Current Expectations for Pharmaceutical Quality Systems

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Topics

- Lifecycle Quality Risk Management
  - Addressing Two Major "Common Causes" of Variation
- A Quality Culture that leads to Sustainable Compliance
- FDA Inspections of the Pharmaceutical Quality System
- What is a CGMP-compliant Quality System?

Quality Risk Management

Types of Risk: Potential for Tension between Commercial and Public Health Interests

- "The probability alpha, also known as the producer's risk, is the risk that adequate product is rejected. The probability beta is known as the consumer's risk because defective product is accepted."
- The associated risk probabilities will depend on "inspecting and scrapping good product" or "the costs of shipping bad product."

[Jim Colton, Quality Digest, Dec., 2011 "Statistical Tools for Pharmaceutical Manufacturing"]

Risk Reduction Opportunities

Two "very" common causes…

1. Deficient Facilities and Processes

- Old Manufacturing Platforms (antiquated facilities, inefficient/unstable processes)
- Unpredictable manufacturing can lead to quality problems, defects, and supply shortfalls
- Many firms do not take advantage of contemporary technology
- Many processing lines require frequent starts and stops to correct problems and to pull samples
  - e.g., Tablet, Sterile manufacturing lines
- Open *vs*. Closed Processes (Also, Unit Operations *vs*. Integrated)
- Manually Intensive Operations vs. Automation
  - **Human Error still very prominent root cause…**

