Overview of the recent FDA Process Validation Guidance for Medicinal Product Development and Manufacture

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Overview of the FDA PV Guidance

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DIT, Kevin St.

Current Regulatory Science Research

- Quality Risk Management (QRM) Toolkit
- Research on impact of Uncertainty and Subjectivity in the assessment of risks to quality
- Process Analytical Technology (PAT) R&D on imaging technologies for use in blending, granulation, roller compaction/milling, compression and packaging processes
- Development of a ICH Q8,9,10 Implementation Methodology and Lean Six Sigma Toolkit
- Research on Knowledge Management tools for capturing, generating and enhancing scientific knowledge
- Research on impact of new US & EU regulations on Process Validation (PV) for pharmaceutical manufacturers

Regulatory Science

- Developing new tools, standard and approaches to ensure the safety, efficacy, quality & performance of regulated products

*Advisory Regulatory Science at PDA

The PSRT at DIT is engaged in Regulatory Science research into the development of implementation and technology solutions for the pharmaceutical manufacturing industry to enable those involved in the manufacture of drug products to meet the expectations of the international pharmaceutical regulatory community.

The PSRT actively engages with industry and regulators to focus on addressing the challenges and opportunities of implementing Science and Risk based manufacturing approaches.

See: http://www.dit.ie/chemistry/research/psrt/
Process Validation: Some Fundamentals

“A phenomenon will be said to be controlled when, through the use of past experience, we can predict, at least within limits, how the phenomenon may be expected to vary in the future”

Shewhart - Economic Control of Quality of Manufactured Product, 1931

Key Publications

Timeline
FDA’s *Guidance for Industry* on Process Validation has been welcomed for:

1. The clarity of its integrated 3 stage lifecycle process
2. Its emphasis on the need for effective scientific knowledge led programs
3. The elimination of the ‘3 Golden Batches’ concept.

**Process Validation - Shift in Emphasis over 25 years?**

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>1987</td>
<td>Process Validation is 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.</td>
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*process validation is defined as 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.*

**What’s in Scope?**

- Human Drugs
- Veterinary Drugs
- API’s
- Drug element of a Combination Product
- Biological’s

**What’s out of Scope?**

- Human Tissue
- Medical Devices
- Type A Medicated Articles / Feeds
- Dietary Supplements
- Investigational Medicinal Products *

* See Note 3: Page 2. Commercial manufacturing processes do not include clinical or treatment IND materials.
Where are the Challenges?

- Science and Risk based PV/PPQ requires product and process understanding, good science, statistical confidence
  - Statistically based sampling plans and acceptance criteria
  - Determination of the number of PPQ/PV batches
- Acceptance criteria across batches
- Validation level sampling and testing beyond PV exercise
- Decision to release PV/PPQ batches based on stage 1 and stage 2 criteria
- Application across broad spectrum

"Effective Process Validation contributes significantly to assuring drug quality"

Basic Principles of Quality Assurance

A drug should be produced that is fit for its intended use;
- Quality, safety, and efficacy are designed or built into the product
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing
- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications

FDA encourages the use of;

Modern Pharmaceutical Development concepts

Product Lifecycle Approach

1. Modern Pharmaceutical Development concepts
2. Quality Risk Management
3. Quality Systems at all stages of the manufacturing process lifecycle

The guidance supports process improvement and innovation through sound science

Ongoing Continuum....

Validation of the process is not a ‘one off’ event but represents an ongoing continuum of scientific knowledge development and ongoing assurance.

"Knowledge gained from development is the foundation for process validation"
ICH-IWG Point to Consider Document Dec 2012
One important point of distinction between the PV guides is that they are written to address different purposes:

- The FDA guidance outlines principles and approaches manufacturers can use to validate the commercial manufacturing processes for drug products.

- The EU draft PV guideline provides information relating to process validation that should be considered as part of the dossier submission, when applying for a Marketing Authorisation and as such is mainly aimed at the pharmaceutical assessors.

- The proposed update to Annex 15 of the EU GMP Guide: Qualification and Validation will contain the details associated with the actual qualification and validation studies undertaken at commercial scale prior to release of product into the marketplace.
Both US and EU guides emphasize the importance of the links between:

1. Product and process design and development
2. Qualification of the commercial manufacturing process
3. Maintenance of the process in a state of control during routine commercial production

Knowledge is the key...

- Both EU and US guidelines note that the success of the validation program will hinge upon the quality and depth of the product and process understanding gained, largely during the development phases of the lifecycle.

- The importance of utilising the knowledge gained through the application of scientific approaches (ICH Q8) and quality risk management (ICH Q9) to the development of a product and its manufacturing process is emphasized.

