

Quality Risk Management (ICH Q9)

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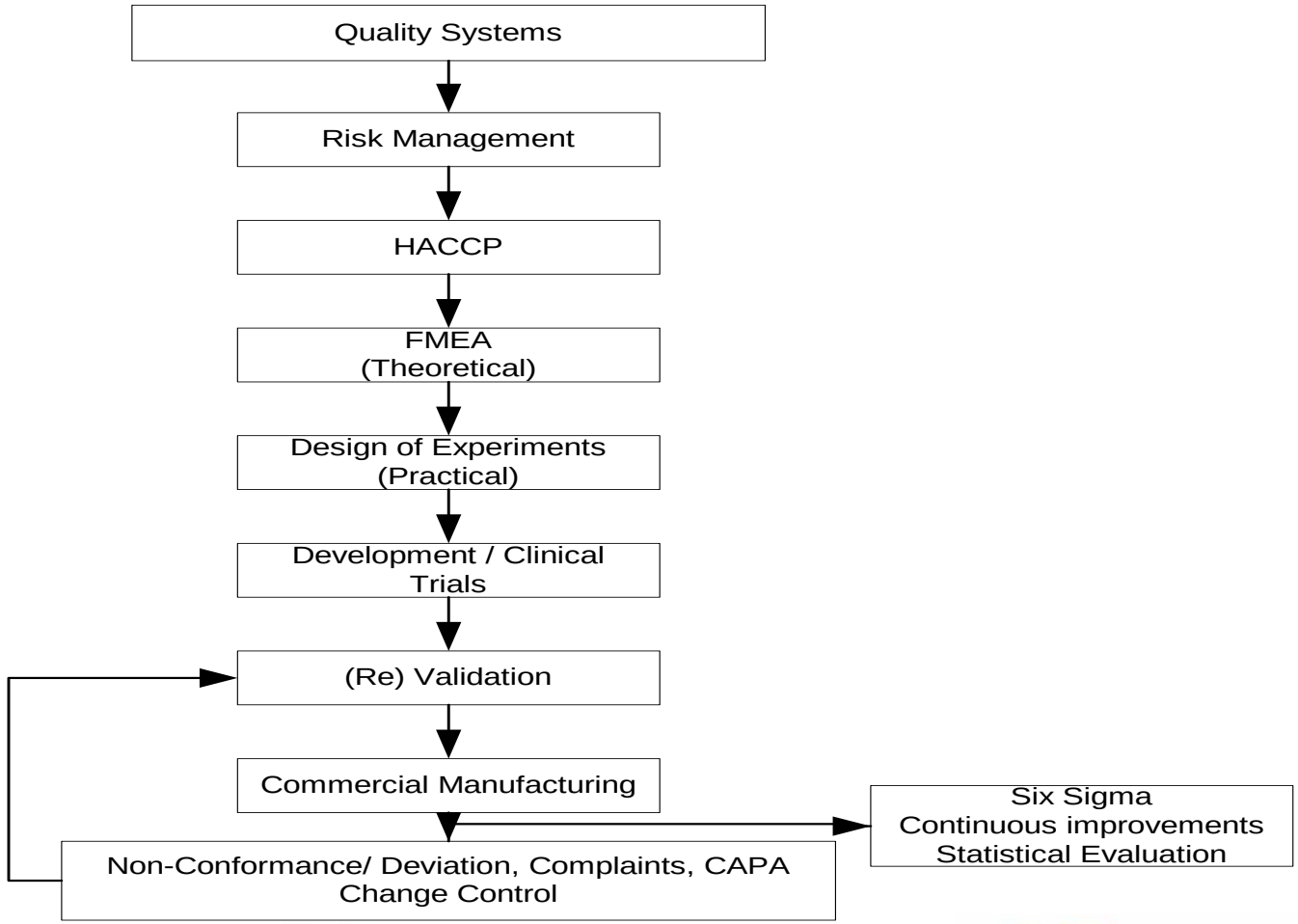
Overview



