Lifecycle Facility Assessment

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OFFICE OF PHARMACEUTICAL QUALITY

Outline

- Science-Based Development
  - Process Validation
  - Inspection Considerations
- Regulatory Framework for Risk Management
  - ICH Q10
- Opportunities for the Pharmaceutical Quality Unit

Decision Making Based on Understanding

- Quantifying risks & weighing risks
- Interrelated variables
- Just as applicable for initial tech transfer as for lifecycle changes
- React in a proportional, appropriate way

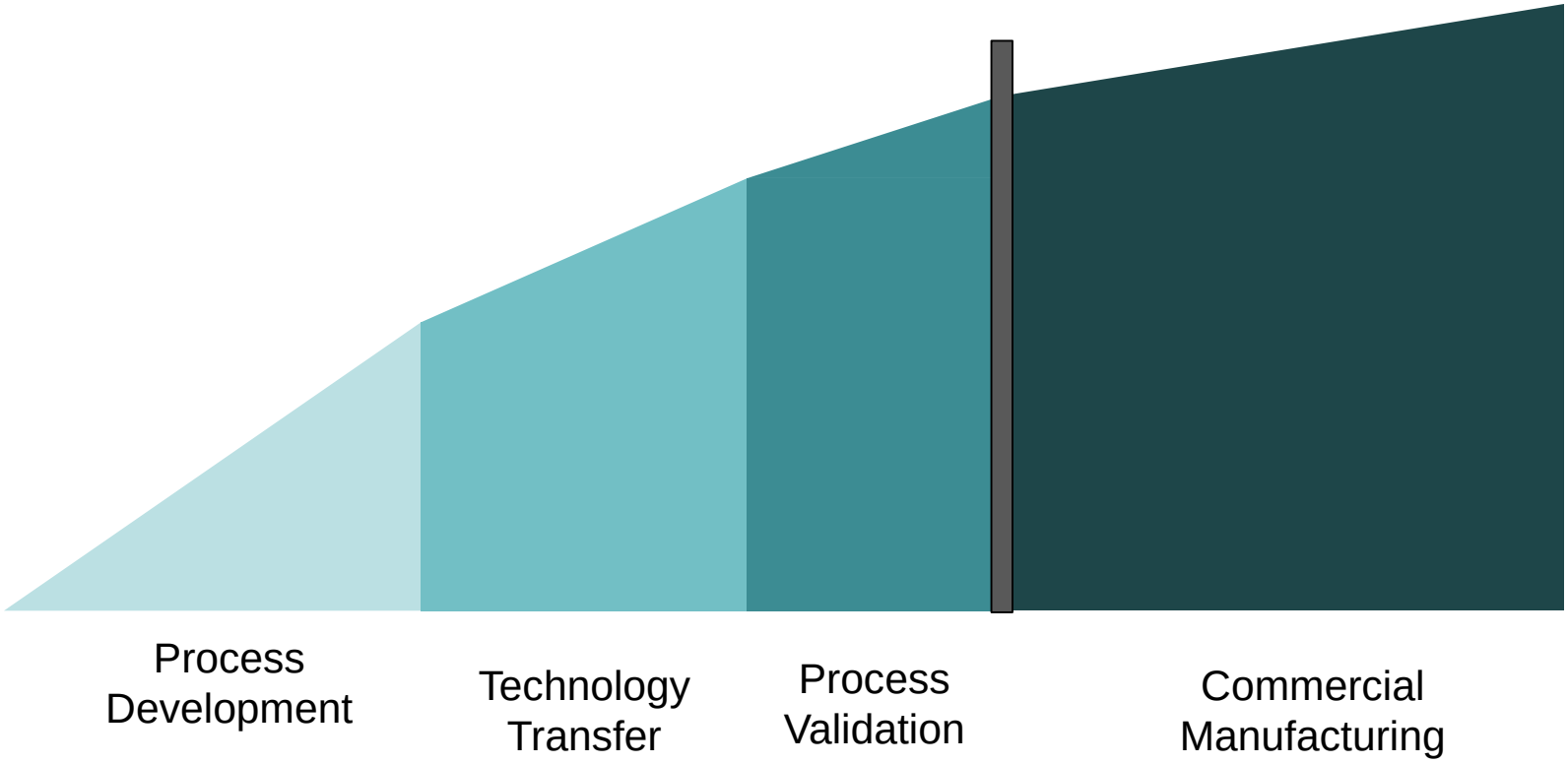
- **Product and process design with scientific understanding is critical for maintaining systems as well as making changes**

