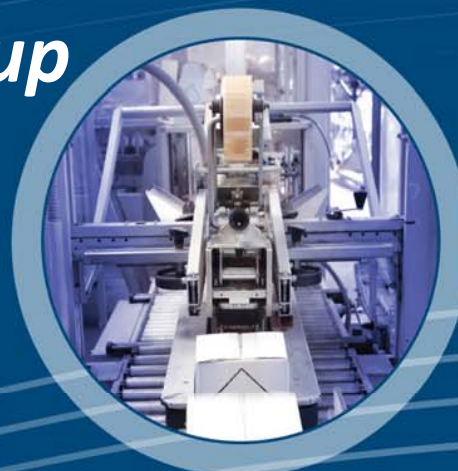




Connecting People, Science and Regulation®

# ***FDA Process Validation Guidance and the PDA Process Validation Interest Group***



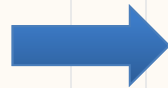
Parenteral Drug Association  
New England Chapter  
Process Validation and FDA Guidance  
Woburn, MA  
March 14, 2012

Hal Baseman  
ValSource LLC



# History of Process Validation

Way in the beginning



Sort of Modern Times



Today

Outbreaks of E. cloacae and Erwinia contam. in LVP bottles ('70-71)

FDA Process Validation Guide Draft Revision Nov. '08

FDA Process Validation Guide Final Jan. '11

Concept of validation proposed by Byers and Loftus,

FDA Process Validation Guide May '87

FDA Aseptic Process Guide Sept. '04

PDA PCMO Process Validation TR 2009 - ?

# 1987 FDA Guidance on General Principles of Process Validation

- Reflection of industry best practices
- Defined:
  - Concurrent, prospective, and retrospective validation
  - IQ, OQ, PQ
  - Worst case
  - Re-validation
  - Process validation (multiple batch demonstration)

# Process validation definition

- *... establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.*
  - '87 FDA Process Validation Guidance

# process performance

- If process validation provides a high degree of assurance that the process works reliably and predictably, then why do processes fail in during commercial manufacture?
- Because *stuff* happens...

*Stuff* = Process Variation

# FDA draft Process Validation Guidance

- Notified industry in 2006
- Issued in draft Nov. 17, 2008
- “reflection of industry practice”
- PDA SAB formed a committee to collect and collate member comments

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## Guidance for Industry

### Process Validation: General Principles and Practices

#### *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Brian Hasselbalch or Grace McNally (CDER) 301-796-3286 or 301-796-3279, Christopher Joneskis (CBER) 301-827-0373, or Dennis Binsley (CVM) 301-827-6956.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Veterinary Medicine (CVM)

November 2008  
Current Good Manufacturing Practices (CGMP)

# Process Validation Definition

- *... establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.*
  - *'87 FDA Process Validation Guidance*
- ... the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.
  - '08 Draft revision to FDA Process Validation Guidance

# Life Cycle Approach

## Stage 1 process design

Process design



**PROCESS  
VALIDATION**

Control strategy



Process monitoring  
need for  
improvement

**Stage 3  
continued process  
verification**



**Stage 2 process qualification**





# Process Design

*(Obtaining information on process capability and variability from process development efforts)*

- Commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Building and capturing knowledge and understanding on process capability and variability from process development efforts
- DOE to identify and establish process parameter relationships and sources of variability
- Risk assessment can be used to minimize and prioritize effort
- Develop process control strategy

# Process Qualification

***(Gaining enough confidence in process to commercially distribute product)***

- During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
- Facility and Equipment qualification
- Process performance qualification
  - Number of batches not an acceptance criteria, but a way to obtain data

# Continued Process Verification

*(Using information obtained about the process after commercial distribution to confirm that it is under control - pretty good way to “validate”)*

- Ongoing assurance is gained during routine production that the process remains in a state of control.
- Using information obtained about the process after commercial distribution to confirm that it is under control
- More than annual product review
- Allows for mid-course correction and improvement

