Second Meeting of the FDA/ACPS Process Analytical Technology: Closing Remarks

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A Reminder

- Quality of drug products available to the US patients is good
  - The current quality assurance system (specifications/controls; GMP; testing,..) is able to prevent the release of low quality product
    - Very few Class I recalls due to quality problems
- Current level of process understanding is low and, therefore, requires a very high level of scrutiny and rejecting product of unacceptable

Process Understanding

- Pharmaceuticals are complex, multivariate, physico-chemical systems
  - Often treated (during development) as a univariate system (one-factor-at-a-time, trial and error experimentation
  - Materials not well characterized -physical attributes
  - Equipment selection – tradition
  - Process factors – limited information (optimal?)
- Development “time crunch”
- Post approval changes require regulatory oversight

Limited, but sufficient for approval, process understanding can lead to …..

- Low process capability
  - Scrap, Rework, or Recall
  - Protracted production cycle times and low capacity utilization
  - Resolution of process related problems slow and difficult
  - High cost of compliance
- Risk of
  - Drug shortages
  - Releasing a poor quality product
  - Recalls
  - Delay in approval of new drugs
  - Quality problems confounding clinical trial data

Note - Quality is the foundation for Safety & Efficacy decisions

Approaches for minimizing "risks"

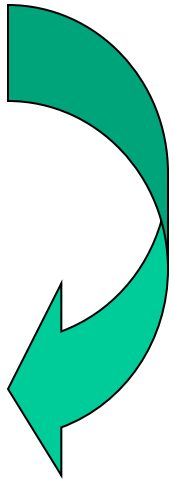
- Option #1 Increase the level of FDA scrutiny
  - FDA resources limited, while number of products and manufacturing establishments are increasing
- Option #2 Increase the level of process understanding (prevention option)
  - PAT is a model

Current System

- Strict adherence to SOP's and all other documented procedures CRITICAL
- Pre-specified Time and Testing are used to document conformance
- Univariate assessment - not a SYSTEMS approach for quality decisions
- Learning essentially stops after "validation"
  - inability to "connect-the-dots"
- Not conducive to continues improvement

PAT System

- Performance based assessments used to confirm conformance throughout the process (prevent manufacture of unacceptable end product quality)
- SYSTEMS approach for quality decisions
- Learning and validation continuos
  - Dots connected
- Conducive to continues improvement
- Strict adherence to SOP’s and all other documented procedures CRITICAL



Emerging PAT Guiding Principles

- NDA/ANDA
  - Should not prolong review times due to introduction of PAT
  - Early meetings with PAT reviewer
    - Expert technical support available
    - GMP issues identified and discussed with PAT inspector
    - Possible - reviewer participates in pre-approval inspection
  - Consider interim specifications (PAT)

Emerging PAT Guiding Principles

- Post-Approval
  - Company collects data to establish PAT proof of concept or suitability
    - Communication with FDA an option
  - PAT meeting with PAT Team
    - Goals and Objectives of this meeting
      - Consensus on how to introduce PAT on an existing line and questions to be addressed (data collection) for validation
      - Safe harbor
      - Submission and inspection strategy

Emerging PAT Guiding Principles

- FDA - Higher level of training, communication, and systems approach
  - CDER/ORA team approach
  - Minimal reliance on Prior Approval Supplement process
  - Increased emphasis on underlying science, mechanisms, and assessed risk of poor quality

Is Industry willing to move?

- FDA is NOT the hurdle
- FDA is working with industry minimize the “risk” side of the equation
- Industry has to determine the “benefit” side of the equation
- Success of this initiative depends on one or two companies who are willing to take the lead
- Can we afford to fail or not move forward?

Meeting #3 (one day meeting)

- Discussion on general principles of validating computer systems and models
- “Dry run” exercise of an mock PAT application, review and inspection decisions
  - Need case studies (PAT@CDER.FDA.GOV and Docket)
- Issues related to rapid microbial testing
  - What information should be incorporated in the general guidance to address RM?
- One day workshop at NIST?