The Importance of Assuring Quality Throughout the Lifecycle

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Agenda

▪ Importance of Quality Throughout the Drug Lifecycle
  • Consistent manufacturing is essential to assure each batch is safe & effective
  • Effective Quality Risk Management (QRM) supports reliable manufacturing throughout the lifecycle

▪ State of Control

▪ Quality System Oversight of Manufacturing
  • Importance of management oversight
  • Systems for identifying supply chain, process control, manufacturing capability and other potential lifecycle risks
Importance of Quality Throughout Drug Lifecycle
Expectations for Quality

Patients and caregivers assume that their drugs:

- Are safe, efficacious, and have the correct identity
- Deliver the same performance as described in the label
- Are made in a manner that ensures quality
- Perform consistently over their shelf life
- Will be available when needed
ICH Q9 (Quality Risk Management) Concept Paper - 2003

- Technology Focus
  - Increase process capability
  - Focus on critical control points

- Product
  - Stabilize manufacturing steps (decrease variability)
  - Guarantee shelf-life

- People
  - Result in behaviours that promote superior performance of the Quality System

- Customer
  - Reduce deviations
  - Reduce market complaint rate
  - Reduce technical-related adverse events

i.e., Improve Quality Performance for the Patient
Satisfied Customers (Patients)

Supply Dependability

Consistent Product Quality

Manufacturing Reliability
State of Control

• **Capability:**
  - "It is upon transfer to Manufacturing that assessment of the true process capability and robustness as well as any process improvement or remediation will begin…"

• **Variation:**
  - "When the product is transitioned to Manufacturing, it will most likely encounter a much wider range of variation on the parameters than seen in development."
  - "For example, [drug product] attribute variability may increase due to a wider range in incoming raw material parameters that cannot feasibly be fully studied in R&D."
Why Quality Matters...

*Impact of Substandard Manufacturing (e.g.)*

- Product (Asthma Drug) is 500% of Label Claim
- Seizure Drug: Capsules partially filled or empty
- Seizure Extended Release Drug: Poor Dissolution
- Non-sterile LVP Bags
- Non-sterile Vials
- Superpotent Narrow Therapeutic Index Tablet (Digoxin)
- Injectable Emulsion with High Pyrogens
- Antiseptic pads contaminated with gram negatives (used to wipe catheters and injection sites; presurgical)
- Microbiologically contaminated Eye Drops (used post-surgery)
- Empty Rescue Inhalers (Asthma)
- NTI Uniformity Failures (Thickness, CU)
- Transdermal dose dumping
- Label Mixups. e.g. Bottle labeled as 3mg Warfarin actually contained 10mg Warfarin (a REMS drug).
- Heparin contamination with toxic substitute
- Autoinjector does not deliver drug (epinephrine)
Sources of Variability

Methods (processes)
Machines
Materials
Measurement Systems
Environment
People

Root Causes & Corrections

Management
Oversight
Operator Competencies
Quality System Oversight of Manufacturing and Quality
A Robust Quality System Assures a State of Control

The Pharmaceutical Quality System:

- **Drives Sound Lifecycle Decision-making**
  - Uses Scientific and Risk-Based Approaches

- Establishes and Maintains a **State of Process Control**
  - **Vigilantly monitors** process performance & product quality
  - Assures reliable processes and products through **management oversight** (checkpoints, escalation, executive involvement) **throughout the supply chain**

- **Creates real “fixes” to problems** (long term, systemic)
  - Continual Improvement
Management Oversight of Manufacturing Quality

In 2012, the FDASIA legislation amended the statutory GMP Definition in the FD&C Act 501 as follows:

“For purposes of paragraph (a)(2)(B), the term ‘current good manufacturing practice’ includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.”

“Section 711: Enhancing the safety and quality of the drug supply” specifies management oversight from Raw Materials to Intermediate Materials to Finished Product
Risk Management: Do you connect the dots in Daily Manufacturing? In your Supply Chain?

