Future of Pharmaceutical Quality and the Path to Get There

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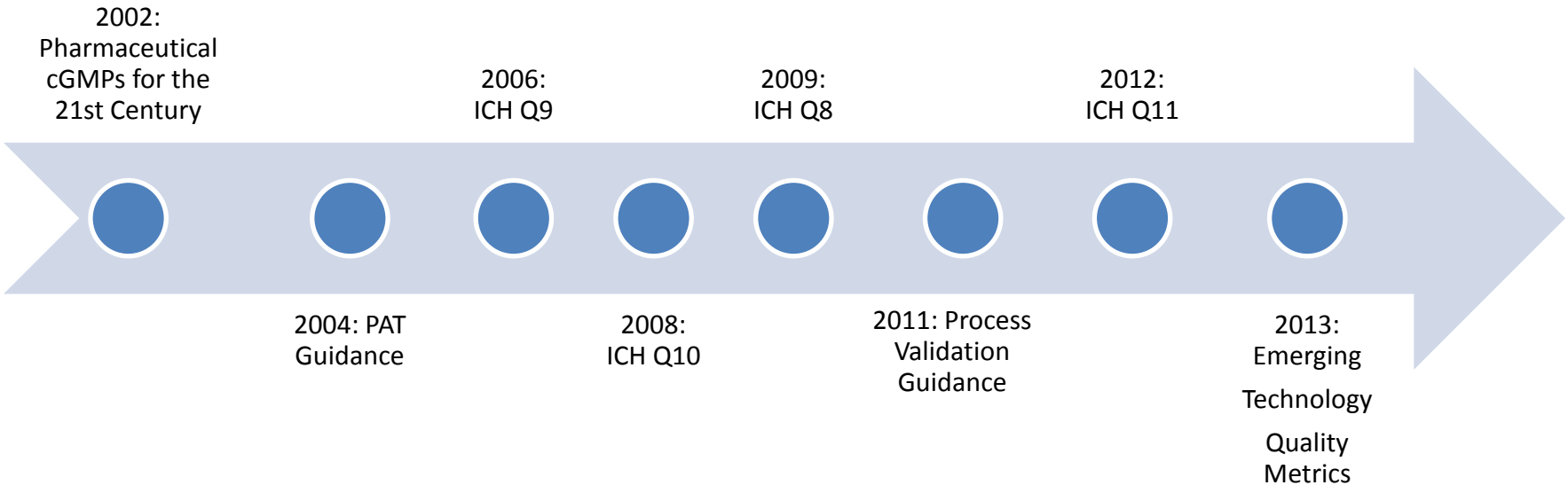
3rd PQRI/FDA Conference on Advancing Product Quality, March 22-24, 2017

Early 2000s: FDA Embarks upon Pharmaceutical Quality for 21st Century Initiative

Vision

> "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight"
>
> -Dr. Janet Woodcock

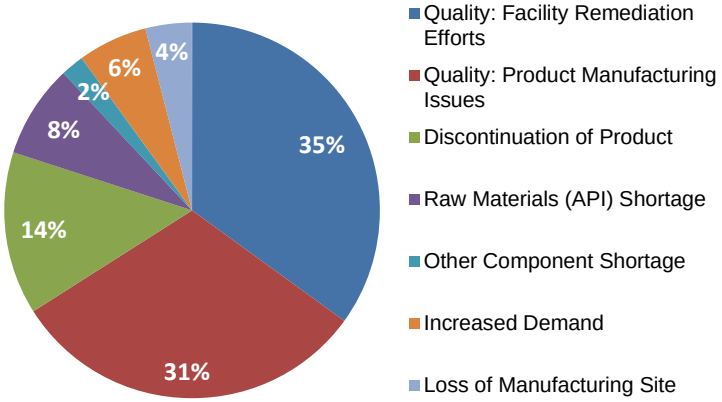
FDA CDER's Quality Journey

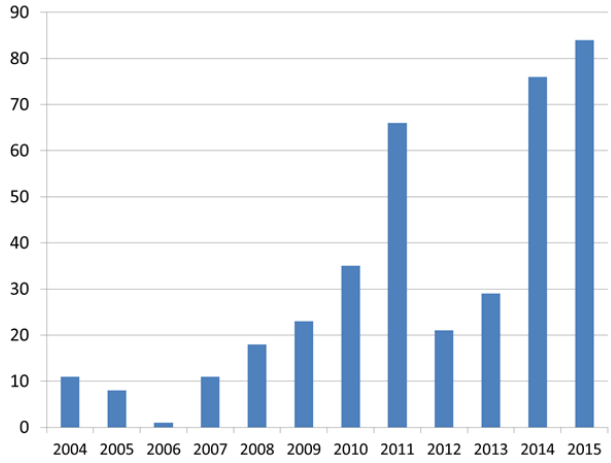


Building the Science and Risk-Based Foundation for the Regulation of Pharmaceutical Quality

Drivers for Modernizing Pharmaceutical Manufacturing

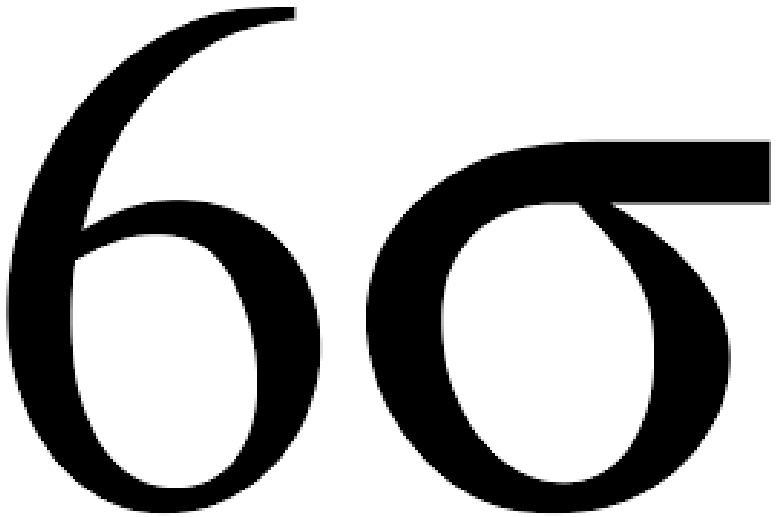
- Quality issues account for 2/3 of drug shortages
- Surge in drug product recalls due to quality issues
- The supply chain is globalized at an unprecedented level
- Major advances in the scientific landscape are pressuring existing regulatory paradigms, especially around biosimilars, precision medicine, combination products and the use of real-world data





Class 1 Drug Product Recalls

Future of Pharmaceutical Quality



A Six Sigma Capable Process is Expected to Have No More than 3.4 Defects per Million Opportunities

Path to Get 6 Sigma

- Economic Driver
- Performance-based Regulation
- Emerging Technologies
- Quality by Design
- Continuous Improvement and Operational Excellence

Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages

Woodcock, J; Wocinska, M. Clin. Pharmacol. & Thera. 93:170-176 (2013)

- The fundamental problem we identify is the inability of the market to observe and reward quality. This lack of reward for quality can reinforce price competition and encourage manufacturers to keep costs down by minimizing quality investments...