Understanding Variation

The FDA guide gives specific recommendations on using this knowledge to:

- Understand the sources of variation within the process
- Detect the presence and degree of variation
- Understand the impact that variation has on the process and ultimately on the product attributes

General Considerations for PV

Importance of making the entire process validation program more effective and efficient

- Good project management
- Robust scientific knowledge collection, management and archiving
- Uniform collection and assessment of information methods
- Reducing the burden of redundant information gathering
- Use of an integrated team approach
- Appropriately documented and planned studies
- All attributes and parameters should be evaluated and reevaluated as new information arises
- Criticality should be viewed as a continuum rather than binary
- Statistical assessment of data capability
3 Stages of Process Validation

Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Stage 2 – Process Qualification

1. Design of a Facility and Qualification of Utilities and Equipment
2. Process Performance Qualification (PPQ)
3. PPQ Protocol
4. Protocol Execution and Report

Stage 1 – Process Design

Design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.

- a. Building and Capturing Process Knowledge and Understanding
- b. Establishing a Strategy for Process Control

Approved for Commercial Distribution

The decision to begin commercial distribution should be supported by data from stage 1 and stage 2.

Batch A
Batch B
Batch C

Released Product and Continued Process Verification

How Many?

Batch A
Batch B
Batch C

Facility and Equipment ‘Qualified’

Products manufactured during this stage, if acceptable, can be released.

Role of QA
Enhanced Monitoring
Fit for Intended Use

GMP/Non-GMP
Variability
DCE
PAT
Commercial Scale Functionality and Constraints
Approved for Commercial Distribution

The decision to begin commercial distribution should be supported by data from commercial batches.

Facility and Equipment ‘Qualified’

Released Product and Continued Process Verification

4 Batches

Stage 3 – Continued Process Verification

Continuously assure that the process remains in a state of control (the validated state) during commercial manufacture.

- Detection of Process Drift
- Ongoing program to collect and analyze product and process data that relate to product quality
- Statistician led analysis
- Detection, control, and/or mitigation strategies
- Continued enhanced monitoring
- Process Optimization
- Maintenance

Approved for Commercial Distribution

The decision to begin commercial distribution should be supported by data from commercial batches.

Facility and Equipment ‘Qualified’

Released Product and Continued Process Verification

? Batches

Success...

The success of the validation program will hinge on the quality of the knowledge gained, developed and enhanced.

- Knowledge *gained* in the product and process development stage
- Knowledge *developed* during the validation studies
- Knowledge *enhance* throughout the ongoing routine manufacture and distribution
Deming’s System of Profound Knowledge

Deming advocated that all managers need to have what he called a System of Profound Knowledge, consisting of four parts:

- **Appreciation of a system**: understanding the overall processes involving suppliers, producers, and customers (or recipients) of goods and services
- **Knowledge of variation**: understanding the range and causes of variation in quality
- **Theory of knowledge**: the concepts explaining knowledge and the limits of what can be known
- **Knowledge of psychology**: understanding the concepts of human nature.

Source: ISPE C&Q Seminar June 2008 Washington—Good Engineering Practice, Nuala Calnan

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Effective Process Validation contributes significantly to assuring drug quality

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Source: Dr. K.O’Donnell, GMP & Market Compliance Info Day, September 2012
IMB Analysis: Serious Quality Defects 2004-2011

**US FDA Recall Statistics**

Q1 2013, 107 drug and pharmaceutical recalls, an increase of 32% from the previous quarter and higher than the average number of events last year.

Dramatic increase of Class I recalls of prescription drugs, which increased by 100% compared to the Q4

**FDA Commissioner Margaret A. Hamburg quoted recently**

Impact of Globalisation in supply *

- 40% of finished pharmaceuticals
- A staggering 80% of the active ingredients used in the drugs consumed in the US come from abroad.

"Today we recognize that to successfully protect U.S. public health, we must think, act, and engage globally. Our interests must be broader than simply those within our own borders."

Product Quality **

Without product quality, none of us can feel confident that the product will be either safe or effective. These concepts go hand in hand. And unfortunately, we’ve seen far too many quality lapses throughout the pharmaceutical industry over the past few years. ... they are warning signals that we can and must do more.

That’s why we’ve chosen to make quality one of our highest priorities this year and we’d like you to do the same."

*Source: Dr. K.O’Donnell, GMP & Market Compliance Info Day, September 2012


**Source: Address to the Annual Meeting Generic Pharmaceutical Association, the Prioritization of Product Quality. FDA: Feb 22 2013.

**Process Validation: Examples of Deficiencies**

1. Poor controls in place for the identification of CPPs
2. Poor linkages between risk assessment activities and PV protocols
3. Insufficient extent of PV testing performed
4. Lack of good science when defining PV acceptance criteria
5. Poor critical evaluation of PV data
6. Lack of good science used in designing PV protocols
7. Insufficient sampling activities
8. Lack of review of validation status following the receipt of important new data
9. Actual manufacturing processes not supported by PV data
10. Poor use of concurrent validation

**Source: Dr. K.O’Donnell, GMP & Market Compliance Info Day, September 2012**
Questions and Answers

Acknowledgements

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