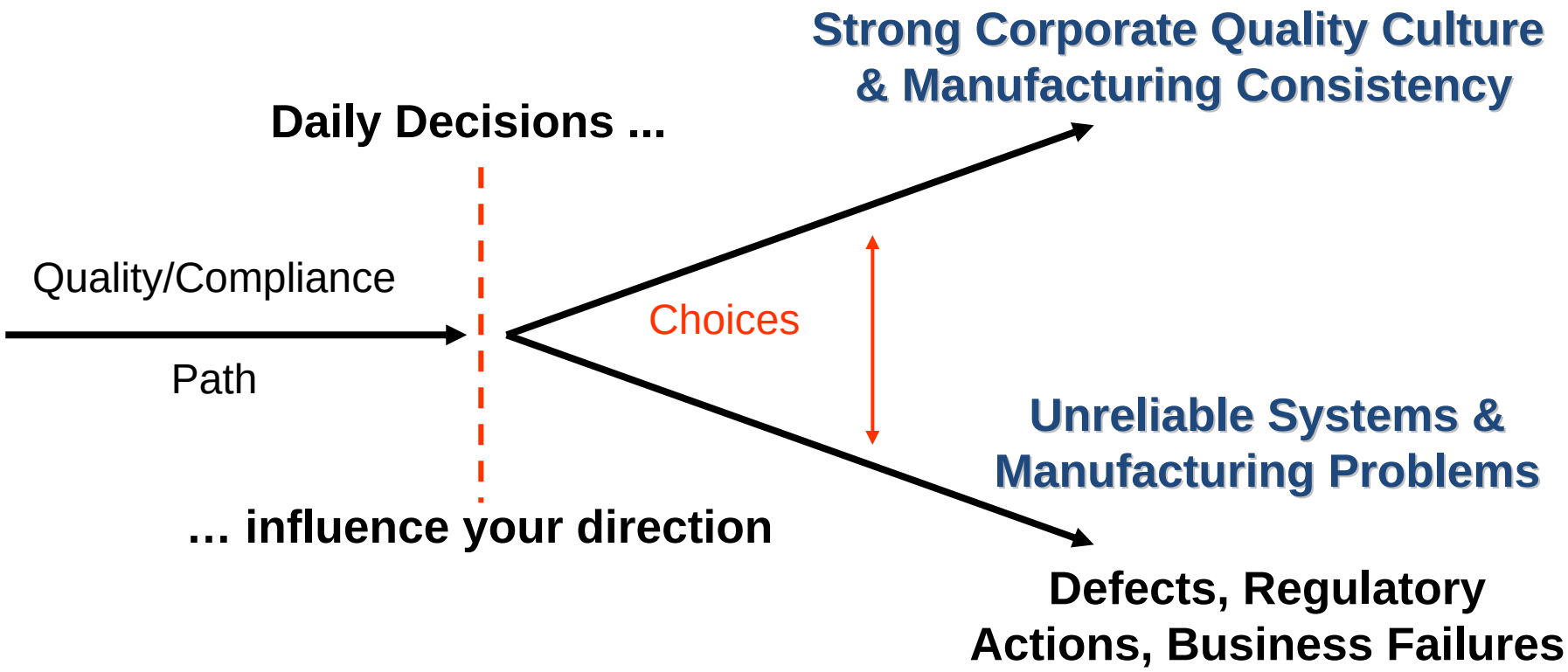
Risk Reduction Opportunities

Two "very" common causes… (cont'd)

1. **Deficient Facilities and Processes (cont'd)**
   - Human Error is cause of substantial variation across the industry
   - Can be prevented by analyzing process for failure modes and increasing automation. A lifecycle QRM opportunity…
     - "Human Error Analysis" – HE training allows for "deeper insights into the underlying causes of human error in order to identify and avoid its sources" *[Migliaccio, et al, Chapter in* **The Pathway to Operational Excellence,** *2010, ECV Publishing]*
2. **Ingredient Variability**
   - Excipients: FDA's *Recall Root Cause Research* findings
   - Most excipients are naturally-derived
   - Use of QRM for supplier selection, monitoring, and management

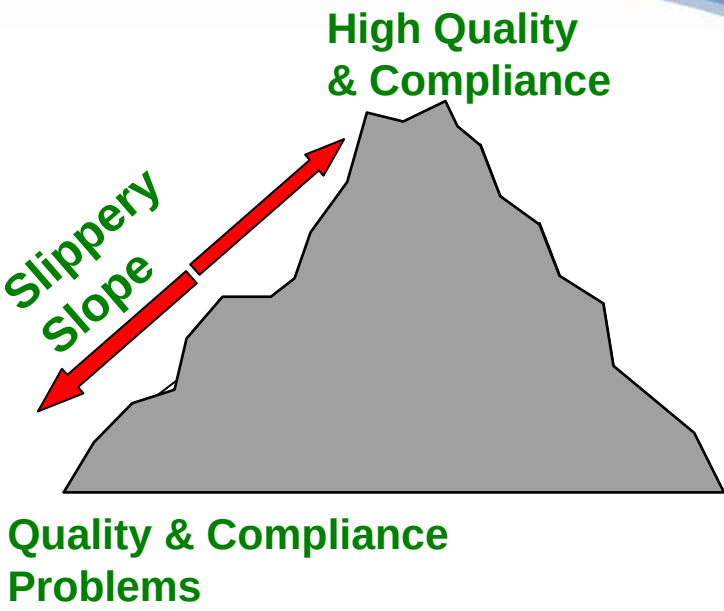
A Quality Culture That Leads to Sustainable Compliance…

Leadership and the Corporate Quality Culture



Adapted from Richard Davis (2004)

Quality Culture



- Support for the Quality Organization
- Actions More Than Words
- Investment in Quality
- Quality Involved in Business Decisions
- The Quality of the Work You Accept Becomes Your Standard
- Organizational Structure: assures that QA is independent and not subordinate to other organizational unit

Adapted from Richard J. Davis

EU: Pharmaceutical Quality System

- A Pharmaceutical Quality System is mandatory to comply with EU GMP
- ICH Q10 reflects current expectations for EU GMP
  - But, early lifecycle (initial development) not subject to explicit GMP
- "The manufacturer shall establish and implement an effective pharmaceutical quality assurance system, involving the active participation of the management and personnel of the different departments" [Art. 6 Directive 2003/94/EC and 91/412/EEC]

