Process Validation Guidance

What Does 'Statistical Confidence' Mean?

PQRI Workshop on Sample Sizes
for Decision Making in New Manufacturing Paradigms
September 13, 2011

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Agenda

- Process Validation and the FD&C Act
- FDA's Guidance and Statistical Confidence
- Stage 1
- Stage 2
- Stage 3

Desired State of Manufacturing

- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes.
- Manufacturers strive for continuous improvement.
- FDA role: Initial verification, subsequent audit.
- No manufacturing supplements needed.

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Process Validation and the FD&C

- Process Validation is an enforceable requirement for *finished drug products*:
  - 21 CFR 211.100(a)
    - "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 shall be established to **monitor the output and validate**"

Process Validation for APIs

Process Validation for *Active Pharmaceutical Ingredients* is enforceable under the Statute.

- Statutory CGMP provision at 501(a)(2)(b) of the Federal Food, Drug, and Cosmetic Act.
  - feasible and valuable
- CGMP guidance available - ICH Q7

FDA's Current Thinking:

Guidance for Industry

Process Validation: General Principles and Practices

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

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

Stage 1: Process Design

- Stage 1 provides the following:

  1. *Building and Capturing Process Knowledge and Understanding*

  2. *Establishing a Strategy for Process Control*

- The knowledge gained in the design stage will lead to achieving confidence in your process during the next stage of validation.

Stage 2: Process Qualification

- On What Basis Can Commercial Distribution Begin?
- Before commercial distribution begins, a manufacturer is expected to have accumulated enough data and knowledge about the commercial production process to support post-approval distribution.

The Process Performance Qualification

- The PPQ is how one demonstrates the knowledge required to support distribution.
- What is FDA's current thinking on the requirements?
- Let's consult the guidance.....

From the PV Guidance:

"In addition, the CGMP regulations regarding sampling set forth a number of requirements for validation: samples must represent the batch under analysis (§ 211.160(b)(3)); the sampling plan must result in statistical confidence (§ 211.165(c) and (d)); and the batch must meet its predetermined specifications (§ 211.165(a)).

From the PV Guidance:

Recommended for the PPQ protocol:

"The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production."

From the PV Guidance:

"We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability.[18]"

Note the words stability and capability

Also, note the footnote:

Note the footnote:

Some references that may be useful include the following: ASTM E2281-03 "Standard Practice for Process and Measurement Capability Indices," ASTM E2500-07 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment," and ASTM E2709-09 "Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure." This is not a complete list of all useful references on this topic. Many industry standards, books, and guides on these topics are available.

Some examples of statistical tools

- From ICH Q9:
  - Design of experiments (DOE)
  - Histograms
  - Pareto charts
  - Control charts
  - Process capability analysis

- There are many other tools available.

The Bottom Line:

- You can use appropriate, recognized, standards and methodologies when designing and analyzing your process validation data.

- However, your process validation sampling plan should be adequate to demonstrate sufficient statistical confidence of quality.

How can the data show confidence?

- So, your sampling plan,
- What does the data need to demonstrate prior to distribution?

- From before:

1. Process Capability
2. Process Stability

Process Capability

- Question: Can the system consistently make product that meets specifications?
- Commonly used Statistical Tool: Process Capability Studies.
- Targets:
  - The demonstrated CPK ensures that Critical Quality Attributes (CQAs) are consistently met.
  - The CPK meets requirements of other steps in the process, particularly for in process data.
  - Remember, "The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination"

Process Capability

Points for Consideration:

- What is you lower bound on your CPK confidence interval?
  - This is tied to the adequacy of your sampling plan.
- Are all the criteria met to analyze the data using this tool?
  - Is the data normal?
  - If the data was transformed, were the specifications transformed accordingly?
  - Was the data collected under homogenous operating conditions – i.e. stability

Process Stability

- Question: Can the system consistently make product that meets specifications?
- Commonly used Statistical Tool: Control Charts
- Unlike capability studies, time is taken into consideration.
- Targets:
  - The system is stable under controlled conditions.
  - Control limits do not exceed CQA specifications.
  - The variation is constant over time.
  - As before, "The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination"

Process Stability

Points for consideration:

- Does the system ensure consistent product, even with varying inputs?
- Do finished attributes "drift" within specifications, or are they stable over time?
- Are you seeing natural variation or special cause variation?
- Do you see acceptable time based variation both within batches and between batches?

