Implementing New Technologies in Regulated Environment

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Chemical and Pharmaceutical Solution

Producing Regulated Products

- Regulatory Groups
  - FDA (USA)
  - EMA (Europe)
  - PMDA (Japan)
  - sFDA (China)
  - TGA (Australia)
  - DCG (India)

Producing Regulated Products

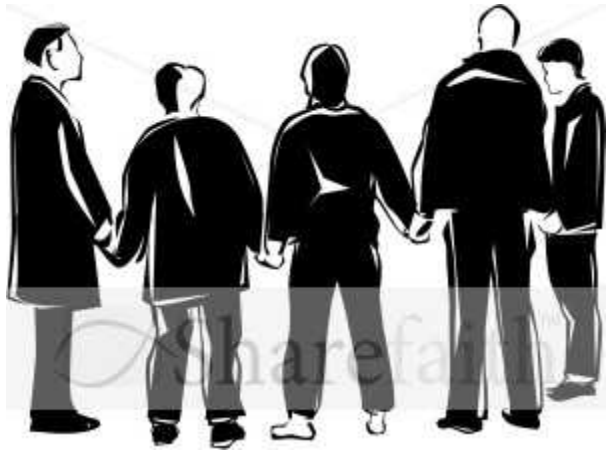
- Harmonization of Rules
  - Difference from country to country
- Harmonization of Inspections
  - Difference in the critical issues

Producing Regulated Products

- Technology has changed
  - Continuous Reactions
  - Simulated Bed Chromatography
  - Single Use
- Improved Analytical
  - Better sensitivity
- More Complex Molecules
  - Biological Drugs

Producing Regulated Products

- Regulatory Changes
  - Risk Based Approach
  - Increased Outsourcing



Producing Regulated Products

- "Batch"
  - 21 CFR 210.3
    - *Batch*-a **specific quantity** of the drug or other material that is **intended to have uniform character and quality**, within specific limits and is produced according to a single manufacturing order **during the same cycle of manufacturing**
    - *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

- *Acceptance criteria* means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

Producing Regulated Products

- *Lot*- a batch or a specific identified portion of a batch having uniform character and quality within specified limits
- *Lot*- for continuous processes, it is a specific identified amount produced in a unit of time or quantity

Producing Regulated Products

- What does dictate a Batch/Lot
  - Quantity
  - Uniform Character and Quality
  - Same Cycle time
- What does not dictate a Batch
  - Does not specify the mode or method of manufacturing

Producing Regulated Products

- Why is this important
  - 21 CFR 211.65(a)
    - Laboratory determination of final specifications for release
  - 21 CFR 211.188
    - Documentation of Manufacturing
  - 21 CFR 211.192
    - Extended investigations of unexplained discrepancies
  - 21 CFR 211.150(b)
    - Recall Situation

Producing Regulated Products

- Batch
  - Ability to Trace it back to the starting Materials
  - Ability to recall appropriate batches is necessary
  - Ability to analyze the “batch” or “lot"

Producing Regulated Products

- Batch
  - Production time limit (i.e. 1 day)
  - Production output (i.e. quantity obtained)
  - Production Variation (i.e. different lots of feedstock
  - Other (based on the science)

Producing Regulated Products

- Ask the question
  - 1. Can I relate this back to a defined lot or batch starting material.
  - 2. Can I compare this to a constant manufacturing process
  - 3. Do I have adequate control of the process and how do I measure this point

Producing Regulated Products

- Regulations for Continuous Flow
  - Other than in the definition of “lot” there are no specific regulation or guidance
  - Consistent with the FDA’s Quality by Design efforts
  - Nothing in regulations or guidance prohibiting continuous manufacturing

Producing Regulated Products

- Monitoring and control
  - NIR (near infra-red)
  - FTIR (Fournier transformation infra red)
  - Laser light (particle size and formation)
  - In-line chromatography

Producing Regulated Products

- Sampling
  - In-process measurements
    - Sample interface
      - Constant over the process
      - Uniformity of the sample space
    - Response time of the instrument
      - Is there sufficient time to get a proper reading
    - Sample Volume
      - Based on the size of the probe is there enough volume to get a proper reading?

Producing Regulated Products

- Cleaning
  - Clean in Place
  - Smaller Volume of “reactors”
  - Single use
  - Levels of detection

Producing Regulated Products

- Validation
  - Old
    - Fixed number of lots/batches to show statistically that the process was in order my measuring a series of parameters
      - Yield, Quality, Manufacturing Time
  - New
    - Fixed time or feed
      - Similar parameters to measure

Producing Regulated Products

- Take Home
  - There are no restrictions to implementing new technology
  - Understand the process and what is going on around it
  - Always remember the basics
  - Always use good science

Producing Regulated Products

Thank you

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