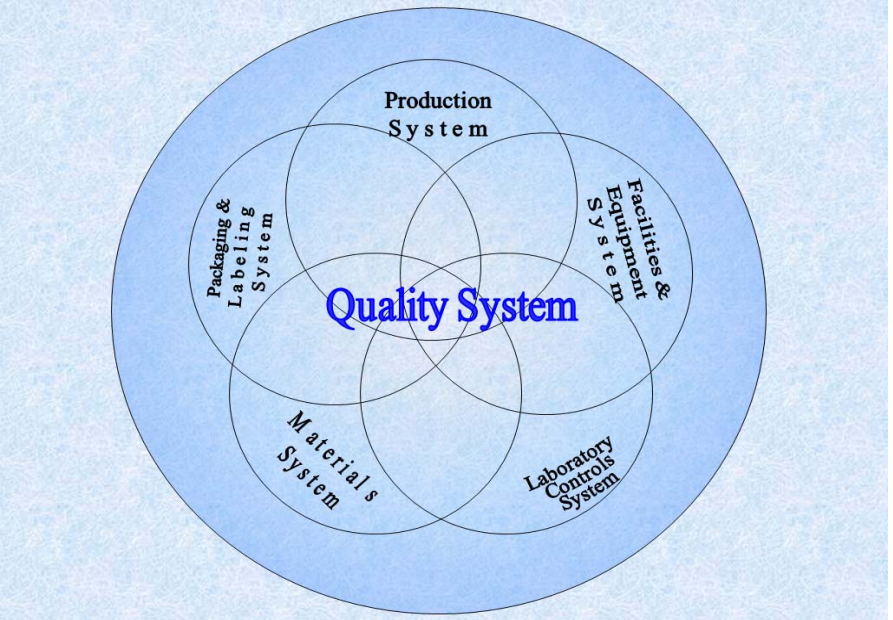
Adapted from ICH Q10 Conference (D. Cockburn, EMA)

FDA Inspections of the Pharmaceutical Quality System

FDA's Inspection/Compliance Program (CPGM 7356.002): Evaluation of the Pharmaceutical Quality System

The organization and personnel ("including appropriate qualifications and training") will be evaluated for each system chosen for inspection.

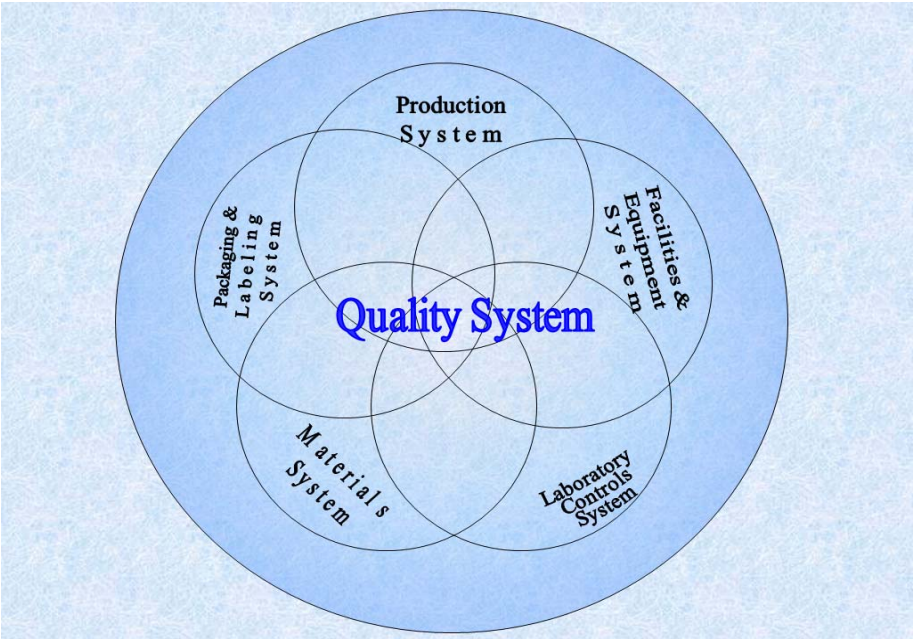
- Production
- Packaging & Labeling
- Equipment & Facilities
- Materials
- Laboratory
- Quality



FDA's Inspection/Compliance Program (CPGM 7356.002): Evaluation of the Pharmaceutical Quality System

FDA's inspection program began evaluating conformance to CGMPs using the **quality systems approach** in 2002.