# PVG points

- Validation is a continuous process of evaluation, rather than an event
  - Understanding and controlling process variation is a key to process control
  - Process variables can and should be gleaned from process development information
  - The more you do in the early stages to understand the process, the less you will need to do to confirm it later

# PVG points

- Decisions should be based on sound scientific and risk to quality related information
  - Emphasizes use of sound statistically based information
- Facility and equipment must be qualified and shown to be reliable and suitable
  - Methodology left to companies
- Legacy processes must be under control
  - Focus should be on Stage 3

# PVG points

- Re-validation and worst case are not defined in the new guidance
  - Consistent with concept that process validation is on-going demonstration of anticipated process parameters and conditions
- Stage 3 continued process verification should involve enhanced sampling
  - Based on risk factors: experience, criticality

# The industry reaction

# The draft comment process

- Initial comment period 60 days
- 400 plus comments sent to PDA throughout December
- Christmas ruined



# Categories of PDA comments

1. Wording and Terminology
2. Approach and Assurance for Commercial Distribution
3. Viral and Impurity Clearance
4. Concurrent Release
5. Scope and Legacy Systems
6. Qualifications, Documentation, Organization, and Regulatory Impact

## 2009 PDA workshops

- March 4, San Francisco
- March 9, Munich, Germany
- April 23, Las Vegas
- June 8-9 Chicago, Ill
- Sept 16- Wash. DC Interest group
- October 26-27, Bethesda, MD
- Nov 20, San Juan, PR

# Process validation questions

- What are the process variables, the things that will cause the process outcome to vary? Are these variables understood and adequately controlled?
- How does your validation prove that the process is under control?
- Does running 3 batches mean that that process is valid and effective?

# It's up to industry to decide how to validate process

- Establish methods to prove their processes are under control
- Determine variability and confirm control
- Reliance on pre and post “PQ” information
- Need for statistical analysis as scientific evidence

# Feedback...

- What we've been asking for...
  - It is what we are – or were supposed to be doing all along...
  - Nothing has really changed...
- 
- *We just spent 30 years being told that validation was all about documentation. Now you want us to switch to a science...*

**January 24<sup>th</sup>, 2011 - final version issued**  
**More industry reaction**

# The life cycle approach to knowledge acquisition

- Process understanding is needed to identify and control process variables
- Process design is key to effective process performance
- Process performance is key to process validation
- The more you do in stage one – the more the process is understood – and the less you may need to do in stage three
- What will regulators expect to see?
- Will inspectors be trained and consistent in expectation?
- How will legacy systems be treated?

# Stage 1 - industry challenges

1. When does S-1 start?
2. What information is needed to understand process?
3. What mechanisms must be set for knowledge transfer between process development and manufacturing
4. How to identify process variables and design adequate control strategies
5. Allocation of resources to determine variables and understanding at process design



# Stage 2 - industry challenges

1. When do you have the confidence to go into commercial manufacture?
2. *What information is required to provide assurance that processes are controlled prior to release for commercial manufacture?*
3. How much data and what type of data is needed and how to interpret that data?
4. How to determine confidence levels for process control?
5. How many batches?

# Stage 3 – industry challenges

1. How to develop an effective program for acquiring and evaluating post commercial manufacturing information?
2. What information to look for?
3. How much data, what type of data, and how to interpret that data?
4. How will OOS, deviations, and process “improvements” be viewed?
5. How much sampling for how long?

# April 2011 workshop feedback

- Wait and see
- Training in guidance content and concepts needed
- Establishing better technology transfer programs
- Gap analysis of current approach to guidance approach
- Set up matrices to evaluate control of process variables and overall process performance for legacy
- Identify and leverage sources of information
- Case studies not easy to find, may be early in process
- Companies may be doing more than they think

# What's the big deal?

- Some still be leaning towards the philosophy that  
If you can do something right three times ...  
you should be able  
to do it that way all  
the time.

# Where do we go from here?

- F2F meeting to address comments February 29<sup>th</sup>  
Tampa
- Continued PV IG focus at PDA Annual
- Chapter meetings in  
Texas, New England
- Publication Q2-3 2012
- TRI course April 2012

Thanks for your attention