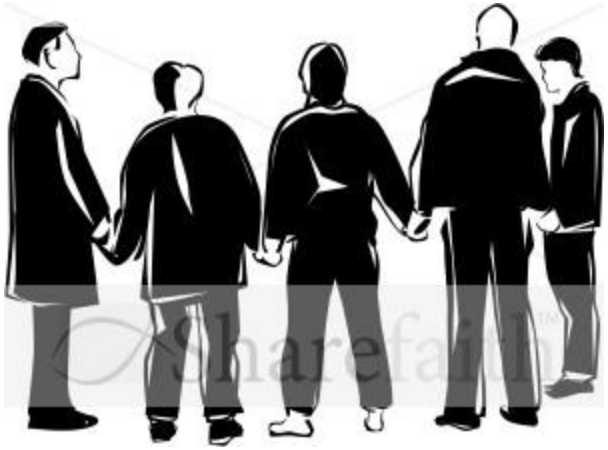
# Implementing Continuous Process Technology in a Regulated Environment

**SK 1st Annual Continuous Process Symposium**
**May 14-15, 2014**
**James R. Bruno**
**Chemical and Pharmaceutical Solution**

# Say a Prayer



# Sacrifice to the God of Quality

# Human Aspect

# What shale we Do

Prepare

# FDA Opinion

- "Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing."

Dr. Janet Woodcock, AAPS Annual meeting
October, 2011

# FDA Opinion

- "There are no regulatory hurdles for implementing innovation in pharmaceutical manufacturing."

  Moheb Nasr, Director of the Office of New Drug Evaluation and Research at the FDA, March 2011, Interphex panel discussion

# FDA Opinion

- The Agency sees definte economic and quality advantages to continuous manufacturing
- The science exists (and technologies to support continuous processes are on the market
- There are “no regulatory hurdles” for the industry to implement continuous practices
- “There is a lack of experience (within in and without the FDA); therefore we really need to work together as we move forward with these approaches

Christine Moore, Deputy Dir. for Science and Policy

# Who Do I Comply to

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

# One rule?

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

# Regulations and Continuous Manufacturing

- No specific regulations or guidance for continuous manufacturing other than the definition of “lot”
- Nothing in regulations or guidance prohibiting continuous manufacturing

# Regulations and Continuous Manufacturing

- Continuous manufacturing consistent with FDA's Quality by Design (QbD) efforts
  - More modern manufacturing approach
  - Potential to improve assurance of quality and consistency of drugs
  - Enables quality to be directly built into process design

# Technology Is Changing

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

# New Approach

- Regulatory Changes
  - Risk Based Approach
  - Increased Outsourcing

# Definitions

- "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**

# Definitions

- "Batch"
  - 21 CFR 210.3
    - *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

# Definitions

- *"Lot"*
  - *21 CFR 210.3*
    - *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

# Definitions

- *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).

# Definitions

- 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

# What Give me the right to enforce

- 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

# Batch?

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

# Batch?

- Batch
  - Production time limit (i.e. 1 day)
  - Production output (i.e. quantity obtained)
  - Production Variation (i.e. different lots of feedstock
  - Dependent on Equipment cycling capability
  - 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

# Regulatory Guidelines for Continuous Chemistry

- Regulations for Continuous Chemistry
  - 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

# Analytical

- Acceptance Criteria
- Specific Quality
- Measure Deviation from the Normal
- PAT

# Analytical

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

# Analytical

- Steady State
  - Steady State is when material properties in the system remains constant with
    - Not the same as equilibrium
    - Time to reach steady state depends upon flow properties

# Analytical

- Steady State
  - When is product acceptable or not acceptable to collect
    - During process start-up and shut down
    - After disturbance (e.g. spike in feed rate)

# Analytical

- Steady State
  - When do all component concentrations and physical properties reach steady state?
    - May necessitate measurements other than concentration of active components

# Analytical Control

- Control Strategies
  - Methods to assure that the product has “uniform character and quality within specific limits”
    - Characterization of in-coming materials
    - In-process measurements
      - Sampling frequency
      - In-process parameters and material attributes
      - Setting of appropriate acceptance criteria
    - Dependent on cycling capacity of equipment
    - Consider interactions amongst unit operations

# Sampling

- Sampling
  - In-process measurements
    - Sample interface
      - Constant over the process
      - Uniformity of the sample space
      - Stratification
      - Interference due to flow
      - Probe effects
    - Response time of the instrument
      - Is there sufficient time to get a proper reading

# Sampling

- Sampling
  - Dependent on the system dynamics
    - Sample frequency capable of detecting process upsets
    - Start up frequency vs. steady state
  - Sample Volume
    - Based on the size of the probe is there enough volume to get a proper reading?

# Cleaning

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

# Cleaning

- How Much Cleaning
  - Breakdown the entire reactor train
  - How would you clean your reactor?
- When do I clean
  - Between batches
  - End of a Campaign

# Validation

- 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

# Validation-Why?

- Process Validation: General Principles and Practices/2011

  process validation underscores the importance of detecting, understanding, and controlling sources of variability over time in order to consistently produce safe, effective drugs that meet all quality attributes.

# Validation-Why?

- Process Validation: General Principles and Practices/2011

  With the advent of the 2011 Guidance and its emphasis on design, lifecycle, and control of variability, the “rule of three” has been effectively rejected

# Validation

- New Regulations
  - Stage 1
    - Process Design
  - Stage 2
    - Process Qualification
  - Stage 3
    - Continuous Process Verification

# Validation

- Stage 1
  - Process Design
    - the commercial process is defined based on knowledge gained through development and scale-up activities

# Validation

- Stage 2
  - Process Qualification
    - the process design is evaluated and assessed to determine if the process is capable of reproducible commercial manufacturing

# Validation

- Stage 3
  - Continuous Process Verification
    - Ongoing assurance is gained during routine production that the process remains in a state of control

# Challenges

- Need for integration of the analytical tools to the control system to support implementation of feed-back or feed forward control
  - Data Management Tools
- Defining the representative sampling to consistently assure product quality over time
  - Location, size and frequency

# Challenges

- Need for enhanced process understanding
  - Mechanistic models for all processing steps
  - Implementation of multivariate analysis for determination of product quality

# 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

James R. Bruno

jamesbruno@capsoln.com