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Team Members

- Quality Assurance
- Engineers (if available)
- Regulatory Affairs
- Production Operations
- R & D (if available)

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Process Development

- Risk management
  - **Systematic** process for the **identification**, **assessment** and **control** of risks to the quality of pharmaceuticals across the product lifecycle

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Process Development

- **Risk analysis**
  - Systematic use of information to identify specific sources of harm and to estimate the risk
  - Information can include designed studies, retrospective analysis, theoretical analysis & informed opinions

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Process Development

- **Risk evaluation**
  - Compares the estimated risk against given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.
    - Quantitative e.g. (0 to 100% likelihood)
    - Qualitative e.g. “high”, “medium” or “low.”

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Process Development

- **Risk management tools**
  - Process mapping
    - The purpose of a process map is to provide a clear and simple visual representation of the steps involved in the process

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Process Development

- **Risk management tools**
  - Process mapping
    - Identify the critical equipment and potential Critical Process Parameters (CPP) as well as the areas of variation that affect the process (5 M's)
      - What are the 5 M's?

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Process Development

- **Risk management tools**
  - Failure Mode Effects Analysis (FMEA)
    - Identifies failure as a result of process step or component failure
    - Once failure modes are established mitigation is then used to eliminate, reduce or control the potential failures

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Process Development

- **Risk management tools**
  - FMEA
    - Powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures
    - A numerical rating system can be used
      - Severity of possible excursions based on each way it could fail
      - Likelihood of the each possible excursion
      - Ability to detect the excursion

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Process Development

- **Risk management tools**
  - FMEA:
    - Risk priority number (RPN) is a multiple of the relative risk
    - Scores for each of these three variables
      - Severity X Likelihood X Detectability = RPN
      - Likelihood can be based on process capability (Avg. +- 3SD) compared to specification
    - Do this for each CPP or potential CQA
    - Then prioritize based on the RPN

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Process Development

- **Risk management tools**
  - FMEA:
    - Control points where the RPN is high are considered critical
    - Create a plan using all feasible organizational capabilities to control risk at these locations

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Process Development

- **Risk management tools**
  - Design of Experiments (DOE)
    - Analyze data to determine the CPP
    - Explore potential interactions
    - Mainly used during the R&D phase
      - Also for retrospective evaluation of established parameters (Proven Acceptable Ranges).

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Process Development

- **Risk management tools**
  - DOE
    - Experimental optimization can be carried out in several ways
    - Most popular is the one-variable-at-a-time approach
    - This approach is extremely inefficient in locating the true optimum when interaction effects are present.

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QS Development

- **Risk management tools**
  - Hazard Analysis of Critical Control Points (HACCP)
    - Conduct risk management and identify preventive measures
    - Determine critical control points (CCP)
    - Establish critical limits

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QS Development

- **Risk management tools**
  - HACCP
    - Monitor each CCP
    - Establish corrective action to be taken when deviation occurs
    - Establish verification procedures
    - Establish record-keeping system

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QS Development

- Risk management tools
  - Integrated Hazard Analysis and Critical Control Point Risk Management (HACCP RM)
    - Total product life-cycle process that integrates the seven principles of HACCP management within the framework in the International Standardization Organization (ISO) 14971 Standard

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QS Development

- **Risk management tools**
  - HACCP RM
    - The foundation of HACCP RM is built upon five principles (5 P's)

      1. Policy
         - Stipulates principle and guidance on who, what and how to manage risk
         - Should include all applicable standards and regulations
         - How to determine risk

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QS Development

- **Risk management tools**
  - HACCP RM
    2. Plan
       - How to manage risk during life-cycle of each product in accordance with the policy



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QS Development

- **Risk management tools**
  - HACCP RM

    3. People
    - Roles and responsibilities of each employee
    - Process Operator
      - Primary customer for the tools and procedures
    - Engineers (Maintenance)
      - Calibration / maintenance
      - Trouble-shooting