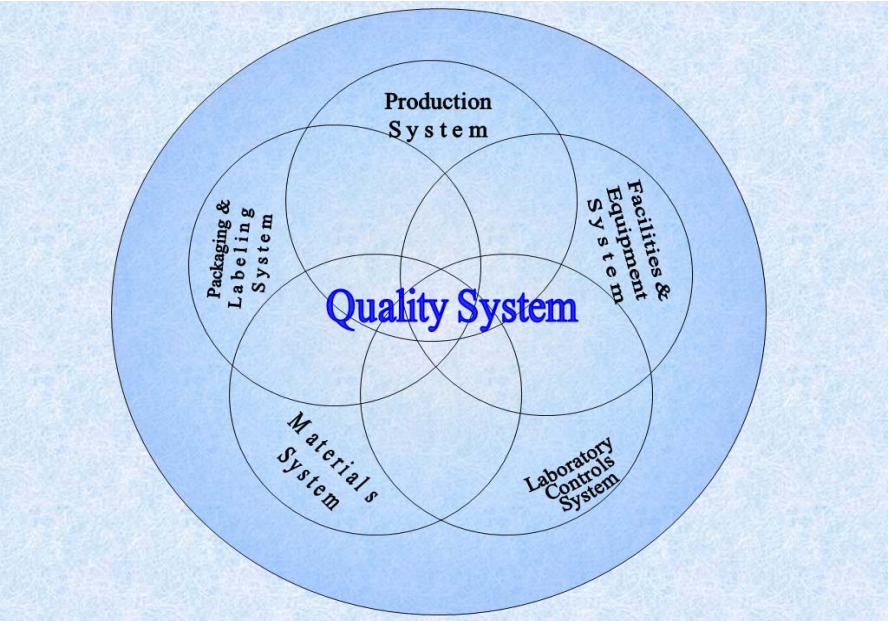
A drug firm is considered to be **operating in a state of control** when it employs conditions and practices that assure compliance with the intent of Sections 501(a)(2)(B) of the Act **and** the CGMP regulations that pertain to their systems.



FDA's Inspection/Compliance Program (CPGM 7356.002): Evaluation of the Pharmaceutical Quality System

Section 501 (21 U.S.C. 351) is amended by adding:

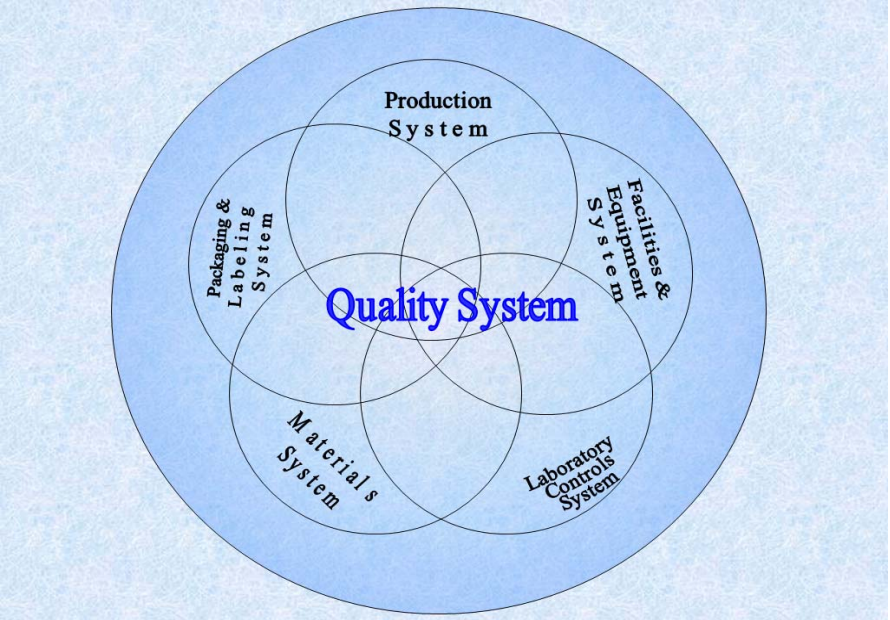
"For purposes of paragraph (a)(2)(B), the term 'current good manufacturing practice' **includes the implementation of oversight and controls over the manufacture** of drugs to ensure quality, including **managing** the **risk** of and establishing the safety of raw materials, materials used in the manufacturing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



FDA's Inspection/Compliance Program (CPGM 7356.002): Evaluation of the Pharmaceutical Quality System

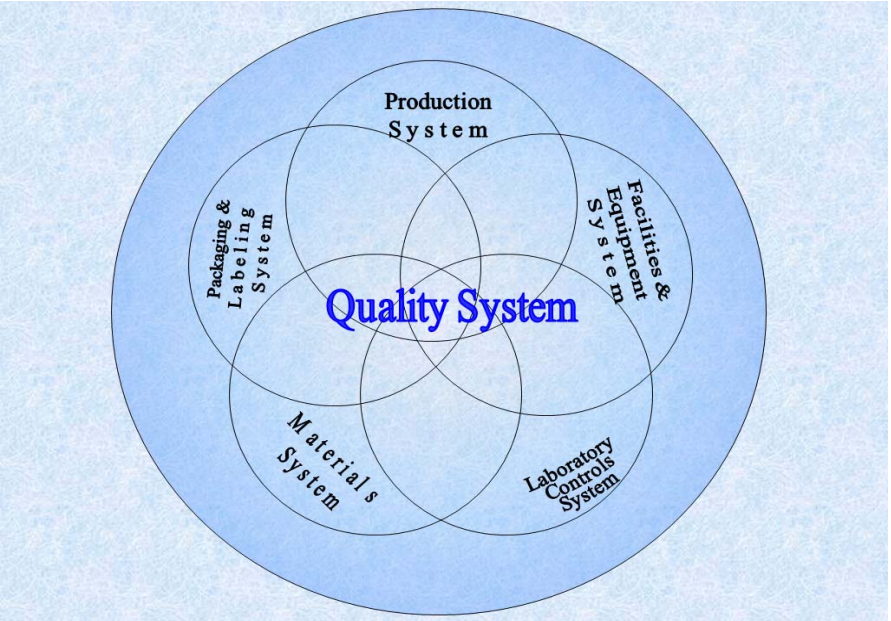
- "Quality System: This system assures **overall** compliance with CGMPs and internal procedures and specifications."

- Not only undertaken or overseen by QA/QC. It involves many other responsible departments.



FDA's Inspection/Compliance Program (CPGM 7356.002): Evaluation of the Pharmaceutical Quality System

When **the management of the firm** is unwilling **or** unable to provide adequate corrective actions in an appropriate time frame, formal agency regulatory actions will be recommended, designed to meet the situation encountered.

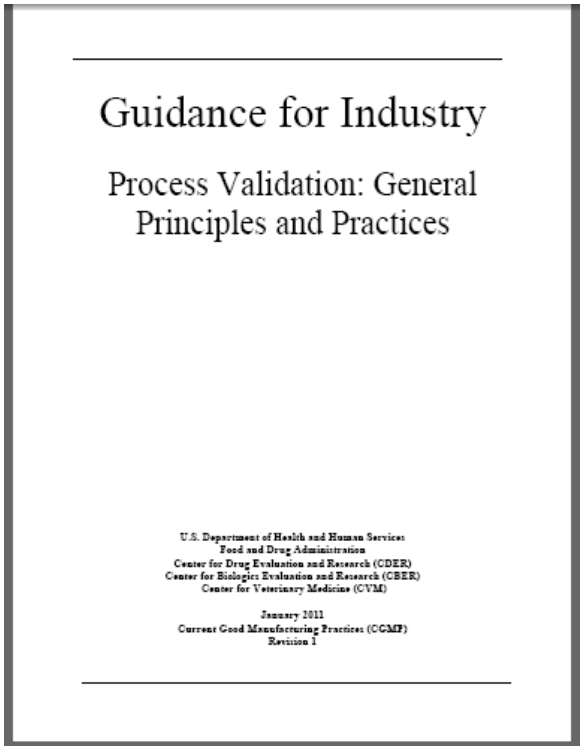


Findings that demonstrate that a firm is not operating in a *state of control* are basis for taking appropriate regulatory actions.

What is a CGMP-compliant Quality System?

Would you consider the following CGMP Compliant?

1. The manufacturing processes is not operating in a *State of Control*.


Guidance for Industry

Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

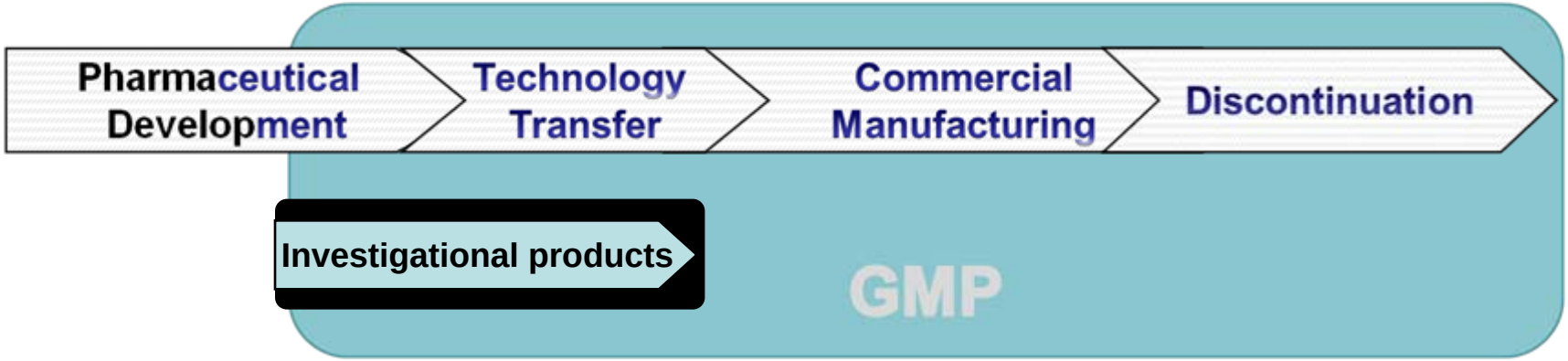
January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

"After establishing and confirming the process, **manufacturers must maintain the process in a state of control over the life of the process,** even as materials, equipment, production environment, personnel, and manufacturing procedures change." (FDA PV Guidance)

State of Control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

Would you consider the following CGMP Compliant?

2. *Technology transfer* (Scale-up) is insufficient to support current commercial operations, leading to problems in commercial manufacturing.



Management Responsibilities

PQS elements

Process Performance & Product Quality Monitoring System
Corrective Action / Preventive Action (CAPA) System
Change Management System
Management Review

Enablers

Knowledge Management

Quality Risk Management

Some GMP References addressing technology transfer and scale-up:

- Guide to Inspections of Oral Solid Dosage Forms Pre/Post Approval Issues (1/94)

- Pre-approval Inspection Compliance Program Guidance Manual (5/10)

- Process Validation: General Principles and Practices (1/11)

- Compliance Policy Guide 490.100 (3/04)

Would you consider the following CGMP Compliant?

3. The firm has an inadequate system for *managing changes.*

Would you consider the following CGMP Compliant?

4. Firm is using significantly outdated production technology that allows for excessive variation, leading to major manufacturing and quality problems. The firm has never implemented any of multiple, highly capable contemporary *innovations* in processing equipment that would resolve the problem. In contrast, these technological improvements to process design are routinely used by many others (feasible and valuable) to assure a robust and reproducible process.

Change Management: CGMP Requirements (21 CFR 211)

MANUFACTURE: "Any changes" in procedures for production and process controls designed to assure identity, strength, quality and purity shall be approved by the appropriate organizational units and reviewed and approved by the quality control unit. **(211.100)**

LABORATORY: "Any change" in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit **(211.160)**

IMPROVEMENT: Firm must review, *at least annually*, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. **(211.180)**

Change Management – ICH Q10

Change Management (3.2.3): "*Innovation*, continual improvement, the outputs of process performance and product quality monitoring, and CAPA drive change. To evaluate, approve, and implement these changes properly, a company should have an effective change management system."

Design

• "OOS results may indicate a *flaw in product or process design.* For example, a lack of robustness in product formulation, inadequate raw material characterization or control, substantial variation introduced by one or more unit operations of the manufacturing process, or a combination of these factors can be the cause of inconsistent product quality. In such cases, it is essential that *redesign* of the product or process be undertaken to ensure reproducible product quality." - *Guidance on Investigating Out-of-Specification Test Results for Pharmaceutical Production*

• "Design" is found many times in the CGMP regulations. For example, production and process controls must be designed in a manner that assures drug product identity, strength, quality, and purity (211.100). CGMP also requires appropriate equipment design, size, and location (21 CFR 211.63).

Would you consider the following CGMP Compliant?

5. The process is not monitored for *process performance and product quality* to maintain a state of control. Instead, the manufacturer routinely reacts to problems (i.e., rejections, complaints, returns, and other quality problems are the principle quality measures).

Building knowledge…
Effective monitoring & control systems

ICH Q10: "To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes."

CGMPs (e.g.):

- 211.110(a) Control Procedures (monitor the output and validate the performance of manufacturing processes)
- 211.192: Investigation of Discrepancies (Any unexplained discrepancy shall be thoroughly investigated. A written record of the investigation shall be made and shall include the conclusions and follow up.)
- 211.22: Quality Unit Responsibilities (complete investigation of errors that have occurred)
- 211.180(e): For each drug, evaluate the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures at least annually.

Building knowledge…
Effective monitoring & control systems

- FDA's 2011 Process Validation Guidance:
  - An ongoing program to collect and analyze product and process data that relate to product quality must be established. The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

  - Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program (lifecycle stage 3).

Would you consider the following CGMP Compliant?

6. Responsible officials were not aware of major product quality problems (e.g., complaints, returns) to enable appropriate *management review*.

- **CGMPs (for example)**

211.180(f): Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations,…

- **ICH Q10**

Ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

Would you consider the following CGMP Compliant?

7.The manufacturer routinley *reacts* to production failures by making corrective actions, but does not take any preventive actions (inadequate *CAPA* program).

CAPA

- See 21 CFR 211.192, 211.22, 211.110, 211.180(e), other regulations
- *Prevention* (of contamination, loss of process control, errors, defects, etc.) is basic theme and purpose of the CGMP regulations
- An effective CAPA program will decrease process variation and improve product quality (Q10, 3.2.2)

Would you consider the following CGMP Compliant?

8. You are the owner and applicant for a multi-use opthalmic product, and learn that your contract manufacturer has received complaints that two batches contain leaking containers. This *contract manufacturing* site produces batches for you when you can't meet demand at your site. The two lots have already been distributed. The investigation of the complaints includes testing retains, and you learn from testing that three other lots produced over the last two years also have a significant number of leakers. You had qualified the facility solely by testing the first three lots it produced.

Managing Outsourced Activities (ICH Q10)

- Extends beyond local site or corporation. Includes management review and control of....
  - Outsourced activities (CMOs)
  - Quality of incoming materials (ingredients)
- Prior to outsourcing operations or selecting material suppliers, assess suitability and competence of the other party to:
  - carry out the activity
  - provide the material using a defined supply chain
- Examples of program elements:
  - audits, material evaluations, quality agreement, monitoring and reviewing supplier performance, etc.

Managing Outsourced Activities

Sec. 200.10 Contract facilities...

(b) The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and **regards extramural facilities as an extension of the manufacturer's own facility.**

(c) The FDA reserves the right to disclose to the pharmaceutical **manufacturer**, **or** to the **applicant** of a new drug application (NDA) or to the sponsor of an Investigational New Drug (IND) Application, any information obtained during the inspection of an extramural facility having a specific bearing on the **compliance** of the manufacturer's, applicant's, or sponsor's **product** with the Federal Food, Drug, and Cosmetic Act.... FDA does not consider results of validation studies of analytical and assay methods and control procedures to be trade secrets that may be withheld from the drug manufacturer by the contracted extramural facility.

[40 FR 13996, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990]

- Also see 211.22 and other relevant regulations

FDA's Inspection/Compliance Program (CPGM 7356.002): Evaluation of the Pharmaceutical Quality System

SEC. 711. ENHANCING THE SAFETY AND **QUALITY** OF THE DRUG SUPPLY.

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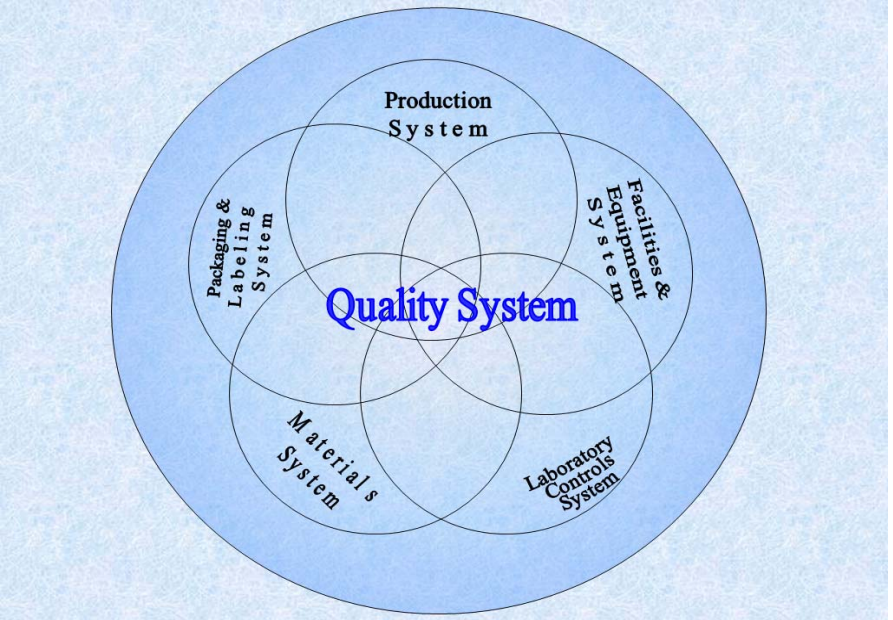

Would you consider the following CGMP Compliant?

9. Management does not provide adequate and appropriate *resources* (human, financial, materials, facilities, and equipment) to sustainably meet CGMP in order to maintain robust operations.

Resources

Some Relevant CGMP Regulations…

211.25(c), 211.63, 211.100, 211.42, 211.58, 211.67, 211.182

ICH Q10:

Management commitment to surfacing emerging issues, quality policy & planning, resource management, and continual improvement.

Pharmaceutical Quality Systems Objective: Assure Quality of Every Batch, Every Day

"We rely upon the manufacturing controls and standards to ensure that time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality… We have to think of the primary customers as people consuming that medicine and we have to think of the statute and what we are guaranteeing in there, that the drug *will continue to be safe and effective and perform as described in the label*."

- Janet Woodcock, M.D.