Path to Get 6 Sigma

- ✓ Economic Driver
- Performance-based Regulation
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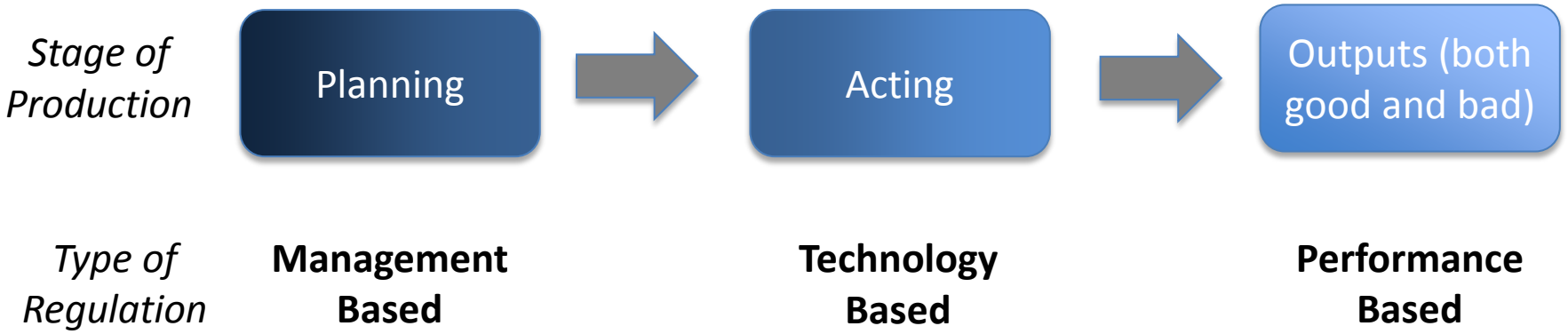
Performance-based Regulation

- A regulatory approach that focuses on desired, measurable outcomes, rather than prescriptive processes, techniques, or procedures. Performance-based regulation leads to defined results without specific direction regarding how those results are to be obtained
- At the Nuclear Regulatory Commission, performance-based regulatory actions focus on identifying performance measures that ensure an adequate safety margin and offer incentives to improve safety without formal regulatory intervention by the agency

Types of Regulations

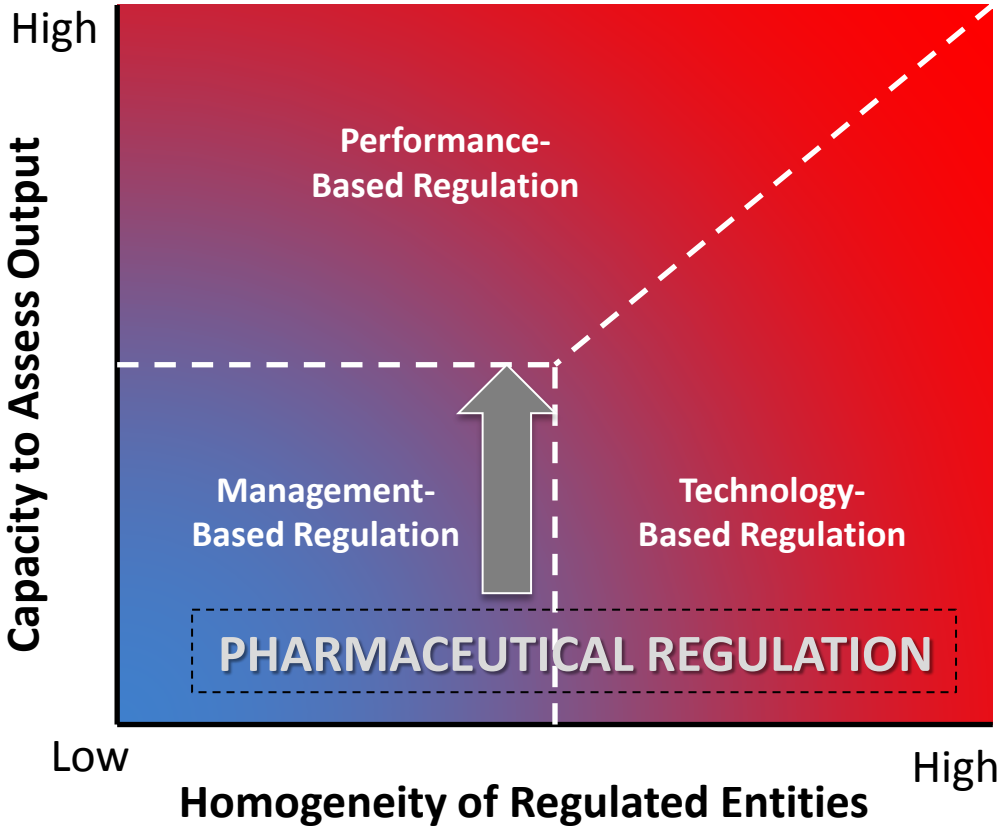
Stages of Organizational Production and Types of Regulation



- Pharmaceutical regulation should be designed to improve the performance of individual and organizational behavior in ways that protect and promote public health

Coglianese, C., & Lazer, D. (2003) *Law & Society Review*, *37*(4), 691-730.

Types of Regulations



Coglianese, C., & Lazer, D. (2003) *Law & Society Review*, *37*(4), 691-730.