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QS Development

- **Risk management tools**
  - HACCP RM

    3. People
    - Process Engineer (if applicable)
      - Use quality data from testing for process improvement
      - Use data for investigating deviations to find root cause
    - Quality Assurance
      - Require knowledge to make quality decisions based on data when reviewing and releasing a batch
      - Training operator
    - Specialist (if applicable)
      - Design, development, and optimization

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QS Development

- **Risk management tools**

  4. Process
     - The process consists of a four part, continuous management process
       - Analyze risk
       - Evaluate risk
       - Control risk
       - Capture & address feedback information

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QS Development

- **Risk management tools**
  - HACCP RM
    5. Paperwork
       - Records all necessary documentation for transfer of knowledge
- HACCP RM is about focusing attention on the few vital hazards that will make verifiable difference

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QS Development

- Risk management tools
  - HACCP RM Provides basis for measuring, comparing, controlling, monitoring and preventing the risks that are critical to companies performance



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QS Development

- **Six sigma (Goal)**
  - Six sigma is basically operating to near perfection
    - Six Sigma translates to 3.4 defects per million or 99.9997% perfection
    - Data driven approach and methodology for eliminating defects
  - A six sigma defect is defined as anything outside of customer specifications

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QS Development

- **Six sigma**
  - QS in place to generally capture, analyze and correct errors
  - Fundamental objective is the implementation of a measurement-based strategy that focuses on process improvement and variation reduction

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QS Development

- **Six sigma**
  - Many high technology companies are operating at four sigma which is 99.4% accuracy and translates to 6,000 defects per one million opportunities

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QS Development

- **Six sigma**
  - Six fundamental steps
    - Mistake-proof the process and eliminate wasted effort. Identify the potential errors at each step and lower the probability of those errors. Simplifying tasks, design of experiments, training to eliminate specific errors and standardization procedures.

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QS Development

- **Six sigma**
  - Six fundamental steps
    - Ensure continuous improvement by measuring and analyzing the improved process
- The annual costs of training for Motorola is over $100 million
- In 1988 versus 1987, sales were up 23% to $8.3 billion and profits were up 44.57 to $445 million

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Variability

- A process is considered well-understood when
  - All critical sources of variability are identified and explained (FMEA / DOE)
  - Variability is managed by the process
    - Process and endpoint monitoring and control tools

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Sources of Variability

- Optimize CPPs
- To isolate & identify particular causes of variability requires special experimental design and analysis

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Sources of Variability

- Limiting variation will tighten U/LSL's
- Variability reduction adds value
  - increases process capability
    - X ± 3SD (normal distribution curve)
    - Cp (centering)
- Limiting variation minimizes the risk of deviations & OOS

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Control of Variation

- Process automation
  - Reduces operator error
- Isolators, closed systems & dedicated equipment
  - Reduces environmental variation
  - Reduces cross contamination
- PAT
  - Controls variation as it occurs

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Analysis of Variation

- Analysis of Variance Tools
  - Control charts
  - Process capability
  - Normal distribution curves

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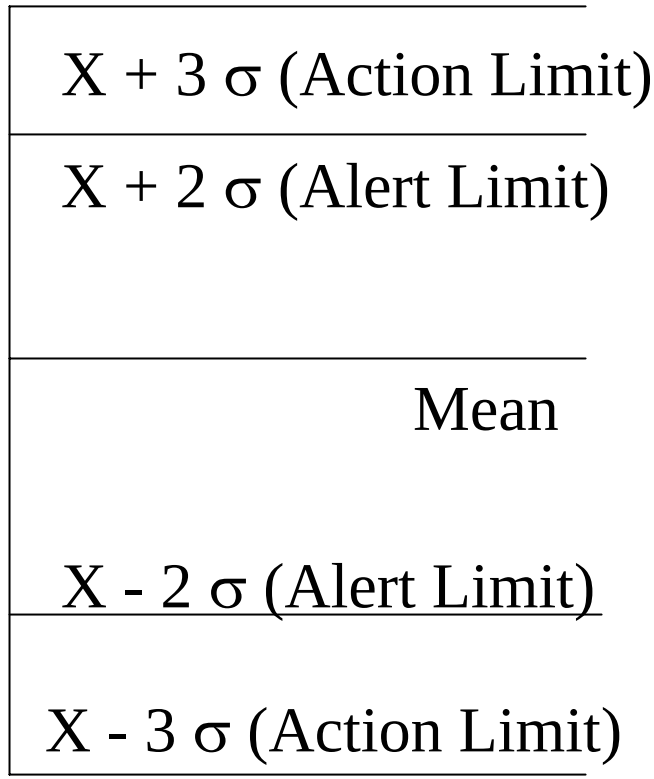
Control Chart (Within Batch)

