PAT
Consensus Standards
Innovation

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The Burning Platform

- Lack of innovation in manufacturing arena
- Bio/Pharma lags other industries by decades
- Quality is based on testing, not design
- Good Manufacturing *Practice* but not Good Manufacturing *Performance*
- Processes are validated, but not controlled

The Challenges

- How to align our practices to science, tried and tested engineering practices?
- How to break down the silos in pharma?
  - Development
  - Manufacturing
  - Quality
  - Regulatory
- How to do good science and not get wacked

PAT Initiative

- An Enabling Framework: for innovation in development, manufacturing and quality assurance by:
  - Removing “regulatory fear/ uncertainty”
  - Utilizing science and risk-based approach to regulatory requirements and oversight
  - Providing a flexible and less burdensome regulatory approach for well understood processes
  - Introduce Consensus standards to CDER, CBER and CVM pharmaceuticals

PAT, Considered by FDA to be

A system for:

- designing, analyzing, and controlling manufacturing
- timely measurements (i.e., during processing)
- critical quality and performance attributes
- raw and in-process materials
- Processes

The goal of PAT is to understand and control the manufacturing process

PAT- Process Understanding

A well understood process:

(1) all critical sources of variability are identified and explained;

(2) variability is managed by the process;

(3) product quality attributes accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.

- The ability to predict reflects a high degree of process understanding.

Real Time Release (RTR)

- RTR facilitates release of product upon completion of processing as assurance of quality is achieved during processing
- The desired quality attributes are ensured through continuous assessment during manufacture.
- Data from production batches can serve to validate the process and reflect the total system design concept
- supporting validation with each manufacturing batch

Process Knowledge

- Facilitates process control
  - Which in turn facilitates process improvement in a controlled manner
- Facilitates operating a valid process, consistently producing quality product
- Facilitates setting appropriate specifications
- Facilitates meeting the regulatory requirements

2011 Process Validation

- Generally FDA Guidances have been prescriptive
- Process Analytical Technology (PAT) was the first to challenge this pattern
  - User based decisions, supported by science
- Process Validation guidance is the second such Guidance
  - No examples
  - Concept of 3 batches is challenged
  - User based decisions required
- It's ultimate goal is to facilitate the control of the manufacturing processes (re-align with the CFR definition)

Continued Process Verification

- How to assure that the process has not changed significantly, and that the process is responsive to changes in materials, environment, equipment (assuming process is “people” independent)
- The goal is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.
- Control charts will be most valuable to assess process performance.

PAT & Process Validation

- ..timely analysis and control loops to adjust the processing conditions so that the output remains constant… can provide a higher degree of process control than non-PAT systems.
- In the case of a strategy using PAT, the approach to process qualification will differ from that used in other process designs.

Process Validation Guidance 2011

CONSENSUS STANDARDS

Value of Standards

- Standards are a critical factor in global economic development.
- International standards and technical regulations directly affect more than 80% of world product trade. (U.S. Department of Commerce Report, Standards and Competitiveness, May 2004)

Policy & Legal Context for the Use of Standards (Public Law 104-113)

- The U.S. Congress enacted Public Law 104-113, also known as the National Technology Transfer and Advancement Act (NTTAA), in March 1996.
- The NTTAA and the Trade Agreements Act (TAA) of 1979, are two key pieces of U.S. legislation affecting the regulatory and procurement use of standards.

Policy & Legal Context for the Use of Standards (Public Law 104-113)

- The NTTAA directs federal agencies to use,
- when practical and not otherwise prohibited by law,
- standards developed by voluntary consensus standards bodies
- to achieve public policy and procurement objectives, and
- the TAA prohibits federal agencies from engaging in any standards-related activity that creates unnecessary obstacles to trade and
- requires federal agencies to take into consideration international standards.
- https://www.nist.gov/sites/default/files/documents/2016/12/30/voluntary_standards_usregs.pd
- (http://standards.gov/standards_gov/index.cfm)

OMB* - A119

- "…this Circular directs agencies to use voluntary consensus standards in lieu of government-unique standards except where inconsistent with law or otherwise impractical."
- "This circular applies to all agencies…"
- "All federal agencies must use voluntary consensus standards in lieu of government-unique standards in their procurement and regulatory activities…"

* Office of Management & Budget

What if standard is impractical?

- “The head of your agency must transmit to [NIST], an explanation of the reason(s) for using government-unique standards in lieu of voluntary consensus standards.”

What about guidance on the same topic?

- “If a voluntary consensus standards body is in the process of developing or adopting a voluntary consensus standard that would likely be lawful and practical for an agency to use, and would likely be developed or adopted on a timely basis,
- an agency should not be developing its own government-unique standard and
- instead should be participating in the activities of the voluntary consensus standards body.”

(OMB-A119)

How does this impact the FDA's authority and responsibilities?

- "This policy does not preempt or restrict agencies' authorities and responsibilities to make regulatory decisions authorized by statute."

(OMB-A119)

OMB's Standard definitions

- Voluntary Consensus Standards
- Non-Consensus Standards
  - Company standards
- Government Unique Standards
  - Guidance
- Standards Mandated by Law
  - USP/NF referenced in 21 U.S.C. 351
- https://www.gpo.gov/fdsys/pkg/USCODE-2011-title21/html/USCODE-2011-title21-chap9-subchapV-partA-sec351.htm

CSO defined in OMB-A119

- How does OMB describe a Consensus Standard Organization (CSO)?
  - Openness
  - Balance of Interest
  - Due process
  - Appeals process
  - Consensus is not necessarily unanimity, but that each objector is advised of the disposition of the objection, the reason why, and the body members then have an opportunity to change their votes

WTO Principles for Defining International Standards

- Transparency
- Openness
- Impartiality & consensus
- Effectiveness & relevance
- Coherence
- Development Dimension

How does FDA Use non-Government Standards

- Participation in development does not connote adoption
  - Does the standard address FDA's science or regulatory concerns/issues
- Uses
  - Cite by FDA in Regulation and Guidance
  - Cite by sponsor as part of documentation
  - As forum to discuss science with industry

FDA Staff Manual Guide: Section 3 (Policy)

3.4- “Where appropriate, FDA encourages sponsors of product applications and manufacturers to cite appropriate voluntary consensus standards in support of their applications and manufacturing process documents. Where the use of voluntary consensus standards would be inconsistent with applicable law or otherwise impractical, citation of other non-government standards should be considered.”

https://www.fda.gov/aboutfda/reportsmanualsforms/staffmanualguides/ucm193332.htm

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"In theory, there is no difference between theory and practice. But in practice, there is."

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