FDA is Moving to Clinically Relevant Specification

- 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 clinical performance
  - Testing itself may not be necessary to release batches

We Need to Decouple Acceptance Criteria from Process Variability

FDA Quality Metrics Program

- Goals: Objective measures
  - Quality of a drug product
  - Quality of a site
- Vision
  - Patients/consumers expect and deserve quality drugs
  - FDA and manufacturers have the shared responsibility to make sure that quality drugs are available
  - The FDA's quality metrics program improves the quality of drugs, accessibility of quality drugs, and effectiveness of the FDA regulatory oversight

Path to Get 6 Sigma

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Guidance for Industry
PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
September 2004
Pharmaceutical CGMPs

Available online at www.sciencedirect.com
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Advanced Drug Delivery Reviews 56 (2004) 349–369
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Applications of process analytical technology to crystallization processes☆

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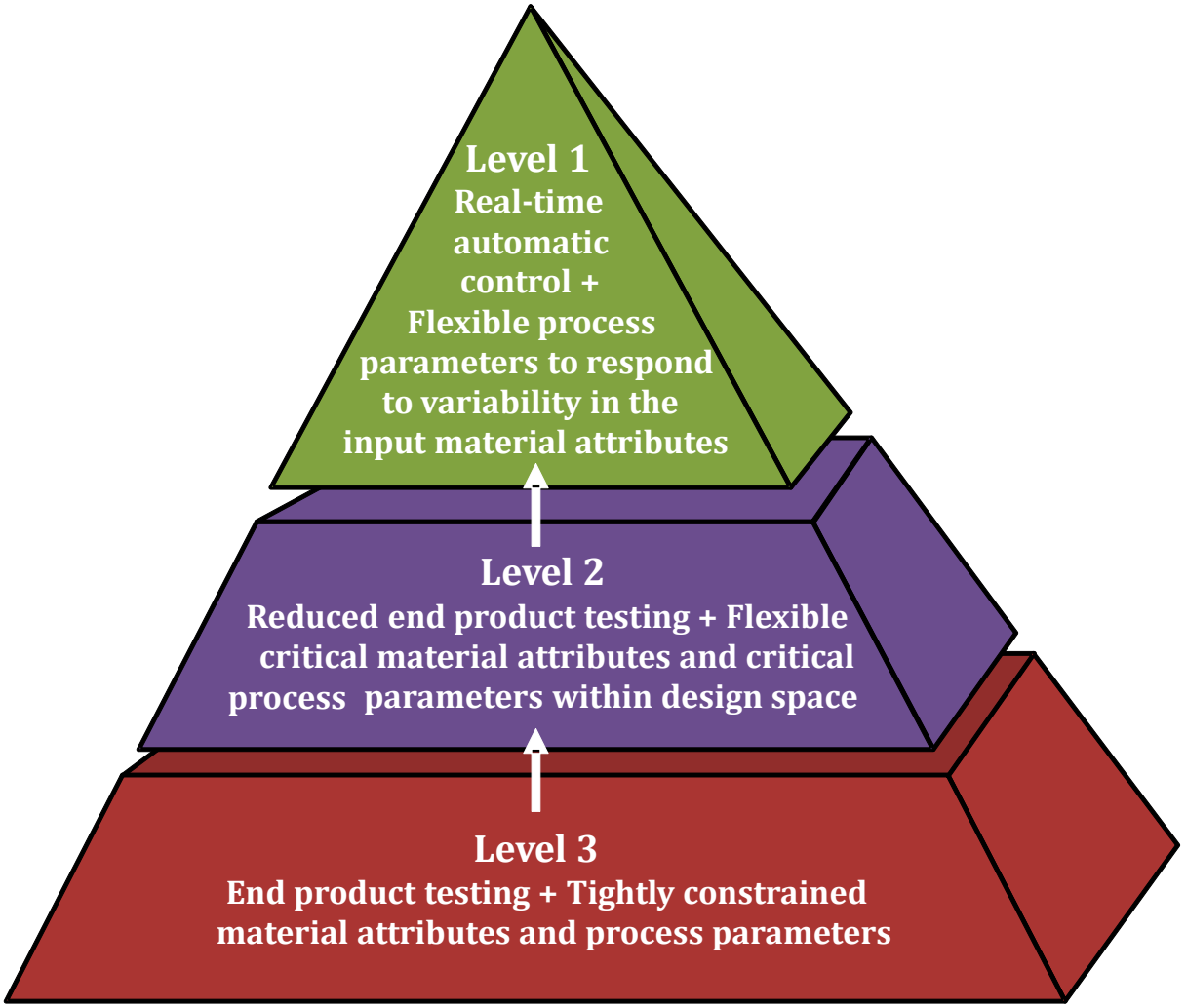
Abstract

Crystallizations of pharmaceutical active ingredients, particularly those that posses multiple polymorphic forms, are among the most critical and least understood pharmaceutical manufacturing processes. Many process and product failures can be traced to a poor understanding and control of crystallization processes. The Food and Drug Administration's process analytical technology (PAT) initiative is a collaborative effort with industry to introduce new and efficient manufacturing technologies into the pharmaceutical industry. PAT's are systems for design, analysis, and control of manufacturing processes. They aim to assure high quality through timely measurements of critical quality and performance attributes of raw materials, in-process materials, and final products. Implementation of PAT involves scientifically based process design and optimization, appropriate sensor technologies, statistical and information tools (chemometrics), and feedback process control strategies working together to produce quality products. This review introduces the concept of PAT and discusses its application to crystallization processes

