine the need for changes in drug product specifications or manufacturing or control procedures.**
  - If actual manufacturing experience signals the need for change, companies are obligated under CGMP to evaluate and address the issue(s).

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ICH Guidelines Q6A and Q6B-Setting Specifications

ICH Q6A - SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR **NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS**: CHEMICAL SUBSTANCES

ICH Q6B – ...FOR BIOTECHNOLOGICAL/ BIOLOGICAL PRODUCTS

- 3.1.1 Definition of Specifications
  - A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

ICH Guidelines Q6A and Q6B- Setting Specifications

- ….When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. …..**Additionally, a reasonable range of expected analytical and manufacturing variability should be considered.**

- …

- If multiple manufacturing sites are planned, it may be valuable to consider data from these sites in establishing the initial tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance or drug product at any particular site. If data from a single representative manufacturing site are used in setting tests and acceptance criteria, product manufactured at all sites should still comply with these criteria.

Suitable Statistical Procedures

- 211. 110 - Sampling and testing of in- process materials and drug products

- 211.110(b)

Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and **shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.**

A tool – Statistical Process Control

- These process average statistic is used in control charting to calculate the control limits, the Voice of the Process.

- Compare the Voice of the Process, graphically displayed by the calculated control limits, with the desired specifications, Voice of the Customer.   Can the process, with its inherent (common cause) variability, consistently produce the drug with attributes the patients needs?

I-MR Chart of In Control In Spec
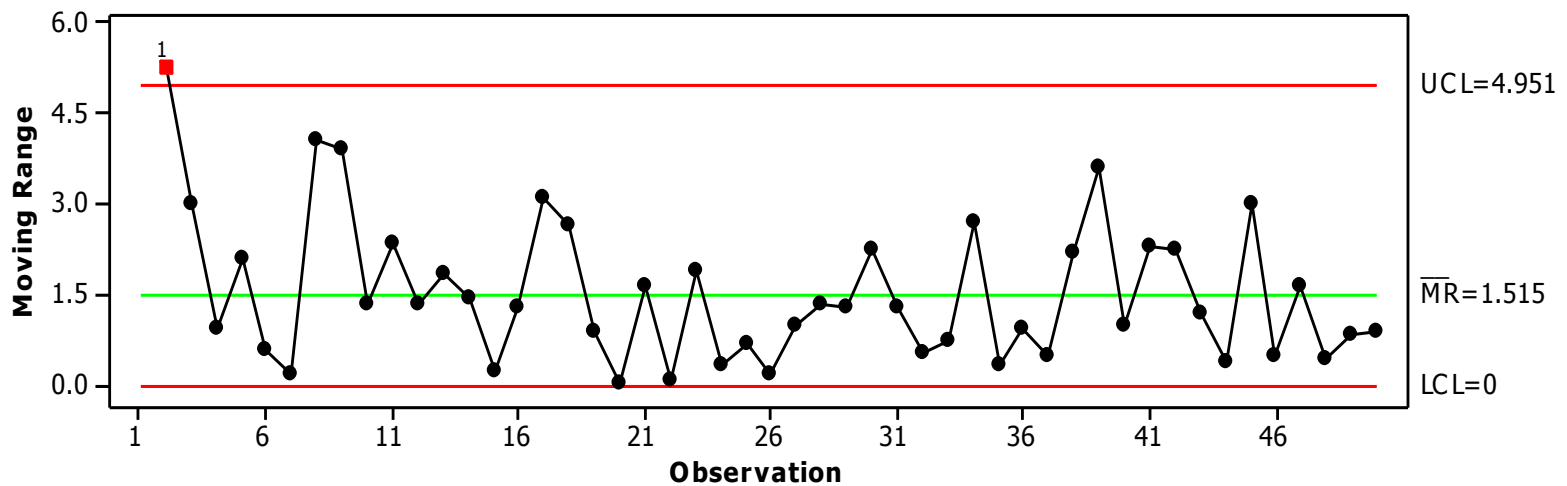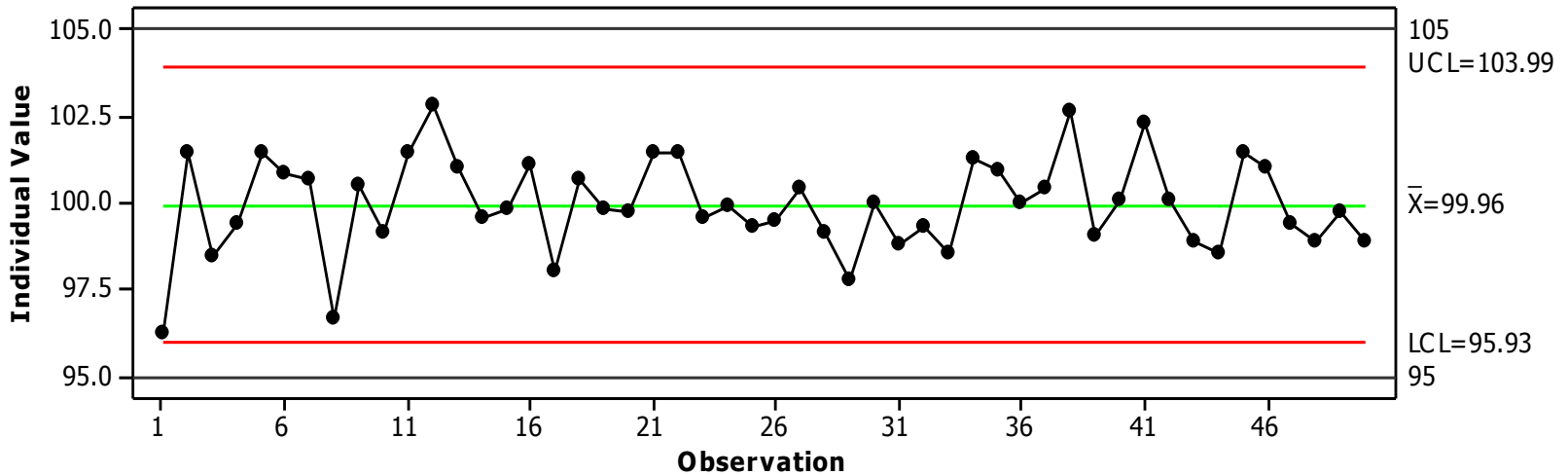
- Developing a strategy for trending and monitoring.
  - What is the goal?
  - For example, to determine machine-to-machine variability, within a machine? May need to tailor approaches, use different tools, for different products and processes.