- All critical CPPs CQAs should have control charts
- Control charts should be placed where the operator can see their performance
- Any **trend** is bad



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Trend Analysis

- Growth of non-uniformity
- What constitutes a trend
  - 2 of 3 consecutive values beyond ± 2.5SD
  - 3 of 5 consecutive values beyond ± 1.5SD
  - 8 consecutive values either below or above the mean

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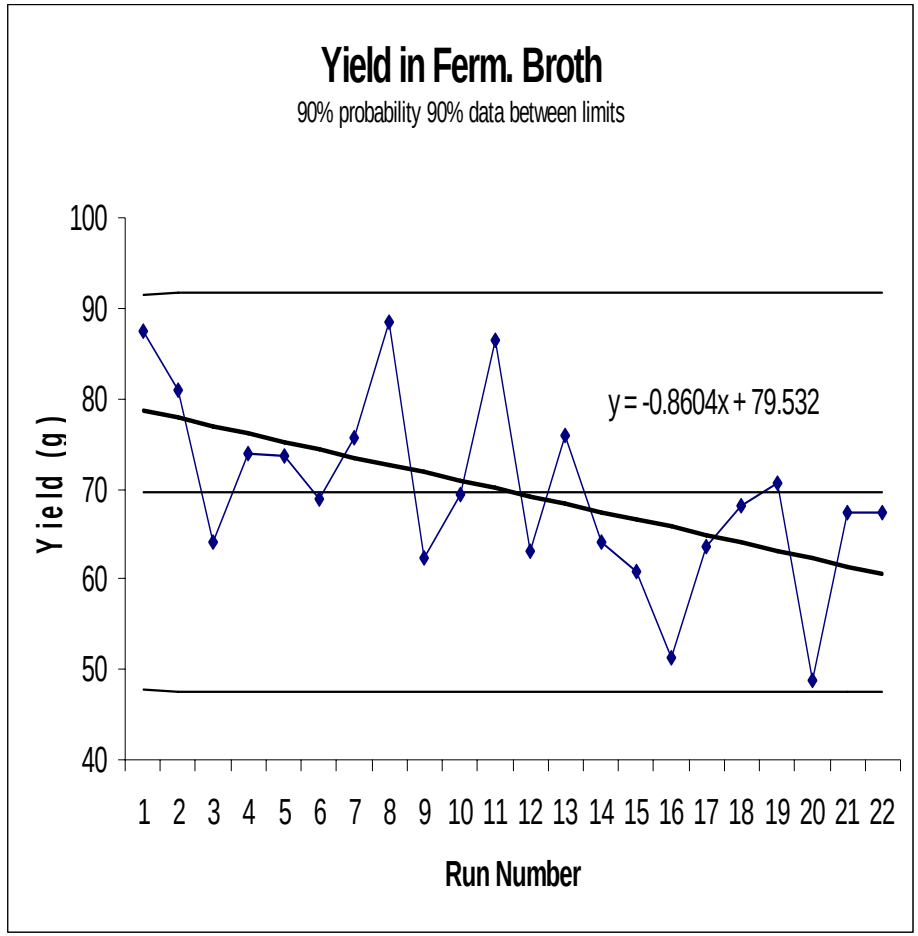
Shewart Control Charts (Between batches)

- Analyze chart for any trends
  - Equation of the line can aid in the analysis
    - y= mx + b



