# Pharmaceutical Product Quality, Quality by Design, cGMP, and Quality Metrics

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# What is Pharmaceutical Quality?

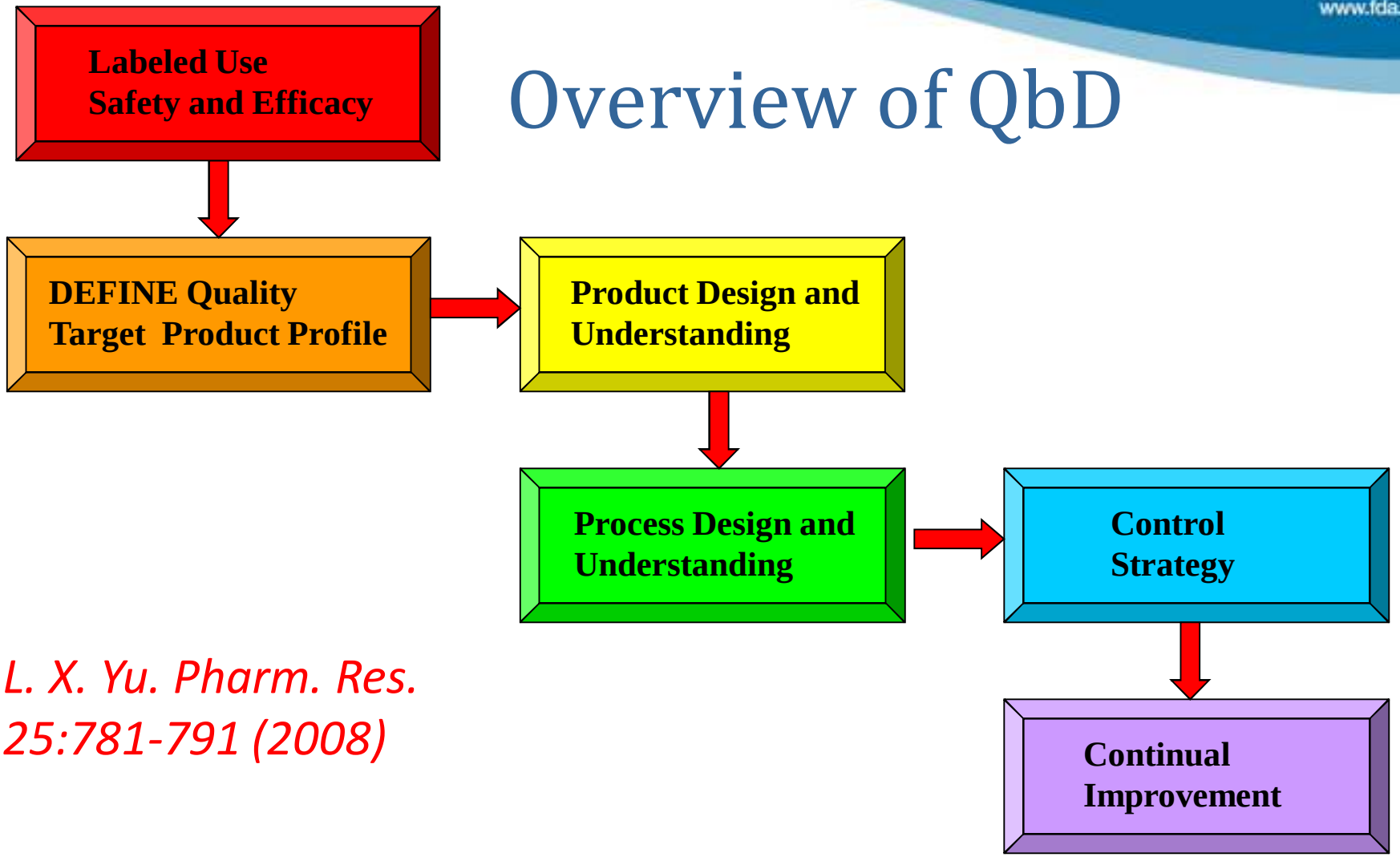
- Janet Woodcock
  - A high quality drug product as a product free of contamination and reproducibly delivering the therapeutic benefit promised in the label
    - Free of contamination: CGMP focus
    - Reproducibly delivering the therapeutic benefit promised in the label: QbD focus
- Therefore, <u>Pharmaceutical Quality = QbD + CGMP?</u>

# What is Quality by Design (QbD)?

- A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

| Systematic approach | |
|---|---|
| **Predefined objectives** | ▪ Define Quality Target Product Profile (QTPP)<br>▪ Identify Critical Quality Attributes (CQA) |
| **Product and process understanding** | ▪ Identify critical material attributes (CMA) and critical process parameters (CPP)<br>▪ Understand the relationship between CMA/CPP and CQA |
| **Process control** | ▪ Establish appropriate Control Strategy, including justifications |
| **Sound science** | ▪ Science-driven development (scientific literature, prior knowledge, DOEs etc.) |
| **Quality risk management** | ▪ Risk-based development (ICH Q9) |

# Overview of QbD




*L. X. Yu. Pharm. Res. 25:781-791 (2008)*

**TARGET** → **DESIGN and UNDERSTANDING** → **IMPLEMENTATION**

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*Research Paper*

# Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control

**Lawrence X. Yu**[1,2]

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***Purpose.*** The purpose of this paper is to discuss the pharmaceutical Quality by Design (QbD) and describe how it can be used to ensure pharmaceutical quality.

***Materials and Methods.*** The QbD was described and some of its elements identified. Process parameters and quality attributes were identified for each unit operation during manufacture of solid oral dosage forms. The use of QbD was contrasted with the evaluation of product quality by testing alone.

