FDA's Guidance for Industry Process Validation: PDA Metro Chapter June 8, 2011

James Agalloco, Agalloco & Associates
Scott Bozzone, Pfizer Inc.
Phil DeSantis, Merck & Co. Inc.
Nate Manco, EcoAnimalHealth, Moderator

Agenda

- Three Brief Presentations on Key Issues
  - Scott Bozzone
    - Number of PPQ Batches
    - Statistical Tools
  - Phil DeSantis
    - Equipment & Facility Impact
    - Change Control
  - Jim Agalloco
    - What's the real scope of the Guidance
    - FDA's Perspectives on Stage 1
    - Did you notice there's a Stage 2½?

Scott Bozzone

Example: Screening DOE in Stage 1

DOE: Efficient method to evaluate the impact of input variables and process parameters (on product CQAs) and their interactions (not just correlations)

Critical input variables/process parameter:
- Polymer concentration
- Roll gap
- Roll force

Intermediate attributes:
- Porosity
- Compressibility

CQAs:
- Dissolution
- Hardness

● Center point

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Discussion Points

Number of PPQ batches ? (Stage 2)

Statistical Tools (any Stage)

Impact of the Sample Size in Stages 1, 2, 3

The statistically appropriate sample size for estimating the population statistics depends on:

- Type of Data - Discrete/Attributes (counts) or Continuous (values)
- Required Statistical Test or Inference
- Standard Deviation or its estimate
- Required Precision or Difference – the acceptable error in estimates, or the desired minimum difference detectable between one or more populations.
- Power - the required probability for detecting a given Difference between two or more groups, when one exists (associated with type II error in Hypothesis testing, typically set at 80%)
- The Confidence Level (usually 95%, associated with type I error)
- Other factors (e.g. Statistical Process Control)

Example: Release Criteria 1: Fill Weight Avg (Stage 3)

◆ The PpK of 1.19 means that the process is capable of meeting the spec 1.232 to 1.341 g/vial.

Process Capability Sixpack of FILL AVERAGE-GP0143$11 (G/VIAL)

Example: Statistical Analysis for a Regulatory Change in Stage 3

Justify deletion of in-process blend potency test

	Product Potency	Average	Range for evaluated lots	Standard deviation	Capability Index	Specification
Blend	25 mg/g	25.0	24.4- 25.5	0.04	1.24	95-105% (23.8- 26.3)
Tablet	2.5 mg	2.46	2.41- 2.55	0.03	2.01	90-110%(2.25- 2.75)
	5.0 mg	4.92	4.83- 5.08	0.05	2.68	90-110% (4.5- 5.5)
	10.0 mg	10.0	9.7- 10.5	0.10	1.69	90-110% (9.0-11.0)

N = 30 lots for blend and tablets; Blend spec is an internal limit.

The Process Capability index values of Tablets (all three strengths) are above 1.67 which are typical of a strong capable process. Blends of 1.24 are typical of a consistent process.

Conclusion: In-process blend testing was shown to be redundant and was approved to be deleted as it did not provide any further assurance of quality.

Examples of Sampling Plans in Stages 1, 2, 3

- **Compendial (e.g. USP <905>, <1010>)**
- **ANSI/ASQ Z1.4 *Sampling Procedures and Tables for Inspection by Attributes* (formerly MLD_STD 105E)**
- **ANSI/ASQ Z*1.9 Sampling Procedures and Tables for Inspection by Variables* for Percent Nonconforming (formerly MLD_STD 414)**
- **Representative throughout batch(es)**
  - Practical and rationale (e.g. Beg, Mid, End, interruptions)
  - Blend Uniformity Analysis (e.g. US FDA-Stratified sampling)
  - $\sqrt{N}+1$ (small lot sizes)
- **Expanded Sampling, Medium sample sizes (e.g. 30-100)**
  - DIJournal, Vol 43, 298-298 (2009), PhrMA –(not fully endorsed)
- **ASTM E122-09, "Calculating Sample Size to Estimate, with Specified Precision the Average for a Characteristic of a Lot or Process"**