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Process Capability

- For variable control charts, it is often desired to include process capability indices in the summary graph
- Cp = (USL - LSL) / 6S
- Compares engineering runs to current process capabilities
- For a "capable" process, the Cp index should be greater than 1

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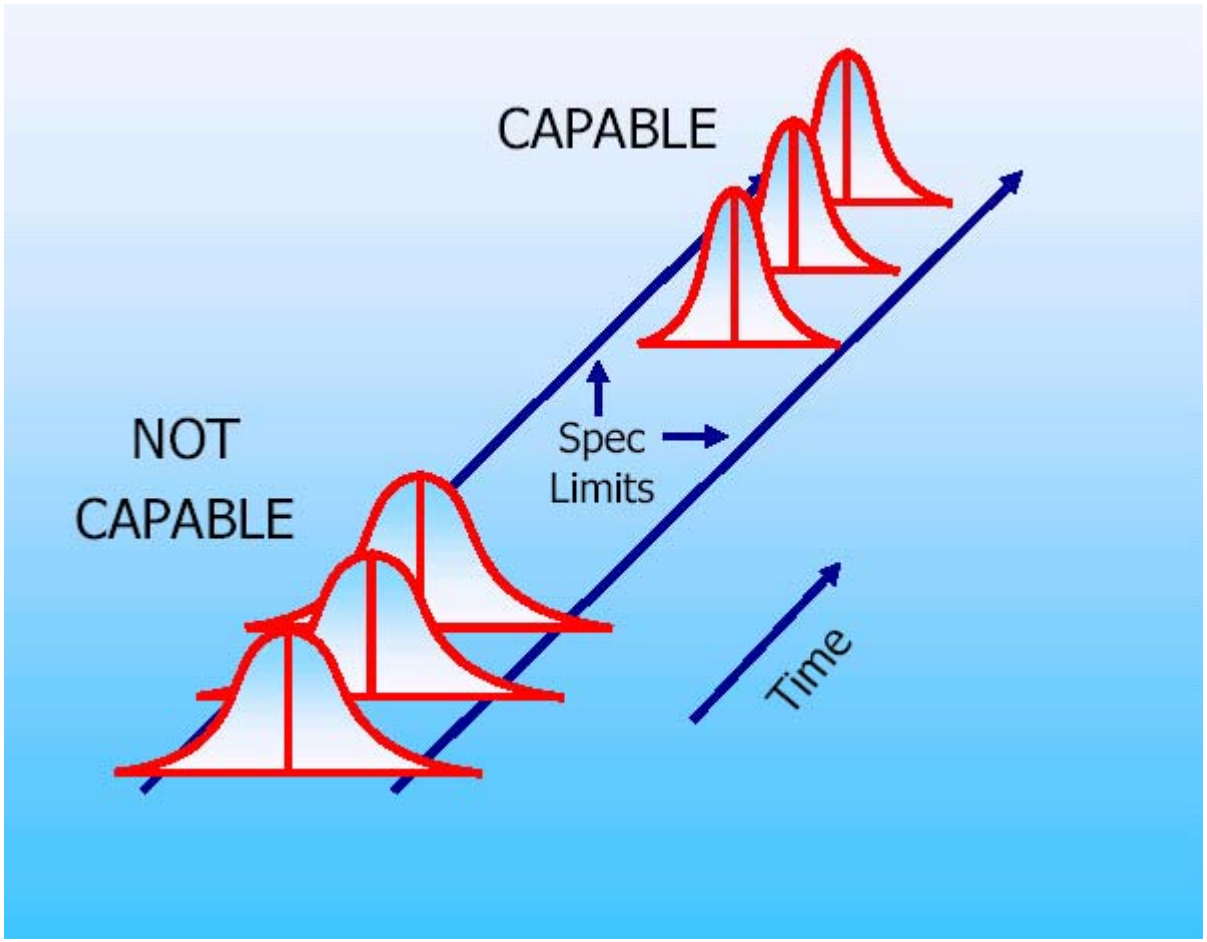
Process Capability



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Normal Distribution

- Model is a response
- The response should be the target value + random error (normally distributed)
- Errors must be normal with constant variance (trend analysis)
- Errors are independent

