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Pharmaceutical and Life Sciences: *Towards a Recipe Driven Company and the Critical Role of the Real Time Infrastructure*

Continuous Process Verification

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Agenda

- A Brief History of Validation
- An Agency Under Pressure
- The Agency Reaction
- Guidance
- What to Expect

A Brief History of Validation

- The law and its limitations (1960s FD&C Act)
  - The law is treated objectively (primarily)
  - Reliance on finished product testing
- Industry requests for guidance and clarity
  - Subjectivity needed with guidance
  - Complexity of processes increasing
  - Integration of complex processes

A Brief History of Validation

- The Response
  - Meetings between FDA, Industry, Academia, and the public
  - FDA goal to apply guidance to all regulated areas
  - Internal FDA "Center" meetings
  - Drafts produced

A Brief History of Validation

- Final output: Guideline on General Principles of Process Validation
  - A "special mandatory guidance"
  - Many joint conferences with Industry
  - Many new words and definitions for FDA
    - IQ, OQ, Verification, Validation, etc.
    - Even implied definitions – PQ (performance, product, process)

The Key Definition

- *Validation*

  Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce product meeting its predetermined specifications and quality attributes

Key Words of the Key Definition

- Establishing – not establish, implies an ongoing process
- Documented evidence – if it isn't documented it did not happen
- High degree of assurance – not perfection but statistically significant

Key Words of the Key Definition

- Consistently – tested enough to provide that required statistical evidence
- Predetermined specifications and quality attributes – required/documented expectations with established goals, limits, levels of acceptability

A Brief History of Validation

- The Response
  - Cast in stone
  - Few ventures by industry into other ways to accomplish the goals
  - Little variance allowed during inspections
  - Many low quality attempts at validation resulting in Agency reactions and even more Industry conservatism
  - Time marches on

An Agency Under Pressure

- Increasing recalls and product withdrawals
- Increasing adverse event reports
- Calls from congress and Industry to modernize
- Increasing international pressures
  - International standards
  - Global supply chain
  - Speed of international regulation change

An Agency Under Pressure

- Ever increasing complexity and number of processes
- Increasing manufacturing speed
- Need for flexibility
- Pressure to simplify to control costs
- And many more

The Agency Reaction

- Slow moving guidance
- Process Analytic Technology
  - Promotion through podium, papers, and policy instead of regulation and guidance
- Agency long-term plans
  - Presentations to congress, the public, and Industry
  - Finally Draft Guidance and ICH updates

Guidance

- Process Validation: General Principles and Practices – January 2011
  - Not a "special guidance" – non-binding
  - You must meet regulations not guidance
  - CDRH, Tobacco, and CFSAN not included
  - "Supplemented" by ICH and other International Guidances

Process Validation: General Principles and Practices - 2011

- "This guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonisation (ICH) guidances for industry, *Q8(R2) Pharmaceutical Development*, *Q9 Quality Risk Management*, and *Q10 Pharmaceutical Quality System*.2 Although this guidance does not repeat the concepts and principles explained in those guidances, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle."

Process Validation: General Principles and Practices – 2011

- Implementation of scientific and risk based approach to pharmaceutical manufacturing and product quality
- Modified definition of validation "… 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."

Process Validation: General Principles and Practices – 2011

- Concepts adopted from other FDA regulated areas
  - Risk management
  - Quality by Design
  - Product, Process, and Development Life-cycles
  - Defines the Risk-Based approach to validation
  - Incorporates HACCP approaches to critical processes, parameters, and variability

Process Validation: General Principles and Practices – 2011

- Concepts adopted from other FDA publications
  - ICH Q8, Q9 and Q10 guidelines
  - Use of PAT technology in process validation
  - Much stronger emphasis and guidance for process knowledge development and scale-up
  - Does not incorporate CDRH Design Controls but does include some elements (design transfer, etc.)

Process Validation: General Principles and Practices – 2011

- Other core concepts
  - Lifecycle broken into phases (process design, process qualification,
  - Emphasis on early process design work yielding scientifically supportable specifications
  - Emphasis on monitoring of equipment and processes to assure meeting specifications
  - Requires documentation

Process Validation: General Principles and Practices – 2011

- Process Qualification emphasized
  - Process performance qualification (PPQ),
  - A formal Protocol, documented Protocol Execution, and Report are required
  - Formal facility, utility, and equipment design and qualification are required
  - Does not use DQ, IQ, OQ terms but the same data is required
  - Formal risk management is required

Process Validation: General Principles and Practices – 2011

- Process Qualification emphasized
  - Statistical evidence is expected – more sampling, testing, and more and better data are required
  - Worst case testing is not required but all PPQ work must be done under real manufacturing processes, procedures, equipment, and with the people who will manufacture the finished product
  - Access to the correct data and data analysis is critical

Process Validation: General Principles and Practices – 2011

- Continual Process Verification
  - This is the forgotten piece of all process validation
  - A validated state must be maintained through an ongoing program of data acquisition and evaluation
  - A statistician or a person trained in statistical process control is required for planning and ongoing evaluation
  - Specifications for acceptance, parameters to be monitored and product attributes must be established

Process Validation: General Principles and Practices – 2011

- Continual Process Verification
  - Variability estimates establish sampling and monitoring frequency
  - Real process data must be used for process optimization and process improvement
  - Quality unit and manufacturing personnel must share observations and data in a formal way

What to Expect

- Software (its control and validation) and data (appropriateness, and compliance with good data practices) become critical
- Statistics and Science are emphasized
- Management of data and knowledge become more and more important
- Technology transfer and lifecycle concepts will require significant implementation control

What to Expect

- Look to ICH, EMA and other sources for further information and guidance.
- Do not expect rapid guidance production from FDA
- FDA Investigation training will take some time
- It is guidance but the edges will be enforced as they are easy to relate directly to GMP

Questions