

Pharm**Out**



FDA's PV Guidance: The Guidance, the Regulator and the Manufacturer

The US FDA PV Guidance

Some clarifications:

- Does not cover regulatory submissions but addresses GMP expectations
- It is a “guidance” and therefore not legally binding
- Alternative approaches to validation are acceptable

The Guidance: Historical Perspective

A product of US FDA's initiative of Sept 2002 to enhance pharmaceutical cGMPs for 21st century

- Implementation of scientific and risk based approach to pharmaceutical manufacturing and product quality
- Greater focus on process and product design
- Involvement of experts from international regulatory agencies, consumer, government, academia and industry groups in preparation of guidance documents

The Guidance: Historical Perspective

US FDA 1987 definition of PV:

“...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 attributes”

The Guidance

US FDA 2011 definition:

“... collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.”

The Guidance

New philosophy, concepts

- QbD
- risk management
- lifecycle
- science
- knowledge and understanding

The Guidance

The Guidance recommends that manufacturers:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product.

The Guidance

FDA current thinking on PV revolves around

- The concept of product lifecycle:
 - **Stage 1** – product and process development;
 - **Stage 2** – the manufacturing process qualification;
 - **Stage 3** – continued process verification
- Integrates the ICH Q8, Q9 and Q10 guidelines
- Ties PAT technology to process validation

Stage 1 – Process Design

Information from product and process development and scale up activities forms a basis for defining commercial manufacturing process. It is expected that manufacturers:

- Build and capture process knowledge and understanding that will be reflected in master production and control records *and*
- Establish a strategy for process control

Stage 1 – Process Design

- It is not expected that the early stages of process design be conducted under GMP (although some such as viral or impurity clearance should be) but sound scientific methods and principles should be applied
- It is not expected that processes should be tested until they fail but rather controlled under conditions of high risk of failure.
 - design of experiments in connection with risk analysis tools
 - Classical laboratory tests acceptable

Stage 1 – Process Design

- Adequate documentation of process understanding based on rationales
- Good documentation practice to be followed
- Process knowledge and understanding – the basis for process controls
- Controls should be designed to reduce input variations and these include material analysis and equipment monitoring

Challenges for the Manufacturer

- Additional efforts, resources, equipment and time required to generate the knowledge and information needed to design a commercial process with an effective process control
- Additional time and effort, and technology tools, including advanced statistic packages required to acquire, process and manage data
- Potential increase in a number of scale up studies

Challenges for the Manufacturer

- Challenges with knowledge and documentation transfer to Stage 2, Process Qualification
 - type of data (to ensure that commercial process is well controlled)
 - point of transfer
 - mechanism of transfer
- Additional resources required to implement and maintain good documentation practice

Stage 2 – Process Qualification (PQ)

Process design is evaluated as being suitable for reproducibly manufacturing commercial batches. This stage has two elements:

- Design of the facility and qualification of equipment and utilities *and*
- Process performance qualification (PPQ), Protocol and Protocol Execution and Report

Recommendations for Project Plan (or PQ Plan) are given

Stage 2 – Process Qualification (PQ)

Qualification activities for equipment and utilities are described but DQ, IQ and OQ are not mentioned

- could be done under individual plan or as part of a project
- risk management to prioritize activities, level of effort, documentation required

Stage 2 – Process Performance Qualification (PPQ)

“A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected”

Stage 2 – Process Performance Qualification (PPQ)

- The PPQ is an important milestone within the product life cycle
- The approach to PPQ should be based on sound science, product and process understanding and demonstrable controls
- Higher level of sampling, additional testing, greater scrutiny of process performance is expected than for commercial batch manufacture
- Biotechnological manufacture and to PAT implementations within the framework of PPQ

Stage 2 – Process Performance Qualification (PPQ)

- Recommendations for the content of PPQ Protocol and the execution of the Protocol and preparation of a Report are discussed

Important to note:

“The commercial manufacturing process and routine procedures must be used during execution of PPQ” and “The PPQ lots should be manufactured under normal conditions...” **No worst case.**

Challenges for the Manufacturer

- Since the approach to PPQ should be based on sound science, objective measures such as statistical metrics should be used
- The type and amount of data required to demonstrate state of control will have to be defined for each process
- On demand access to the correct data and data analysis becomes of particular importance

Stage 3 – Continued Process Verification

Continual assurance that commercial manufacturing process remains in a validated state (state of control) and detect any unplanned process variations.

This is achieved by ongoing program for acquisition and evaluation of process performance data (§ 211.180(e))

Stage 3 – Continued Process Verification

The Guidance recommends that:

- A statistician or a person trained in statistical process control should:
 - develop data collection plan
 - decide on the use of appropriate statistical methods for measuring process stability and capability
 - carry out trending and analysis of process data
 - wherever possible, quantitative tools should be used
- Continuous monitoring of process parameters and product attributes at PPQ level should be used to establish variability estimates

Stage 3 – Continued Process Verification

- Variability estimates should be used to establish sampling and monitoring frequency
- The collected process data should be used to optimise or improve the manufacturing process
- Production operators and quality unit personnel should be encouraged to provide feedback on process performance
- Regular meetings between the quality unit and production staff should be held to evaluate data, trends etc.

Challenges for the Manufacturer

- Have to have appropriate software capabilities in place to access, aggregate, analyse and report data on-demand by end users in a meaningful context, such as one that allows correlation of upstream parameters with downstream process outcomes
- Staff member(s) trained in statistics
- On demand access to data
- Regular meetings between quality unit and production personnel to discuss process performance
- Knowledge management

Globalization and Contract Manufacture

Contract globalized manufacturers and especially those manufacturing large number of products will face significant challenge with regard to:

- Maintenance of the life cycle approach
- Technology transfer
- Knowledge management
- Grouping of products / matrix approach

The Guidance and the Regulatory Requirements

The PV Guidance is supported by the current US FDA Act and cGMP regulations 21 CFR parts 210 and 211 that require:

processes to be designed and controlled to assure that in-process materials and finished products meet predetermined quality requirements and do so consistently and reliably.

The Guidance and the Regulatory Requirements

EMA

- Jan 2009: issued overview of the proposed FDA's PV Guidance
- Feb 2010: published a draft paper revising the "Note for Guidance on PV" to harmonise with FDA
- Anticipated release at the end of 2011

(The Inspectors Working Group, the EMA PAT Team, the Biologics Working Party, the Immunologicals Working Party and the Herbal Medicinal Products Committee)

The Guidance and the Regulatory Requirements

TGA

- Up to date there were no publications relating the FDA PV Guidance
- Likely to adopt the EMA Guidance.
- Changes to the PIC/S Guide to GMP?

THANK YOU