- Complaints
- Rejections
- Feedback from “Shop Floor”
- Maintenance Issues
- Deviations
- Returned goods
- OOS Results
- Stability Results
- Current Staff Competencies
- Raw Material Data
- Results of Audits & Inspections
- Process Trending Data
Daily Risk Management Decisions Determine Reliability of Quality and Supply

A drug manufacturer is responsible for implementing dependable daily operations that assure consistent drug quality. **Management’s daily decisions** on myriad issues involving equipment, materials, maintenance, staff qualifications, supervision, process control, and investigations will **ultimately determine the quality** of the drugs that are shipped from a given facility.

Supply Chain Management

**Figure 1:** Supply Chain Process Flow

- ID Material to Buy
- ID Potential Supplier
- Define Business/Quality Requirements
- Select/Approve Supplier
- Manage Supplier/Supply Chain

**Figure 2:** Major Paradigm Shift revealed through Failure Mode Analysis

“Our Suppliers Are Causing Problems”

We are Causing Problems

Recognition that it is a failure of the Owner’s Supplier Management Program when they are **unaware of a problem or change** at the supplier that may affect quality (i.e., basic knowledge needed for effective quality risk management).
Ongoing Supply Chain Oversight: Selection, Qualification, Monitoring and Risk Review

II. Poor Supply Chain Development and Management Theme

Many manufacturers have supplier selection and supplier approval processes in place, yet demands on speed to market often result in circumvention of these processes. It has also been found that supply agreements often conflict with the requirements of other agreements and drive the wrong behavior on both sides of the relationship. Additionally, although supplier qualification is not a new concept, it has been found that the elements of risk assessed are often not representative of key cross-functional requirements, and therefore, do not provide a complete representation of risk.
Infrastructure Modernization

How Reliable is the Facility and Process (whether in-house or CMO)?

- Inadequate manufacturing capability is a frequent cause of drug defects and critical drug supply shortfalls

  ➢ For example, ISPE’s industry survey cited lyophilization and sterile manufacturing as two areas in need of improvement.

- “Some...inspections have found operations with antiquated or obsolete facility or process elements, and operations with high defect rates in violation of cGMP. These operations are receiving higher focus, while manufacturing operations that have been upgraded and are more dependable have been deemphasized.”

Janet Woodcock, M.D., CDER Center Director (December, 2013)
20th Century Paradigm: Manually intensive operation. 

VS.

21st Century Paradigm: Manufacturing changes remove direct human-machine interaction.
How Do You Know If Your PQS is a Healthy One?

Prevention
Diet & Exercise

Correction
Medication

Remediation
Invasive Procedures
Quality Culture: What halts or delays implementation of needed change/improvement?

Factors in managing complex change (Knoster, Villa, Thousand, 2000)
What is “Compliance?”

- The degree of constancy and accuracy with which a patient follows a prescribed regimen, as distinguished from adherence or maintenance. (Medicine)

  Q: What is the result of the failure to comply with taking a drug (e.g., antiseizure, heart failure, antibiotic) as directed?
  
  A: Remedy is likely less effective. Health outcome is less predictable.

- The act or process of complying to a regimen. (Manufacturing)

  Q: What happens if you do not follow the Proven Process, or the Pre-Defined Procedure? Is the result as robust?

  A: When the process/method proven to be reliable is not followed, the quality of the final output is less certain.
Summary

- Senior management is responsible for assuring an effective Quality System
- Know your processes; know your business partners
- Quality Risk Management
  - Robust manufacturing design
  - Strong supplier management programs
  - Ongoing vigilance to assure predictable quality and supply, and identify areas needing improvement

“There is no longer such a thing as an American drug supply; there is a global drug supply... We know that, every day, some of those in the manufacturing and distribution chains for these products cut corners in small or large ways. They gain a competitive advantage or a monetary windfall from this non-compliance. But, they put our citizens at risk, and we cannot tolerate that.”

  – Former Commissioner Margaret Hamburg, Geneva, Switzerland (2011)
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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm095412.htm

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