Process Validation

The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivery quality products.

FDA Guidance for Industry – Process Validation: General Principles and Practices

Product Knowledge



PV Stage 1 – Basic Process Design

- Critical Quality Attribute Identification
  - Impurity levels, content uniformity, dissolution
- Appropriate manufacturing process
  - Reactions, equipment, environmental assessment
- Suitable control strategy
  - Proven Acceptable Range/Normal Operating Range, in process and release testing

PV Stage 2 – Process Qualification

- Design of Building and Facilities
  - Appropriateness and capability of equipment
- Understand and incorporate material variability
- Process Performance Qualification (PPQ)
  - Fully evolved control strategy for commercialization
  - Protocol design, execution, and interpretation

Pre-Approval Inspection

- Readiness for Commercial Manufacturing
  - Equipment, Procedures and Quality Management Processes in place
- Conformance to Application
  - Equipment scale
  - Process as proposed in submission
- Data Integrity
  - Submission information, raw data, and application context is accurate

PV Stage 3 - Continued Process Verification

- Continual assurance that the process remains in a state of control
- Monitoring using a control strategy developed with an understanding of the process and its risk
- Analysis of incoming material properties or other variables to manufacturing

Post-Approval Inspection

- Product-specific; following application approval
- Assigned/requested; carefully selected
- Covers aspects of Quality System
  - Not ready during application review period
  - More critical to assure quality
- Includes:
  - Process Performance Qualification batches and report
  - Component supplier qualification
  - Stability

Surveillance Inspections

- Determine compliance with CGMP requirements; provide evidence for action necessary
- Support application approval decisions
- Provide feedback to firms to improve their compliance
- Aid FDA in determining the adequacy of CGMP requirements, regulatory policy, and guidance

Continued Process Verification

Ongoing assurance is gained during routine production the process remains in a state of control.

FDA Guidance for Industry – Process Validation

An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement.

FDA Guidance for Industry – Q10 Pharmaceutical Quality Systems

Regulatory Basis of the Quality Unit

- **21 CFR 211.22**

  There shall be a quality control unit that shall have the responsibility and authority to….

- QCU scope applies to the entire process: material receipt, creation of written procedures, testing investigations, release, etc.
- CGMP describe cooperation between the QCU and other departments
- But for final authority: **"The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company."**

ICH Q10 – Pharmaceutical Quality System

- A harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an **integrated approach to quality risk management and science**

ICH Q10 – Pharmaceutical Quality System

1. Monitoring System
   - Ensure a state of control
   - Control strategy developed with process and risk understanding
   - In line with Process Validation Phase III
2. CAPA System
   - Corrective Actions: Retrospective fixes
   - Preventive Actions: Prospective changes
   - Continual Improvement