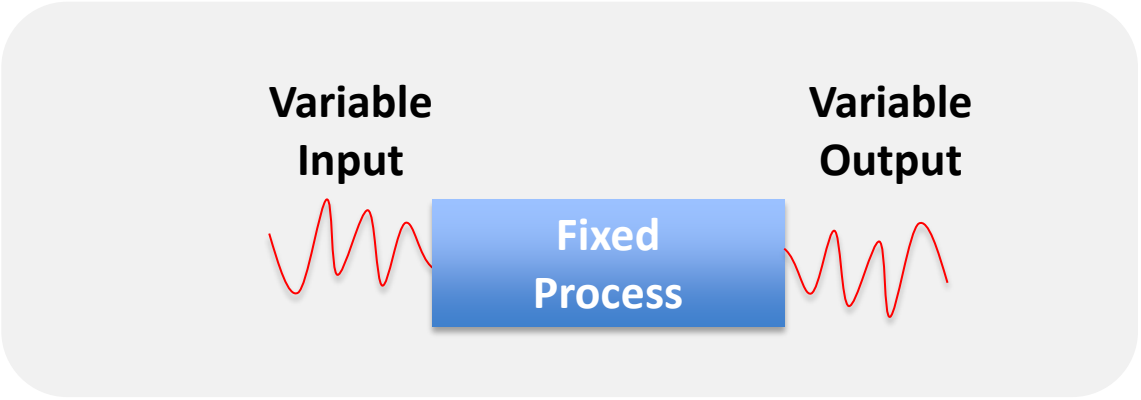
Control Strategy Implementation Options

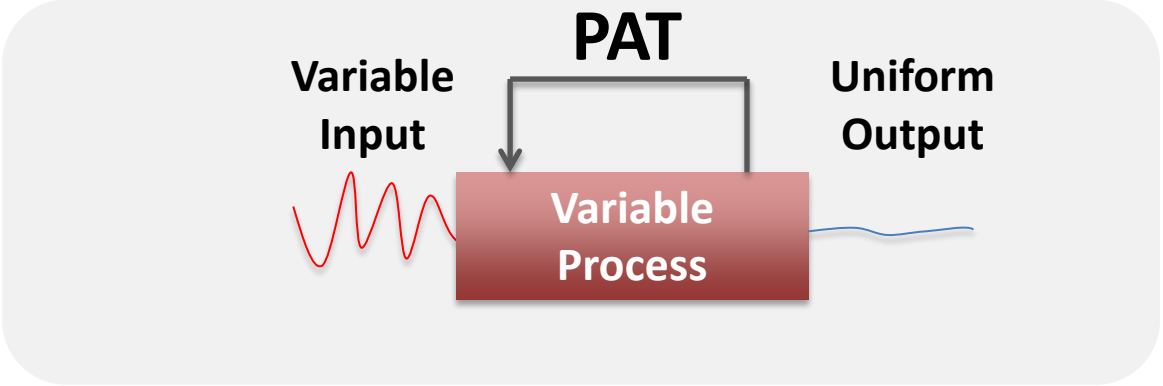
Enhanced Approach



Traditional Approach

Impact of Active Control





J Pharm Innov
DOI 10.1007/s12247-015-9215-8

REVIEW ARTICLE

Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

Sau L. Lee · Thomas F. O'Connor · Xiaochuan Yang · Celia N. Cruz · Sharmista Chatterjee · Rapti D. Madurawe · Christine M. V. Moore · Lawrence X. Yu · Janet Woodcock

© Springer Science+Business Media New York (outside the USA) 2015

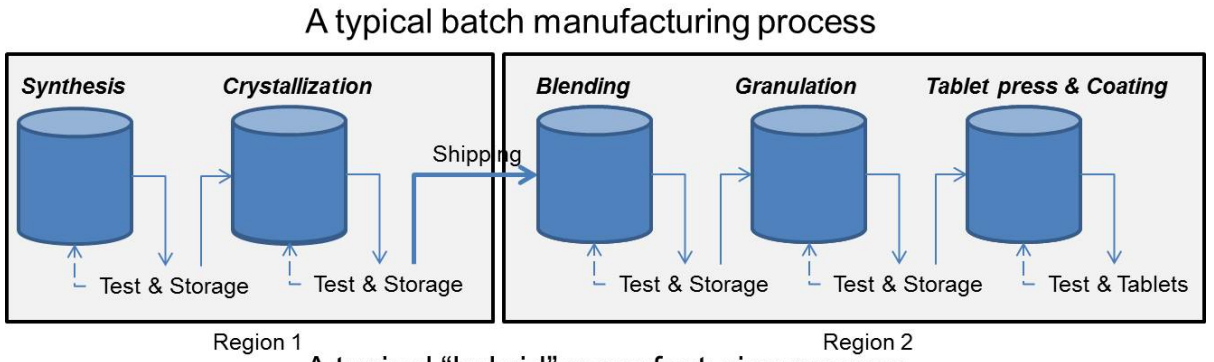
Abstract The Food and Drug Administration (FDA) regulates pharmaceutical drug products to ensure a continuous supply of high-quality drugs in the USA. Continuous processing has a great deal of potential to address issues of agility, flexibility, cost, and robustness in the development of pharmaceutical manufacturing processes. Over the past decade, there have been significant advancements in science and engineering to support the implementation of continuous pharmaceutical manufacturing. These investments along

efficient, agile, flexible pharmaceutical sector that reliably produces high-quality drugs without extensive regulatory oversight [1]. The pharmaceutical manufacturing sector is in transition, but overall processes, which are largely batch in nature, remain relatively inefficient and less understood as compared with those in other chemical process industries [2].

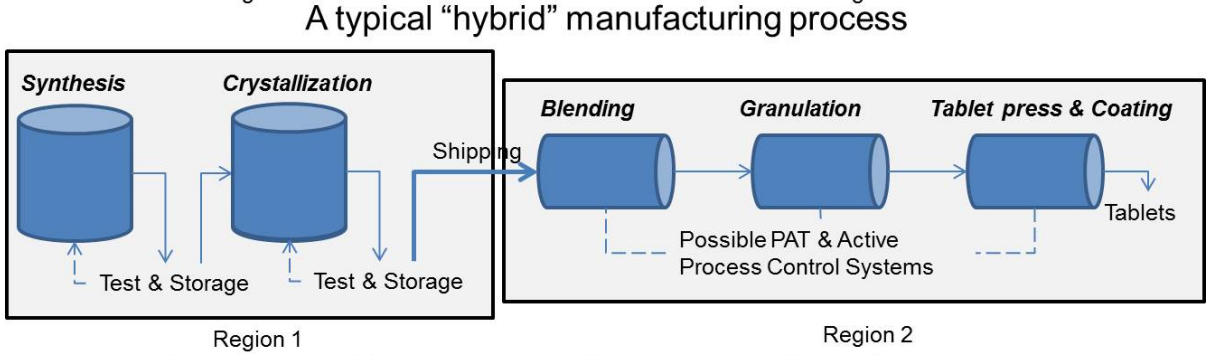
The lack of agility, flexibility, and robustness in the pharmaceutical manufacturing sector poses a potential public health threat as failures within manufacturing facilities that

Continuous Manufacturing

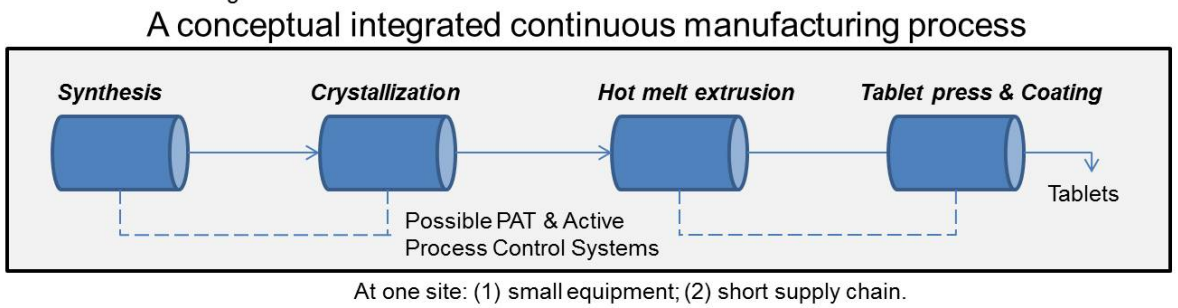
(1) Batch



(2) Hybrid



(3) End-to-End



At one site: (1) small equipment; (2) short supply chain.