- Obtain expertise in the use of statistical tools in manufacturing.

- Further refine the control strategy if necessary

PV Guidance recommendation - sampling/monitoring after Stage 2

- 2008 Draft lines 533-537:
  - "We recommend continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates. Once the variability is known, sampling and/or monitoring should be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and sampling and/or monitoring adjusted accordingly."

Language to be finalized in PV Guidance

- …recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates. **These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process**. Monitoring can then be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and monitoring adjusted accordingly.

PV Guidance recommendation - sampling/monitoring after Stage 2

- Comment – Purpose of the recommendation?
  - To establish the appropriate levels and frequency of routine sampling and monitoring for that particular product and process.
  - Stepped down approach to monitoring, particularly for new processes with no previous comparable experience, or significant change.
  - Objective basis to meet CGMPs requirement of "statistically appropriate and representative levels"

PV Guidance recommendation - sampling/monitoring after Stage 2

- Consider complexity of product and process

- Language to be finalized PV Guidance
  - Considerations for the duration of the heightened sampling and monitoring period could include, but are not limited to, volume of production, process complexity, level of process understanding, and experience with similar products and processes.

"It met specifications"

- Conclusions from sampling and testing are probabilistic.

- Interplay between sample size, process variability, confidence desired and probability.

- The outcome from conducting a single USP test cannot be assumed for all the untested units in the batch.

USP-29 General Notices (2006)

- Test Results, Statistics, and Standards
  - "Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance.

USP-29 General Notices (2006)

Test Results, Statistics, and Standards – cont'd

- "Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, …

- "Some tests, such as those for Dissolution and Uniformity of dosage units, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. (USP, 2006)

Subpart E--Control of Components and Drug Product Containers and Closures

- Sec. 211.84
- ((b) Representative samples of each shipment of each lot shall be collected for testing or examination. **The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier**, and the quantity needed for analysis and reserve where required by 211.170.

211.160(b)

- b) Laboratory controls shall include the establishment of **scientifically sound and appropriate specifications**, **standards**, **sampling plans, and test procedures** designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

211.165(d)

- 21 CFR 211.165(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products **meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release**. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

1978 preamble - statistics references

- 392. Several comments objected to or redefined the concepts of acceptable quality level (AQL) and unacceptable quality level (UQL) used in establishing acceptance criteria and statistical quality control criteria as proposed in 211.165(d). The comments pointed out that the concepts of AQL and UQL are not uniformly interpreted, and their use in establishing acceptance criteria and statistical quality control criteria is not uniformly applied.

1978 preamble - statistics references

Comments expressed concern that the concepts of AQL and UQL as acceptance criteria are premature and not currently a part of good manufacturing practice. One comment suggested that these proposed CGMP regulations would require extensive changes in testing procedures, facilities, and use of manpower. **Several objections were raised relative to the "usually 95 percent" level of high probability of acceptance.** Respondents pointed out that this figure might be applicable for some pharmaceutical dosage forms, but would be too high for others. **As anticipated by the Commissioner, the concepts of AQL and UQL in establishing acceptance and statistical quality proved quite controversial.** From an analysis of the comments, the Commissioner believes that it is impractical at this time to establish a uniform system of AQL and UQL as proposed in the regulations. Section 211.165 is therefore **modified to allow greater latitude in establishing acceptance criteria,** while retaining the basic requirements that acceptance criteria for sampling and testing, and for acceptance levels, **be based on appropriate statistical quality control criteria.**

1978 preamble - statistics references

Response to comments regarding 211.110(b): {CONTINUED}

The Commissioner is convinced that sound statistical methodology should be applied to the procedures for testing of attributes or variables that impact on the quality of drug products and the evaluation of the results of such testing to determine acceptance or rejection of the lot. **The uses of AQL and UQL are examples of statistically derived levels for acceptance or rejection. The Commissioner believes that more study must be given to this aspect of manufacturing practice and advises that in the future FDA will invite additional industry comment regarding revision of this section.**

1978 preamble

Title 21--Food and Drugs

CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

- SUBCHAPTER C--DRUGS: GENERAL
- [Docket No. 75N-0339]
- HUMAN AND VETERINARY DRUGS
- Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding
- AGENCY: Food and Drug Administration.
- ACTION: Final rule.

- http://www.fda.gov/cder/dmpq/preamble.txt

Acknowledgements

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