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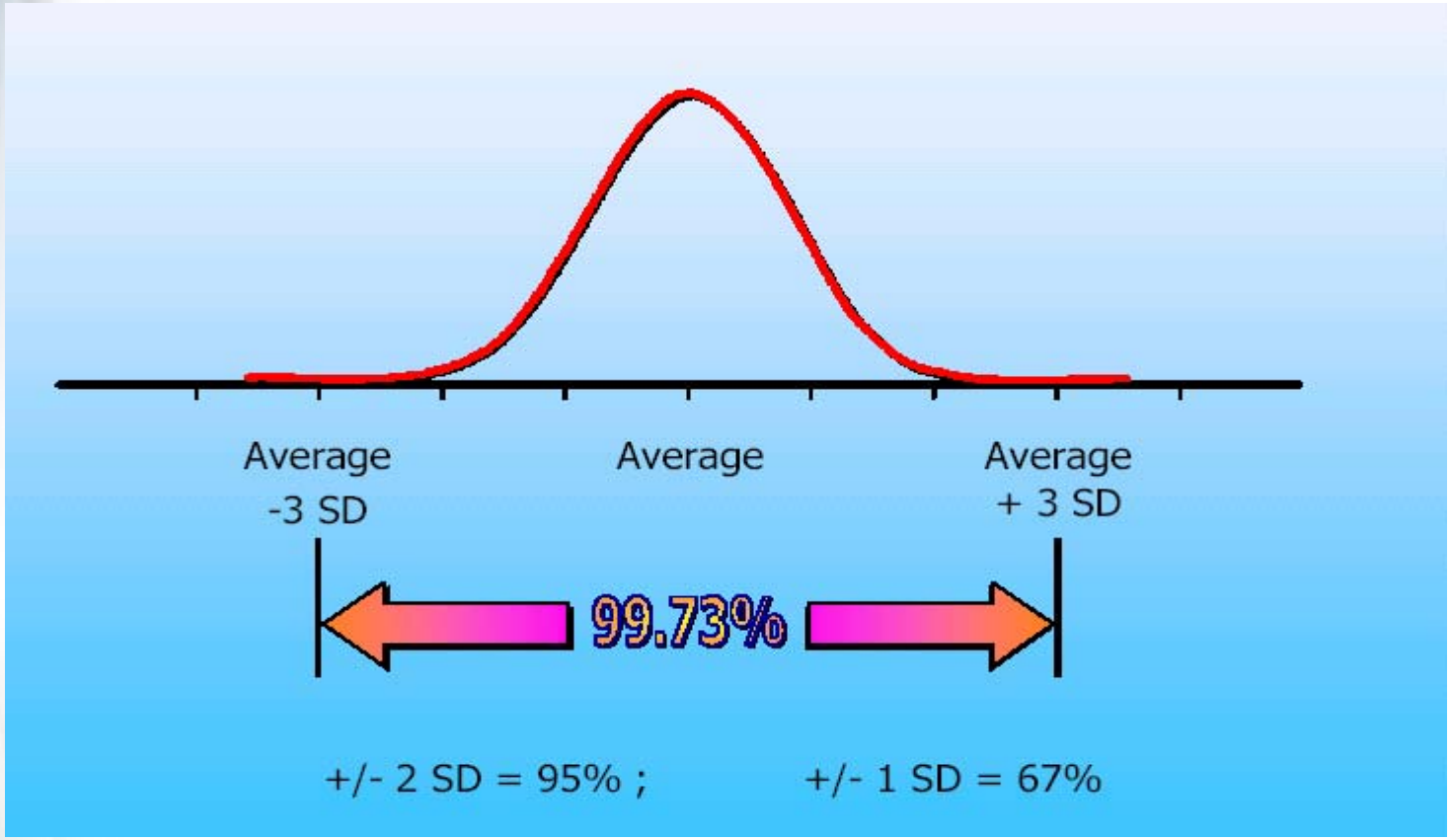
Normal Distribution Curve (Population)