Trends in Continuous Manufacturing

- Vertex's ORKAMBI™ (lumacaftor/ivacaftor)
  - 1st NDA approval for using a continuous manufacturing technology for production of the Cystic Fibrosis drug (tablets) (July 2015)
- Prezista (darunavir)
  - 1st NDA supplement approval for switching from batch manufacturing to continuous manufacturing process for an FDA-approved HIV drug (tablet) (April 2016)
- Over 15 ETT-Industry meetings
  - Drug substance
  - Drug product
  - Small-molecule and biotechnology products
  - Control strategy utilizing models

Path to Get 6 Sigma

- ✓ Economic Driver
- ✓ Performance-based Regulation
- ✓ Emerging Technologies
- Quality by Design
- Continuous Improvement and Operational Excellence

Quality by Design

- ICH Q8(R2)
  - Pharmaceutical Quality by Design (QbD) is 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
- Quality by Design Tools
  - Prior knowledge
  - Risk assessment
  - Design of experiments (DOE) and data analysis
  - Process analytical technology (PAT) tools

Quality by Design: Objectives

- To achieve meaningful product specifications that are based on clinical performance
- To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control
- To increase product development and manufacturing efficiencies
- To enhance post-approval change management

Pharmaceutical Research, Vol. 25, No. 4, April 2008 (© 2007)
DOI: 10.1007/s11095-007-9511-1

Research Paper

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

Lawrence X. Yu[1,2]

Received September 9, 2007; accepted November 26, 2007; published online January 10, 2008

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.

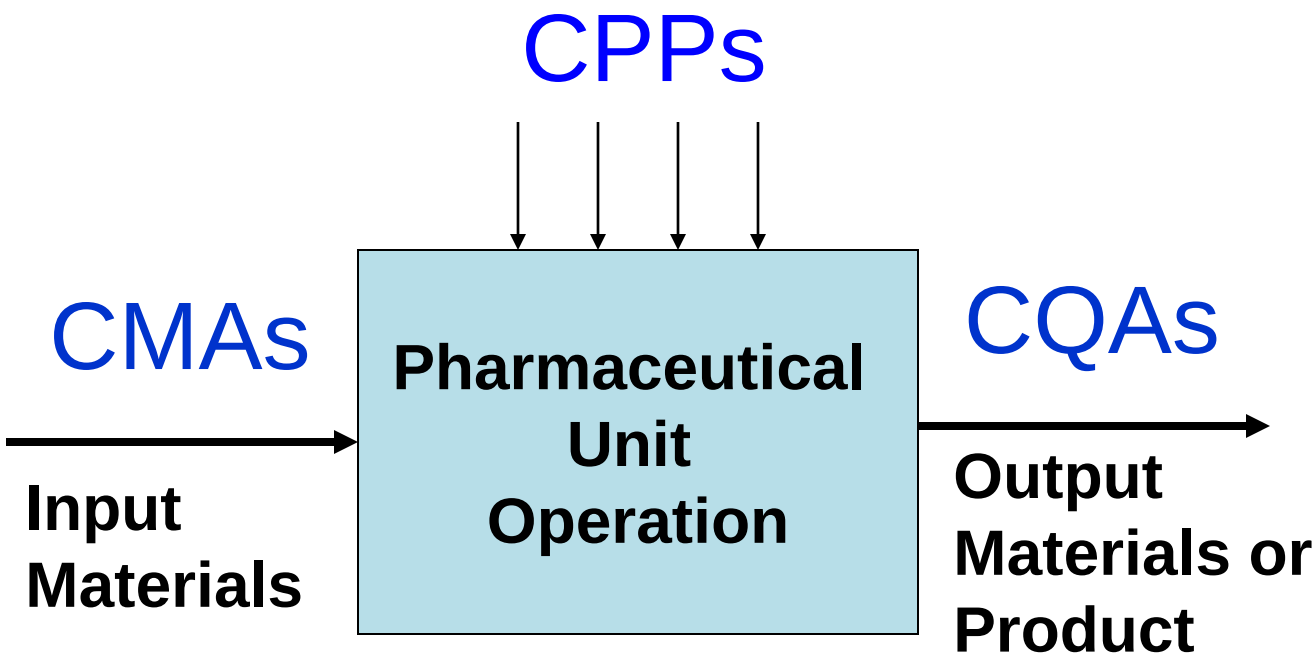
Results. The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Some of the QbD elements include:

- 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.

Relationship of CMA, CPP, and CQA



A CQA of an output material may become a CMA if it becomes an input material of another unit operation

The AAPS Journal (© 2014)
DOI: 10.1208/s12248-014-9598-3

Review Article

Understanding Pharmaceutical Quality by Design

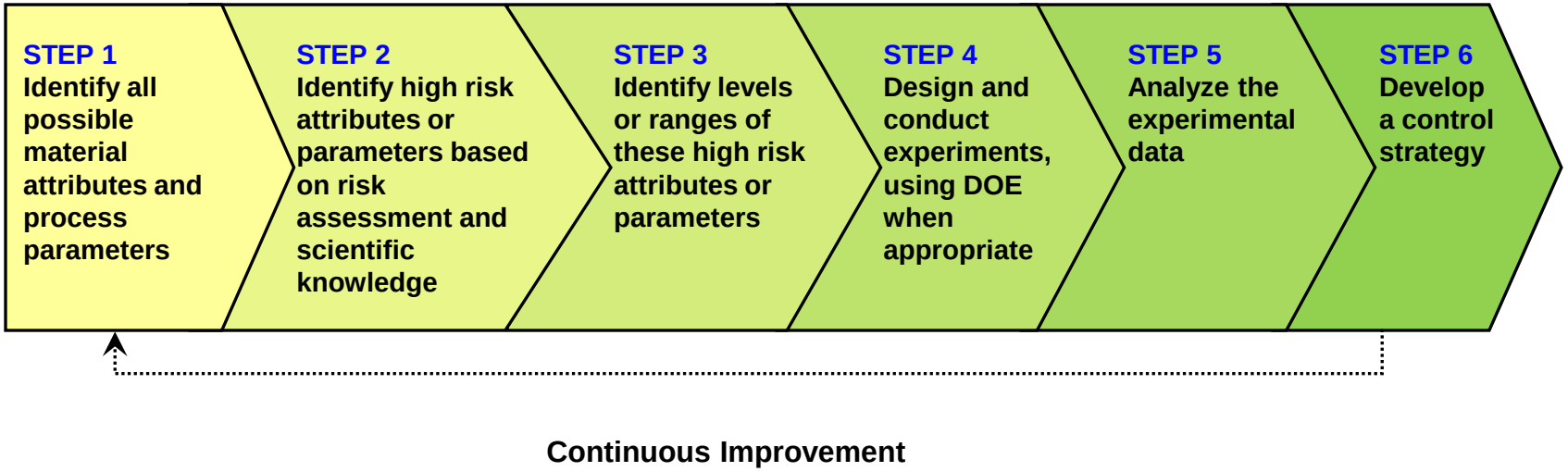
Lawrence X. Yu,[1,6] Gregory Amidon,[2] Mansoor A. Khan,[1] Stephen W. Hoag,[3] James Polli,[3] G. K. Raju,[4,5] and Janet Woodcock[1]

Received 17 November 2013; accepted 24 March 2014

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.