ICH Q10 – Pharmaceutical Quality System

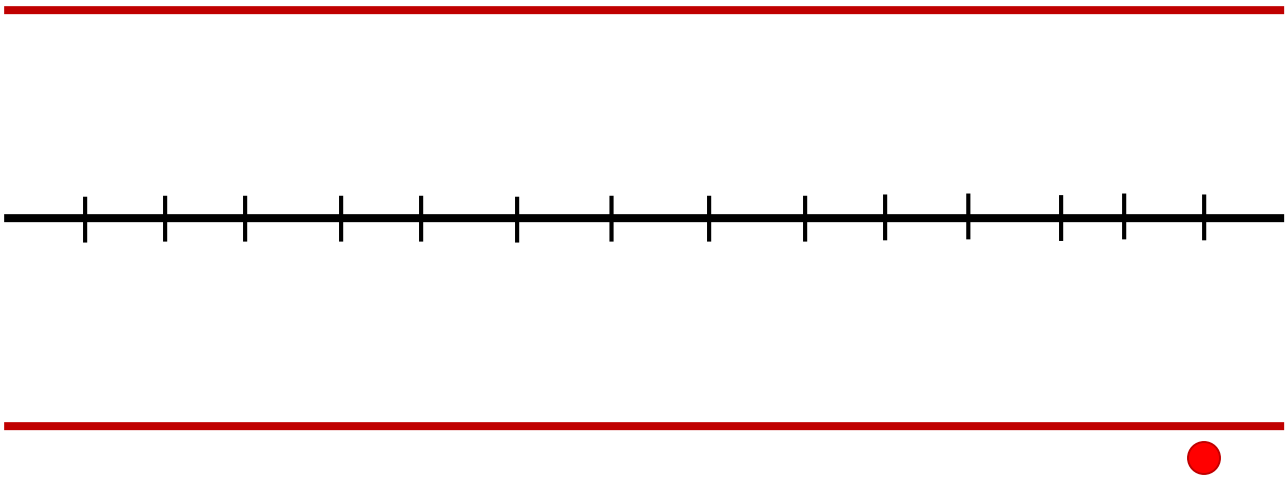
3. Change Management System
   - Understand implications of change across functions and on the entire manufacturing process
   - Regulatory connection
4. Management Responsibility
   - Align resources and culture accordingly
   - FDASIA 711 (July 2012): CGMPs “includes the implementation of oversight and controls over the manufacture of drugs…,”

Quality Opportunities for Risk Management

Proactive Trending	• Surveillance mindset • Connect everything: production data, deviations, CA's & PA's
Product & Process Continuous Improvement	• Refine processes & control strategy • "Development" mind-set should not end at commercialization
Integrated Process Understanding	• Process & Facility Risk Assessment • Making critical connections between understanding and practices