Source: Process Validation Guidance, GHTF, 1999

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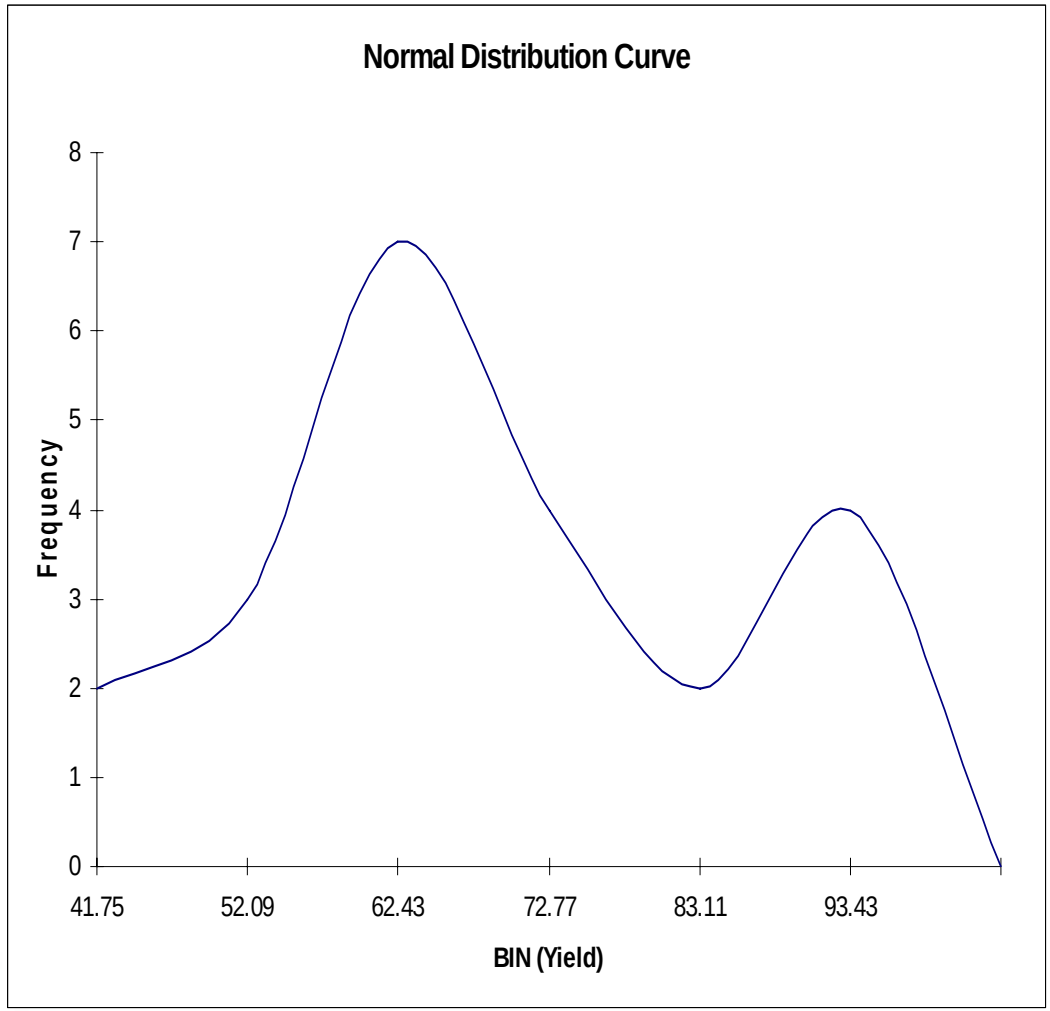
Normal Distribution

- Evaluation: Two distinct populations (Bi-modal)
- Possible reasons:
  - Sampling Methods
  - Different Inputs
    - CPPs
  - Different equipment
- Possible Solutions:
  - Try to segregate 2 populations
    - 2 different shifts
    - 2 different equipment
    - 2 different operators



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References

- ICH Q9 Quality Risk Management
- ICH Q8 Pharmaceutical Development

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