Product & Process Understanding



QbD Improves Product Quality

This article presents the results of a survey conducted by the ISPE United Kingdom/Ireland PAT COP.

The Business Benefits of Quality by Design (QbD)

by Theodora Kourti and Bruce Davis

Introduction

The business case for Quality by Design (QbD) was a hot discussion topic during a meeting of the Process Analytical Technology Community of Practice of United Kingdom/Ireland (PAT COP UK/IR). The discussion concluded with a plan to conduct a survey that would aim to gather actual experiences, examples and candid industry opinions on the business benefits of QbD. The questions one questionnaire. Written answers also were produced for the telephone interviews and these were approved by the interviewees. Interviewees were from development, manufacturing and regulatory while the companies range from large and small, both small molecule and biotech.

In total, we received 15 completed questionnaires from 12 companies. The responses were received between November 2010 and September 2011. The companies agreed to have their

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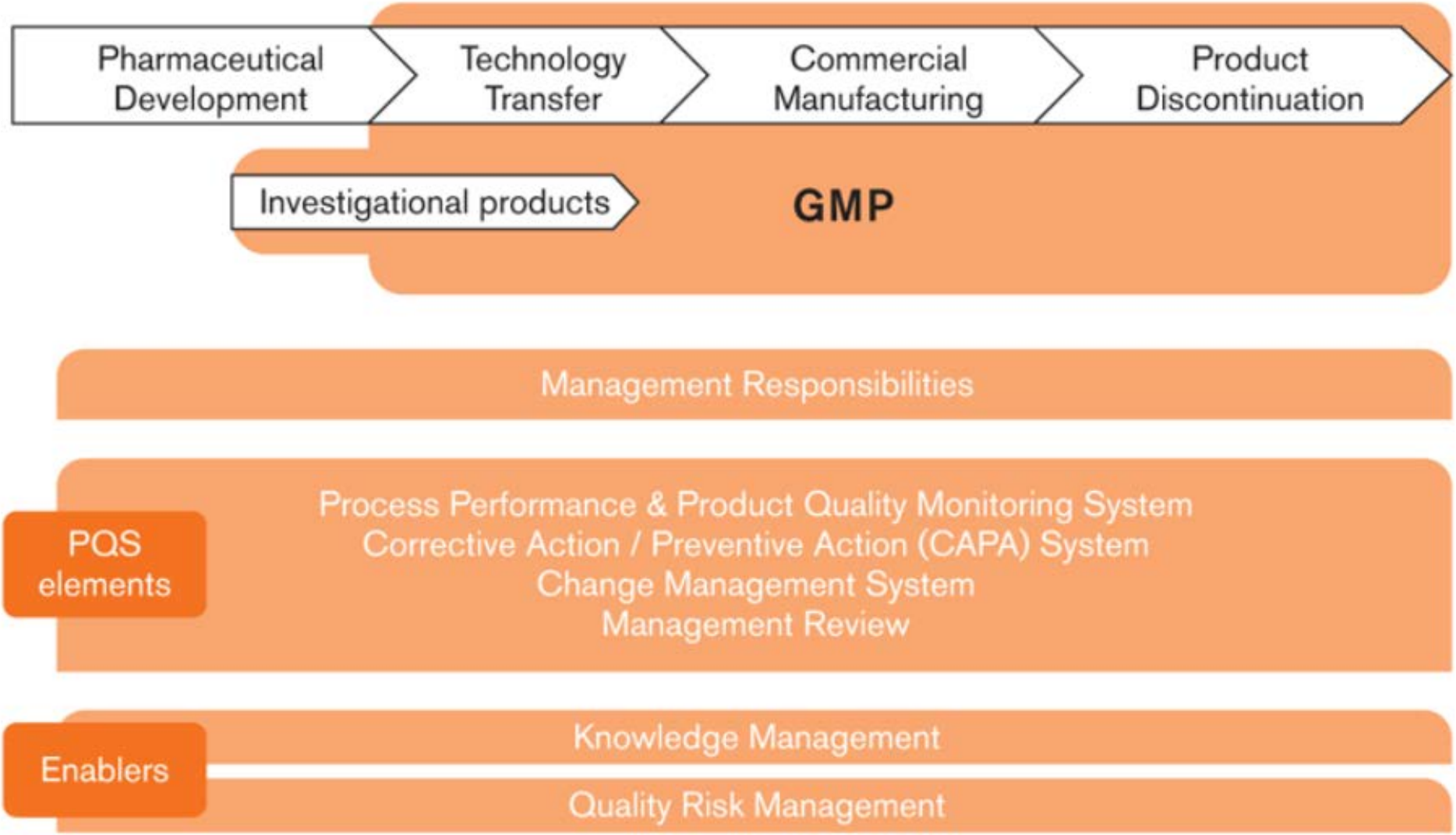
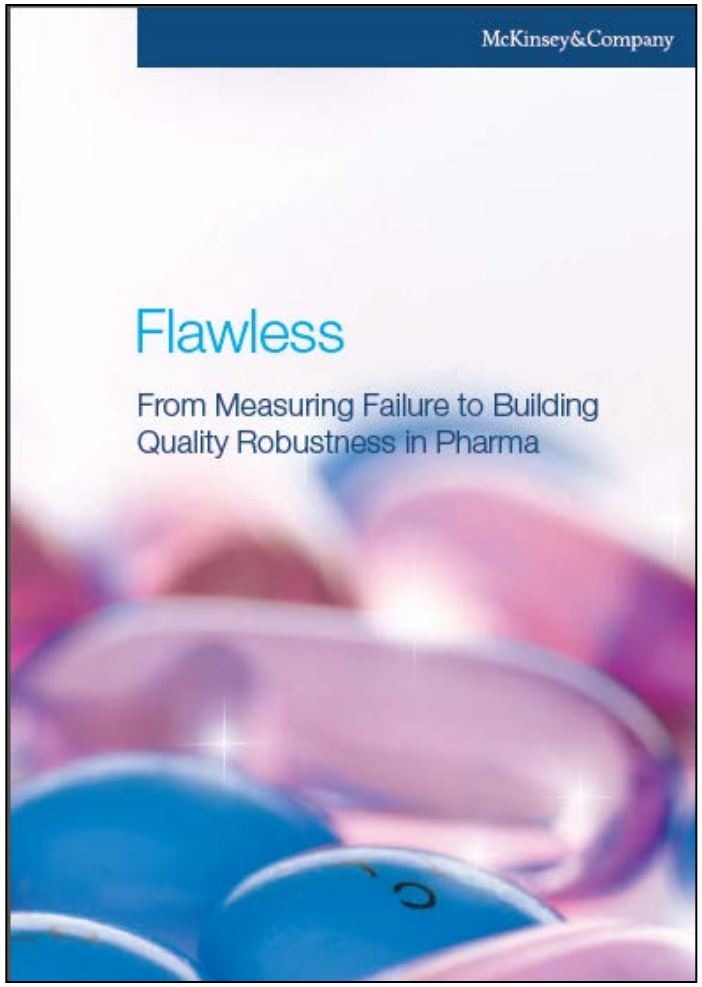
ICH Q10
Pharmaceutical Quality System





McKinsey: "Flawless: From measuring failures to building quality robustness in pharma"

- "There's…the challenge of shifting mind-sets across industry that has focused predominantly on compliance rather than on truly knowing the root causes and effects on quality issues"

Creating a Culture of Quality

S. Srinivasan and B. Kurey, Harvard Business Review, 2014

- Culture of quality: An environment in which employees not only follow quality guidelines but also consistently see others taking quality-focused actions, hear others talking about quality, and feel quality all around them
- Four Essentials of Quality
  - Maintaining a leadership emphasis on quality
  - Ensuring message credibility
  - Encouraging peer involvement
  - Increasing employee ownership and empowerment

Characteristics of Culture for Quality

- Clearly visible, engaged and unwavering senior management support for quality
- Clearly articulated vision and values
- Active and ongoing engagement with customers to continually identify and address current and evolving needs
- Clearly stated quality goals
- Performance expectations for all individuals throughout the company that clearly link to quality goals
- Appropriate incentives—which can favor monetary or recognition-based awards, depending on individual circumstances.

Continuous Improvement

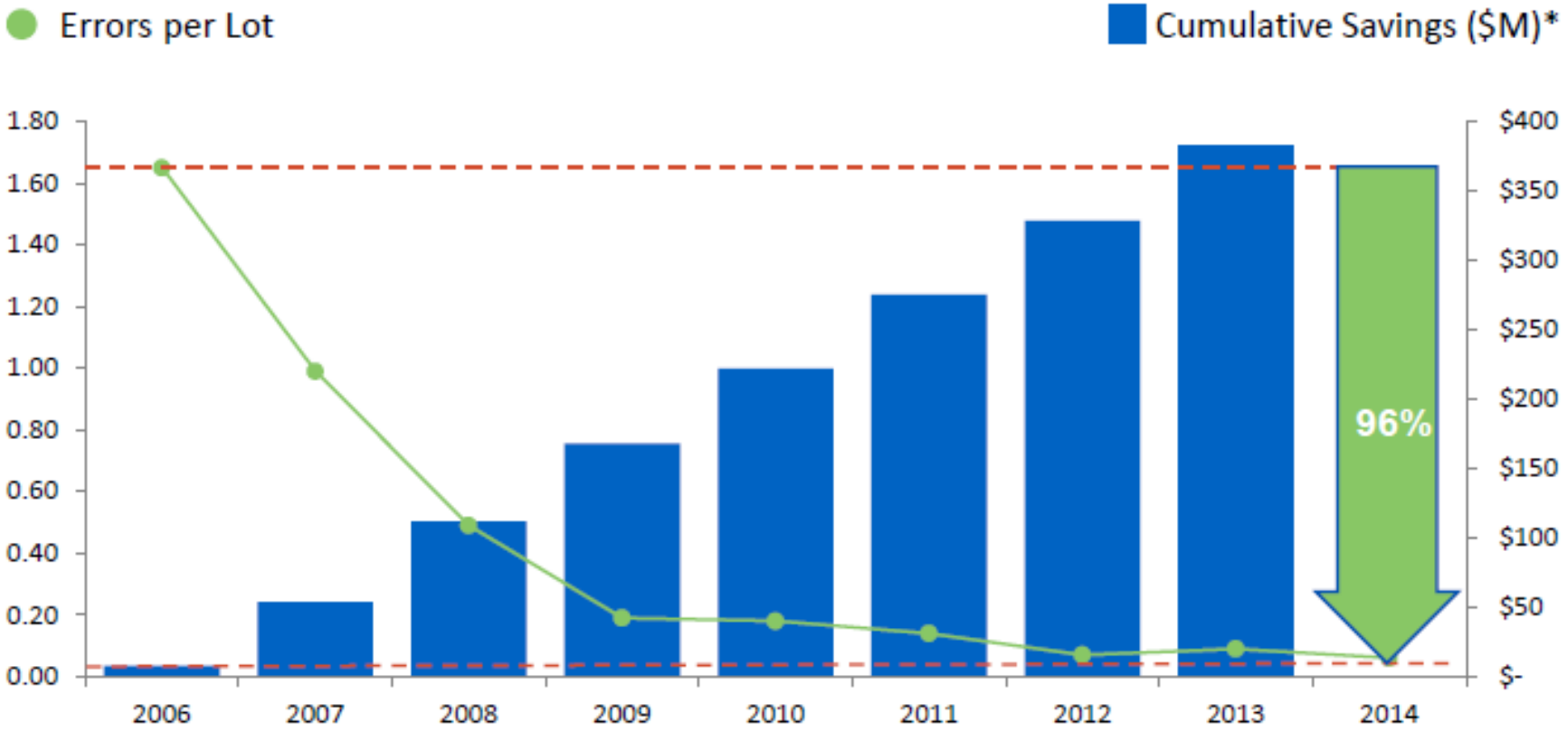
- Leaders must take the lead in quality improvement
- Investments in quality improvement must be substantial
- Modern tools for improvement must be put to use
- Flawless execution, focusing on quality, not compliance/enforcement
- Communications among industry, patients, and regulators must be open and carefully maintained

Yu et al. The Use of Process Capability to Ensure Product Quality

Pharm. Eng. (2015)

The process capability has been widely used by several industry segments, for example the automobile, electronic devices, and chemical industries, to determine how well a process produces a quality product.[5-8] There are also a few publications that discuss process capability in pharmaceutical industry.[9-16] Despite its usefulness, articles on process capability have not been widely discussed in the literature as a tool to ensure pharmaceutical product quality. In this paper, we will discuss the use of process capability as a tool to ensure drug product quality. We first give a brief overview of the definitions and calculation of process capability index and process performance index. Then, we discuss the differences between the process capability index and the process performance index. Further, we discuss the relationship between process capability and potential product batch failure rate. Finally, we describe the use of the process capability index in product development, process scale-up and qualification, and commercial production.

When You Succeed – The Power of Error Reduction



Less Capable

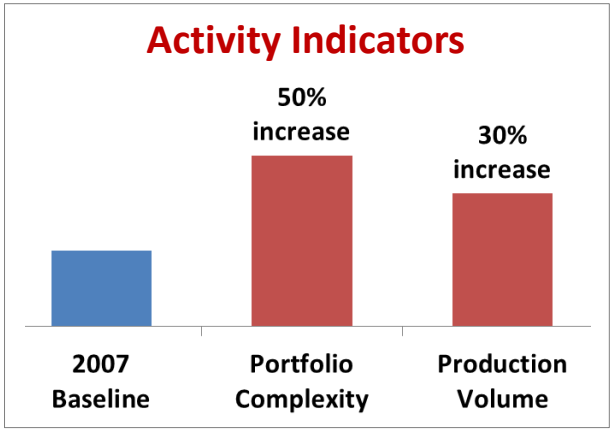
More Capable

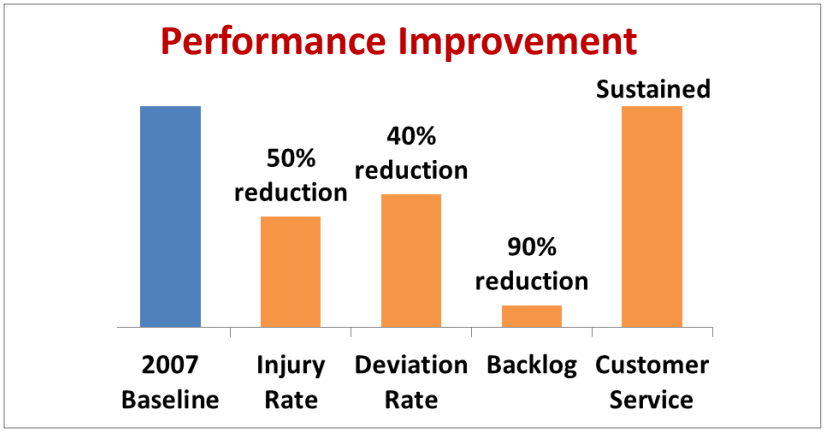
* Computed using 2014 avg wt NC costs:
C1 $560; C2 $6,700; C3 $86,000

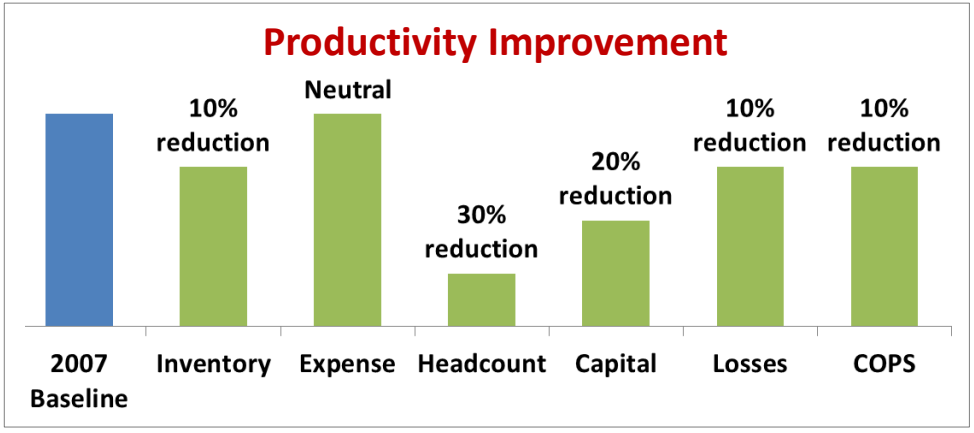
AMGEN

A Sustained Focus on Quality Risk Management Has Delivered Improvements in Product Quality

Comparison of 2013 Performance to 2007 Baseline







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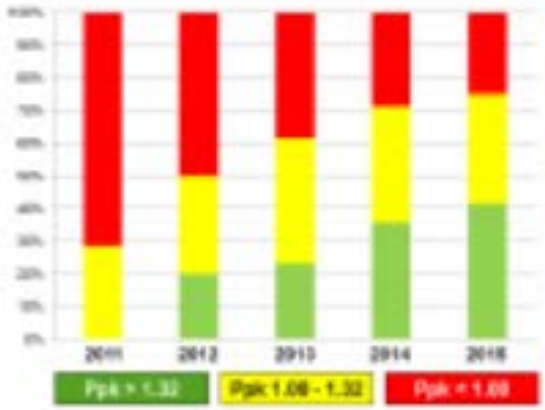
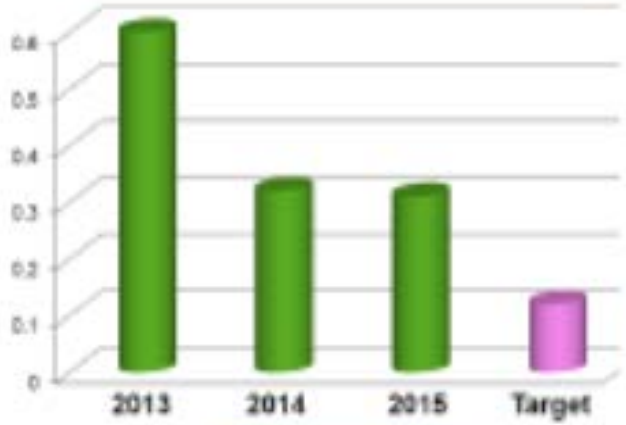
2015 Results

Performance Index



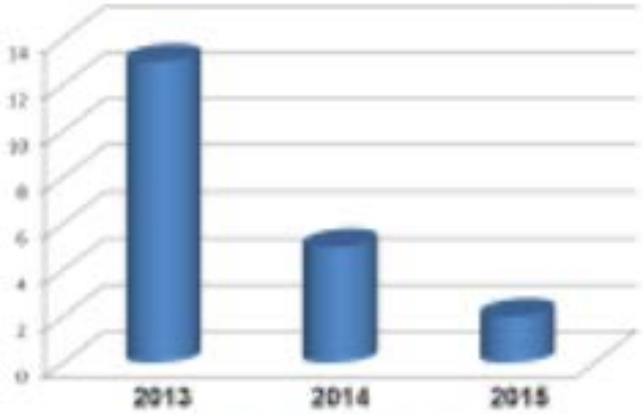
75% Products > 1.00 Ppk

Actual Failure Rate



99.7% Lot Acceptance Rate

Deviation Rate



2% Deviation Rate

- ⇧ Lot Acceptance Rate
- ⇩ Working Capital
- ⇧ Capacity
- ⇩ Cycle-Time
- ⇧ Available FTEs
- ⇩ Inventory

Shire

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