So what's next?

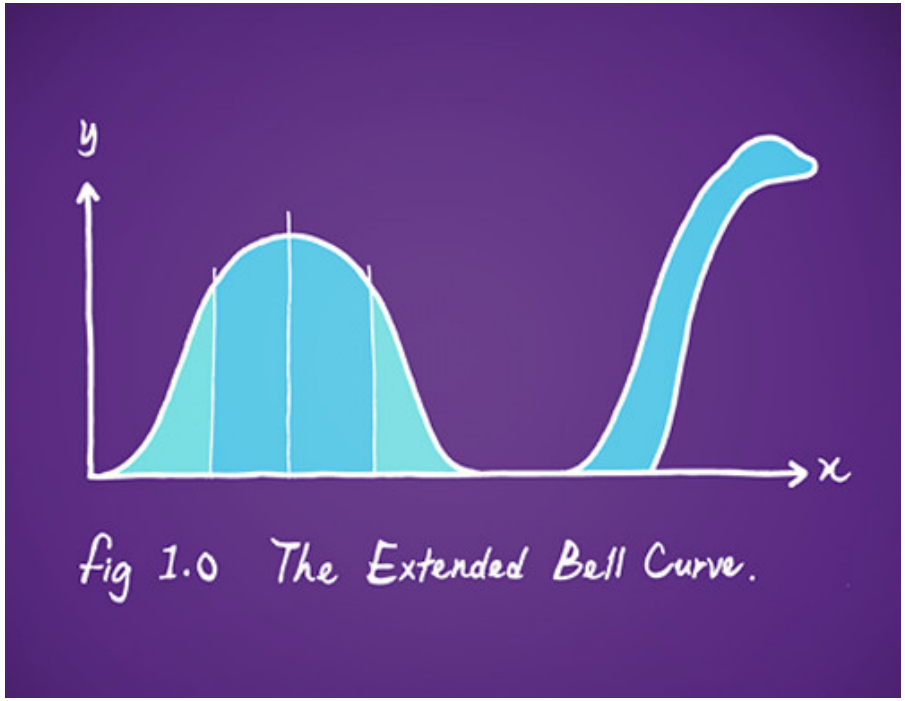
- The sampling plan was adequate
- The system is stable
- The system is capable

- Reviewed by quality

- Cleared for distribution

Stage 3: Continued Process Verification

- During commercial manufacturing
- Perform activities to continually assure that the process remains in a state of control.



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

What the regulations say:

- Sampling and Statistics (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.

What the regulations say:

- Sampling and Statistics (21 CFR 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. Examination and testing of samples shall assure that the drug product and in-process material conform to specification.

What the PV guidance says:

"We recommend that the manufacturer use quantitative, statistical methods whenever appropriate and feasible. Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program under § 211.180(e)."

So, what does 211.180(e) specify

- 211.180(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.

So what does all of this mean?

- Every batch manufactured provides more data.
- With more data, one can enhance process and product understanding
- It is the manufacturer's responsibility to update the following accordingly:
  - Specifications
  - In process or manufacturing controls
  - Sampling plans

In Closing

- Process Validation is required of drug manufacturers
- Confidence is required prior to distribution of product
- Ongoing process verification optimizes a validated process

Every batch, Every day…

We rely upon the manufacturing controls and standards to ensure that time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality…"

Janet Woodcock, M.D., Director
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Acknowledgements

- Tara Gooen
- Grace McNally
- Karthik Iyer
- Brian Hasselbalch

Questions?

For more CGMP information…

CGMP Subject Contacts

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm

Questions and Answers

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm