



Regulatory Education for Industry (REdI): Focus on CGMPs & FDA Inspections

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The Pharmaceutical Quality System (PQS)

Robert Iser
Senior Scientific Advisor (acting)
Office of Process & Facilities / OPQ / CDER



Introduction & Objectives

- **A robust PQS is critical to assuring drug products are manufactured to meet the desired quality and performance attributes**
- **PQS is the key system evaluated during FDA inspection, and is also key in providing FDA confidence that appropriate (science and risk based) support information is used to make decisions (e.g., in submissions).**
- **This presentation will explore:**
 - **PQS Elements in ICH Q10**
 - **Inspection strategies in evaluating a PQS [CPGM 7356.002]**
 - **21 CFR 210 & 211 Components of the Quality System**
 - **Linkage of PQS to Submissions**



First Things First...

What is Quality?



What is Quality [of a pharmaceutical product]?

- **“It delivers the properties described on the label and is not contaminated” – Dr. Woodcock**
- **"fitness for intended use"***
- **“freedom from defects”***
- **"meeting or exceeding customer expectations"***
- **“customer's definition of quality is the only one that matters”***

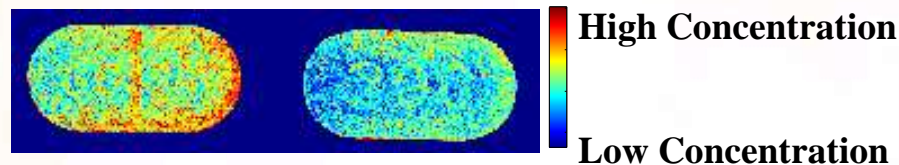
*Modified from Juran & Deming



What is Quality?

For a Drug Product, Typically the Patient Cannot “See” Quality!

Which product is sub-potent?



The Patient Expects Quality!!



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

Perform
consistently
over their
shelf life

Are **made** in
a manner
that ensures
quality

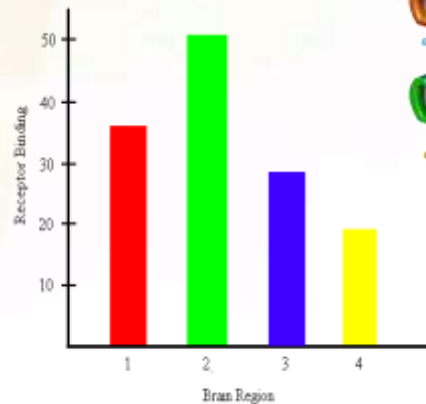
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when
needed





Expectations for Quality

A single FDA reviewer does not get the “full picture” of quality based on the submission...





Office of Pharmaceutical Quality

Immediate Office
Acting Director: Janet Woodcock
Deputy Director: Lawrence Yu

Office of Lifecycle Drug Products
Acting Director:
Susan Rosencrance

Office of New Products
Acting Director:

Office of Biotech. Products
Director:
Steven Kozlowski

Office of Surveillance
Acting Director:
Russell West

Office of Process and Facilities
Acting Director:
Christine Moore

Office of Regulatory Operations
Acting Director:
Giuseppe Randazzo

Office of Policy for Pharma. Quality
Acting Director:
Ashley Boam

Office of Testing and Research
Director:
Cindy Buhse

Will this assure Quality?

What really assures Quality?

Quality • Production • Laboratory • Materials • Facilities and Equipment • Packaging and Labeling



The Real Assurance of Quality

A robust pharmaceutical quality system!!!

3 Standards & Expectations – Regulations & CGMPs

1 QS Elements / Framework - ICH Q10

2 FDA Evaluation – Inspection & Review



Background: ICH Q10 - Pharmaceutical Quality System

Objectives:

- Achieve product realization
- Establish and maintain a *state of control*
- Facilitate *continual improvement*
- Facilitate effective knowledge transfer and management

Enablers:

- Knowledge & Quality Risk Management



Background: ICH Q10 - Pharmaceutical Quality System

The pharmaceutical quality system “**assures** that the desired product quality is routinely met, suitable **process performance** is achieved, the **set of controls** are appropriate, **improvement opportunities** are identified and evaluated, and the **body of knowledge** is continually **expanded.**”

ICH Q10, Section 3.1.3 Commercial Manufacturing



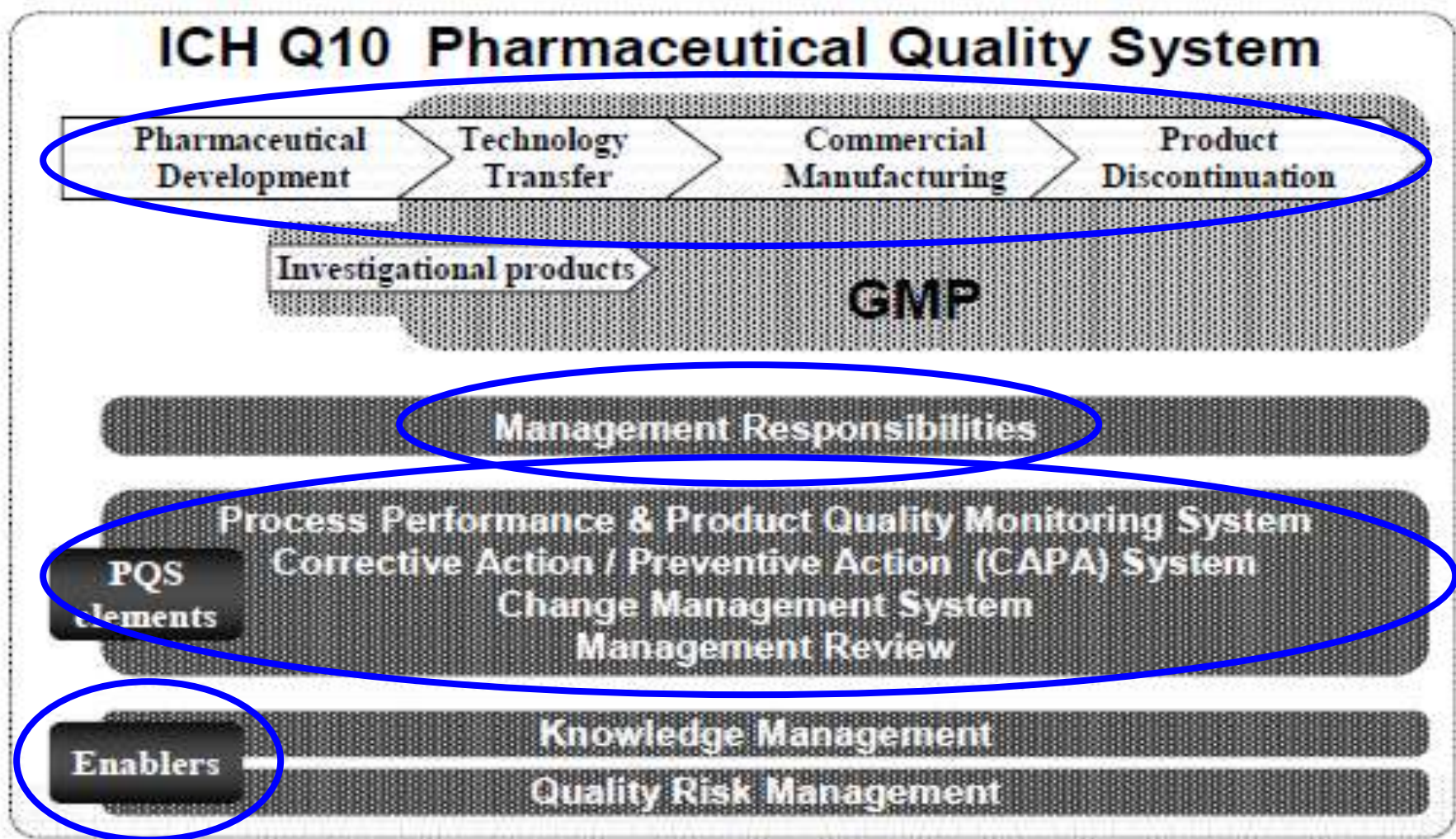
ICH Q10 - Pharmaceutical Quality System

- **Foundation of Q10 - Regional GMPs, ICH Q7 and ISO QMS**
- **Augments GMPs by describing specific quality system elements...helping industry and regulators achieve harmonization...**





ICH Q10 - Pharmaceutical Quality System





ICH Q10 - Pharmaceutical Quality System

Lifecycle Stages - 1

Pharmaceutical Development

- **DS development; DP formulation development (including IND & CCS)**
- **Manufacturing process development and scale-up**
- **Analytical method development**

Goal – design a product and process that consistently delivers intended performance and meets needs of customer



ICH Q10 - Pharmaceutical Quality System *Lifecycle Stages - 2*

Technology Transfer

- **New product transfers during development through manufacturing**
- **Transfers within or between manufacturing and testing sites for marketed products**

Goal – transfer product and process knowledge to achieve realization



ICH Q10 - Pharmaceutical Quality System *Lifecycle Stages - 3*

Commercial Manufacturing

- Acquisition and control of materials
- Provision of facilities, utilities, and equipment
- Production (including packaging and labeling)
- Quality control and assurance (including release, storage, distribution)

Goal – achieving realization, establishing and maintaining a state of control and facilitating continual improvement



ICH Q10 - Pharmaceutical Quality System

Lifecycle Stages - 4

Product Discontinuation

- **Continued product assessment and reporting**
- **Document archiving; sample retention**

Goal – manage terminal stage of lifecycle effectively



ICH Q10 - Pharmaceutical Quality System Elements

Four Pharmaceutical QS elements:

- 1. Process performance and product quality monitoring system**
- 2. Corrective action and preventive action (CAPA) system**
- 3. Change management system**
- 4. Management review of process performance and product quality**



Process & Product Monitoring

Table I: Application of Process Performance and Product Quality Monitoring System Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale-up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.



CAPA

Table II: Application of Corrective Action and Preventive Action System Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward, and continual improvement.	CAPA should be used, and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered, as well as other products that might be affected.



Change Management

Table III: Application of Change Management System Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science- and risk-based assessments.	Any changes after product discontinuation should go through an appropriate change management system.



Management Review

Table IV: Application of Management Review of Process Performance and Product Quality Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale.	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality complaints.



ICH Q10 - Pharmaceutical Quality System *Highlights*

Quality Manual or equivalent documentation

- (a) The *quality policy*.**
- (b) The scope of the pharmaceutical quality system.**
- (c) Identification of the pharmaceutical quality system processes, as well as their sequences, linkages, and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner.**
- (d) Management responsibilities within the pharmaceutical quality system.**



ICH Q10 - Pharmaceutical Quality System *Highlights*

- **Management Responsibility**
 - **Leadership and commitment to quality**
 - **Quality Planning**
 - **Resource Management**
 - **Internal communication**
 - **Management Review**
 - **Oversight of Outsourced Activities**

**How is the PQS evaluated by
FDA?**

**Has your PQS been
evaluated?**

Were you concerned?



FDA Evaluation of PQS on Inspection

- **Compliance Program Guidance Manual (CPGM) 7356.002 - Quality System –**
- **The quality system (QS) includes the quality control unit and all its review and approval duties**
- **The QS assures / governs manufacture of quality product**
 - See CGMPs, 21 CFR 211 Subparts B, E ,F, G, I, J, K
- **The QS also assures overall compliance with CGMPs and internal procedures and specifications**

<http://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/ucm125404.pdf>



PQS – FDA Inspection Coverage

- QS assessment is two phased:
 - Quality (Control) Unit has fulfilled responsibilities – review & approve
 - Assess Data collected to ID quality issues – link to other systems
 - Facilities & Equipment
 - Materials
 - Production
 - Packaging & Labeling
 - Laboratory Controls





Quality Procedures Needed

- **Product Reviews – at least annually [product review, trending – 21 CFR 211.180 (e)]**
- **Product Issues - Complaint Reviews (quality & medical), Discrepancy & Failure Investigations, Reprocess/ Rework, Returns / Salvage, Rejects, Stability Failures, Quarantine**
- **Lifecycle – Validation, Training / Qualification, Change Control & Product Improvement Projects**

What is the Quality (Control) Unit and What Do They Do?



21 CFR 210.3 - Definitions

(15) **Quality Control Unit:**

Any person or organizational element designated by the firm to be responsible for the duties relating to quality control

Does this mean *only* the QC Unit is responsible for quality?



§211.22 Responsibilities of the Quality Control Unit

- a) Responsibility and authority to:
- Approve or reject
 - Approve or reject drug product “processed” under contract by another company
 - Review production records (e.g., identify errors)
 - Have the errors fully investigated (if errors occur)
- b) Responsible for having adequate laboratory facilities for testing and approval or rejection
- c) Responsible for approving or rejecting all procedures or specifications impacting the quality of drug product
- d) Responsibilities must be in writing and followed



§211.42 (c)(1) Design and construction features

Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the **quality control unit before release for manufacturing or packaging;**



§211.84 Testing and Approval or Rejection of components, drug product containers, and closures

Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the **quality control unit.**



§211.87 Retesting of approved components, drug product containers, and closures

Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the **quality control unit** in accordance with 211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure



§211.100 Written procedures; deviations

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the **quality control unit.**



§211.101 Charge-in of components

(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of **component dispensed to manufacturing shall be examined by a second person to assure that:**

(1) The component was released by the **quality control unit**



§211.110 Sampling and testing of in-process materials and drug products continued

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the **quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.**



§211.115 Reprocessing

(b) Reprocessing shall not be performed without the review and approval of the quality control unit.



§211.142 Warehousing procedures

Written procedures describing the warehousing of drug products shall be established and followed.

They shall include:

(a) Quarantine of drug products before release by the **quality control unit.**



§211.160 General requirements

(a) The establishment of any specifications, ...shall be drafted by the appropriate organizational unit and reviewed and approved by the **quality control unit.**



§211.165 Testing and release for distribution

(d) Acceptance criteria for the sampling and testing conducted by the **quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release.**



§211.180 Testing and release for distribution

(e) Written records required by this part shall be maintained so that data therein can be used for **evaluating, 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. Written procedures shall be established and followed for such evaluations and shall include provisions for:

- (1) A **review** of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.
- (2) A **review** of complaints, recalls, returned or salvaged drug products, and investigations conducted under § 211.192 for each drug product.



§211.192 Production record review

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the **quality control unit**....

Any unexplained discrepancy or the failure...shall be thoroughly investigated.... The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record....



§211.198 Complaint files

Written procedures...complaints regarding a drug product shall be established and followed. Such procedures...review by the **quality control unit**, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with 211.192.

Such procedures shall include provisions ...

Hello!

Where's the Quality Unit?



CP 7356.002 Drug Manufacturing Inspections Quality System—Deficiencies

Identify any pattern of failure to:

- **Control batches before release to market**
- **Conduct investigations and resolve discrepancies, failures, deviations, complaints**
- **Review/approve procedures**
- **Document execution of operations, as required**
- **Pattern of failure to assess other systems or areas to assure conformance with SOPs and CGMP**



Example § 211.22 Citations

You have not established a **quality control unit** with the responsibility and authority to approve or reject..., and the authority to review production records to assure that no errors have occurred. [21 CFR § 211.22(a)]

Failure to have, and adequately follow, responsibilities and procedures applicable to the **quality control unit** in writing. [21 CFR § 211.22(d)]

Failure of your **quality control unit** to fully investigate errors such as laboratory deviations. [21 CFR § 211.22(a)]



PQS & “Quality Culture”



- **Manufacturer responsible for quality**
- **All manufacturing changes evaluated under robust PQS**
 - **Focus on meeting patients’ expectations**
 - **Regulators’ expectations considered minimal approach**
- **Strive for continual improvement**
- **Management and organizational commitment to prioritizing quality**
- **Each person in organization understands and embraces their role in quality**



Lifecycle Aspects – Linking PQS to Submissions

- **Established conditions** - the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure process performance and quality of an approved product.

From draft Established Conditions Guidance:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM448638.pdf>



Lifecycle Aspects – Linking PQS to Submissions

- **...changes after approval...must be managed and executed in conformance with current good manufacturing practices (CGMP)**
- **21 CFR 314.70 & 601.12 state that...an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided...**



Lifecycle Aspects – Linking PQS to Submissions

- Applicants should use knowledge obtained during transfer, scale up, and commercial activities to improve the control strategy.





Lifecycle Aspects – Linking PQS to Submissions

- **During commercial manufacturing, per 21 CFR Part 211, the applicant must assure:**
 - **the desired product quality is routinely met,**
 - **suitable process performance is achieved,**
 - **the set of controls are appropriate,**
 - **improvement opportunities are identified and evaluated, and**
 - **the body of knowledge is continually expanded.**



Lifecycle Aspects – Linking PQS to Submissions

- **Recommendations for product lifecycle activities to monitor continual assurance of the validated state and continual improvement principles**

See:

Guidance for industry on *Process Validation: General Principles and Practices*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

Guidance for industry on *Q10 Pharmaceutical Quality System*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf>



Lifecycle Aspects – Linking PQS to Submissions

- Established conditions are evaluated as part of an original application...
- The control strategy should be updated as new knowledge is gained and/or as new risks emerge...
- If control strategy or supporting information is/ **What does this mean? If PQS does not meet expectations (CGMPs, ICH Q10, etc.) this may impact an applicant's regulatory strategy** or evidence **the applicant lacks the ability to adequately manage change, FDA may reassess the established conditions**



A Robust PQS *Fosters* Excellence

- **A Robust PQS is:**
 - **In line with CGMPs**
 - **Comprehensive**
 - **Proactive**
 - **Science and risk-based**
 - **Accountable**
- **Benefits include:**
 - **Meeting Patient Needs More Effectively and Efficiently**
 - **Flexible Regulatory Strategies**
 - **Predictability**
 - **Increased Regulator Confidence**

Thank you for your attention!



OPQ Questions?

CDER-OPQ-Inquiries@fda.hhs.gov

Evaluation: surveymonkey.com/r/GDF-D1S2