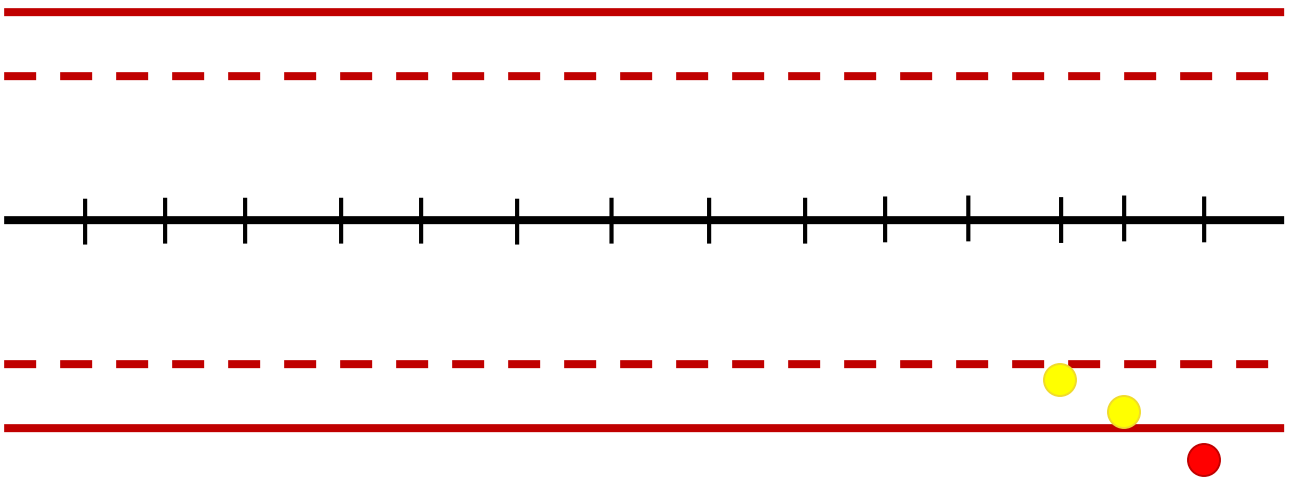
Pro-Active Trending & Quality Oversight

- **Reactive** – Waiting for OOS's & Deviations



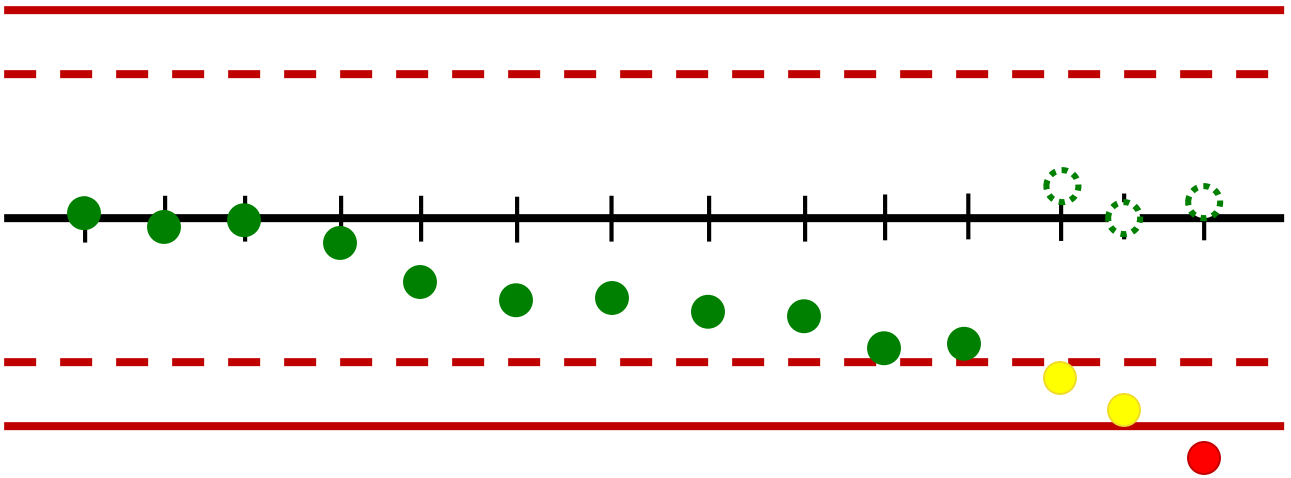
Pro-Active Trending & Quality Oversight

- **Risk Based** – Uses internal standards as process alerts



Pro-Active Trending & Quality Oversight

- **Proactive Quality Analysis** – Seeks broad understanding of performance for optimization



Continuous Improvement

Finding Knowledge Gaps

- Previously unrecognized attribute-parameter interactions or stronger/weaker interactions
- Incomplete understanding of scale factors
- Greater or unanticipated input variability at commercial scale from:
  - Operators
  - Equipment
  - Incoming materials
  - Manufacturing instructions
  - Measurement systems
- Risk assessment out of date

Central Knowledge Base

Integrated Process Understanding

- Risk Assessment for each process step
- Integrate risk assessment into operations
- Understand failure modes
- Anticipate rather than react
  - Leading indicators & “out-of-control” plan
- Understanding of criticality enables appropriate course of action for voluntary business changes

Life Cycle Management:
Decisions Making Through Understanding

- Build quality into the process
- Identify critical process parameters & implement appropriate monitoring strategy
- Continue to refine process and risk models
- Lifecycle decision-making based on a foundation of scientific knowledge

Thank you!

Additional Questions: CDER-OPQ-Inquiries@fda.hhs.gov

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