Other References

- ASTM E2281-08(a) Standard Practice for Process and Measurement Capability Indices (Stage 3)- Describes CpK and PpK
- ASTM E2709-09 "Demonstrating Capability to Comply with a Lot Acceptance Procedure" - Using statistics for setting multi-stage specifications
- ASTM E2334- Sample size and confidence; Sample size and fraction non-conforming.
- ASTM E2587- Statistical Process Control Charts (stage 3 and 2)
- NIST Engineering Statistics Handbook
  http://www.itl.nist.gov/div898/handbook/

Phil DeSantis

Facilities and Equipment

- Even the best process will not work in wrong or sub-standard equipment
- Facilities and utilities play an equally important role
- Equipment must reliably meet its intended purpose
- Equipment Qualification required per Stage 2
- EQ is really also a three-stage effort

Facilities and Equipment

Stage 3 – Change Control

Product/Process Requirements

Quality Critical Attributes CQAs, CPPs, Design Space Regulations

Qualify

Engineering (Functional) Specs

Commissioning

Design Details

FAT, SAT

Stage 1 - Design

Stage 2 - Qualify

Change Control

◆ Stage 3
◆ Applies to process, equipment, facility/utilities
◆ "Risk-driven"
 - Rigor dependent upon product/process impact
 - Relate to CQAs, CPPs, Design Space
◆ "If everything is critical, then nothing is critical."
◆ *Some* changes drive return to Stage 2 (or maybe Stage 2½)

Jim Agalloco

In or out of Scope?

Activity	Stage I	Stage II	Stage III
Utilities	🟥	🟨	🟩
Environments	🟥	🟨	🟩
Computerized	⬛	⬛	⬛
Clean / Prep	🟩	🟨	🟥
Inspection	🟥	🟨	🟥
Manual	⬛	⬛	⬛
Sterilization	🟨	🟨	🟥
Aseptic Processing	🟥	🟥	⬛

Excellent 🟩　Good 🟨　Poor 🟥　Not Applicable ⬛

Stage 1

- A clear expectation for QbD for all processes. This places a much increased burden on resource constrained firms.
- Throwing it over the wall is not an option.
- Technology transfer between organizational units, sites and companies will be increasingly important.
- Look closely at ICH Q8 – Pharmaceutical Development.
- The tools are all widely known, is the commitment there to use them?

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Current vs. QbD Approach to Pharmaceutical Development

C. Chen & C.Moore, FDA - 2006

Current Approach	QbD Approach
Quality assured by testing and inspection	Quality built into product & process by design, based on scientific understanding
Data intensive submission – disjointed information without "big picture"	Knowledge rich submission – showing product knowledge & process understanding
Specifications based on batch history	Specifications based on product performance requirements
"Frozen process," discouraging changes	Flexible process within design space, allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on robustness – understanding and controlling variation

Stage 1: Process Design

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- Building and Capturing Process Knowledge and Understanding
  - Initially happening contemporaneously with product development. This PV GFI focuses on the 'manufacturing process' and does not attempt to address product development. Product and process design are linked and overlap at points in the lifecycle.
  - ICH Q8R2, ICH Q9, other standards and guidances are relevant and useful.

Grace McNally, FDA – April 13, 2011

There's a Stage 2½?

- Stage 2½ - sampling and testing of batches as in Stage 2 with release on an individual basis (real-time comparison to all prior results). When variability is understood and routine sampling plan established this changes to ----->

- Stage 3 - sampling on a lower level with release on an individual basis (real-time comparison to all prior results).

- Validation life-cycle support activities – change control, calibration, preventive maintenance (similar to what is currently done). On major change revert to Stage 1 for redevelopment and Stage 2 for new PPQ and eventually Stage 3.