***Results.*** The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Some of the QbD elements include:

- Defining target product quality profile
- Designing product and manufacturing processes
- Identifying critical quality attributes, process parameters, and sources of variability
- Controlling manufacturing processes to produce consistent quality over time

***Conclusions.*** Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. Product testing confirms the product quality. Implementation of QbD will enable transformation of the chemistry, manufacturing, and controls (CMC) review of abbreviated new drug applications (ANDAs) into a science-based pharmaceutical quality assessment.

**KEY WORDS:** pharmaceutical quality by design; pharmaceutical quality by testing; process control; process design; process parameter; process variability; product design; quality attribute; question-based review.

# Quality by Testing vs. Quality by Design

- Quality by Testing
  - Specification acceptance criteria are based on one or more batch data
  - Testing must be made to release batches
- Quality by Design
  - Specification acceptance criteria are based on performance
  - Testing may not be necessary to release batches

*L. X. Yu. Pharm. Res. 25:781-791 (2008)*

*The AAPS Journal* (© 2014)
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*Review Article*

# Understanding Pharmaceutical Quality by Design

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***Abstract.*** This review further clarifies the concept of pharmaceutical quality by design (QbD) and describes its objectives. QbD elements include the following: (1) a quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product; (2) product design and understanding including identification of critical material attributes (CMAs); (3) process design and understanding including identification of critical process parameters (CPPs), linking CMAs and CPPs to CQAs; (4) a control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process; and (5) process capability and continual improvement. QbD tools and studies include prior knowledge, risk assessment, mechanistic models, design of experiments (DoE) and data analysis, and process analytical technology (PAT). As the pharmaceutical industry moves toward the implementation of pharmaceutical QbD, a common terminology, understanding of concepts and expectations are necessary. This understanding will facilitate better communication between those involved in risk-based drug development and drug application review.

**KEY WORDS:** control strategy; critical quality attributes; pharmaceutical quality by design; process understanding; product understanding.

# Pharmaceutical QbD Objectives

- Achieve meaningful product quality specifications that are based on assuring clinical performance
- Increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control
- Increase product development and manufacturing efficiencies
- Enhance root cause analysis and post-approval change management

*L. X. Yu et al. AAPS J. 16:771-83 (2014)*

# What are CGMPs?

- CGMP refers to the Current Good Manufacturing Practice regulations... CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities... This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors.

# CGMP: New Inspection Protocol Project

- Goal: To develop a new paradigm for inspections and reports that will advance pharmaceutical quality
  - Standardized approach to inspection
  - Data gathering to inform "quality intelligence" of sites and products
  - Risk based and rule based process, using expert questions
  - Semi-quantitative scoring to allow for comparisons within and between sites
  - More common inspection report structure
  - Recognize and reward positive behaviors in cases where facilities exceed basic compliance

# NIPP Project Organization

**New Inspection Protocols Project (NIPP)**
**CDER and ORA**

| Pre-Approval Inspection Subgroup | Surveillance Inspection Subgroup | For Cause Inspection Subgroup |
|---|---|---|
| *Observations to inform premarket review decisions* | *Observations on state of quality in a facility to assess quality risk* | *Evidence of cGMP violations to support enforcement* |

Draft Protocol

Draft Protocol


*Escalation/ transition to "For Cause" when conditions indicate*

# Quality Metrics

- Vision
  - A more rigorous and comprehensive approach to quality surveillance that allows for improved monitoring of current status across the inventory of FDA-regulated drug products and manufacturing sites
- Goals: Objective measures
  - Quality of a drug product
  - Quality of a site
  - Effectiveness of systems associated with the manufacture of pharmaceutical products
- Draft Guidance published July 27, 2015
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM455957.pdf

# FDA Draft Quality Metrics Guidance, July, 2015

- Metrics FDA Intends to Calculate
  - Lot acceptance rate
  - Product quality complaint rate
  - Invalidated Out-of-Specification rate
  - Annual product review or product quality review on time rate

# FDA Draft Quality Metrics Guidance, July, 2015 (continued)

- Optional Metrics
  - Quality Culture
    - Senior management engagement
    - corrective action and preventive action effectiveness
    - percentage of your corrective actions involved re-training of personnel
  - Process Capability/Performance
    - Process capability is a leading, useful indicator. However, its calculation is relative complex

# Concept of Process Capability/Performance

- First introduced in *Statistical Quality Control Handbook* by the Western Electric Company (1956).
  - "process capability" is defined as "the natural or undisturbed performance after extraneous influences are eliminated. This is determined by plotting data on a control chart."
- ISO, AIAG, ASQ, ASTM ….. published their guideline or manual on process capability index calculation

# Nomenclature

- Four indices:
  - $C_p$: process capability index
  - $C_{pk}$: minimum process capability index
  - $P_p$: process performance index
  - $P_{pk}$: minimum process performance index

ASTM E2281: Standard Practice for Process and Measurement Capability Indices

# Difference between $C_{pk}$ and $P_{pk}$

- Cpk represents the potential process capability (i.e. how well a given process **could perform** when all special causes have been eliminated).
- Ppk addresses how the process **has performed** without the demonstration of the process to be stable.
- Forecast future batch failure rate
  - **Cpk (Yes)** ; **Ppk (No)**

# Yu et al. Use Process Capability to Ensure Product Quality. *Pharm. Eng.* (2015)

- In this paper, we introduce the definition and calculation of process capability, illustrate their uses in pharmaceutical industry, and describe the relationship of process capability with production batch failure rate. We also describe the use of process capability in product development, process scale up and qualification, and commercial production.

# Summary

- Process capability is a leading, useful indicator. However, its calculation is relative complicated
- Promise: Quality standard is clinically relevant and a surrogate of clinical performance, then
  - Pharmaceutical Quality = QbD + CGMP??
  - Ppk = Cpk + CGMP???