Pharmaceutical Product Development: Evolving Regulatory Landscape

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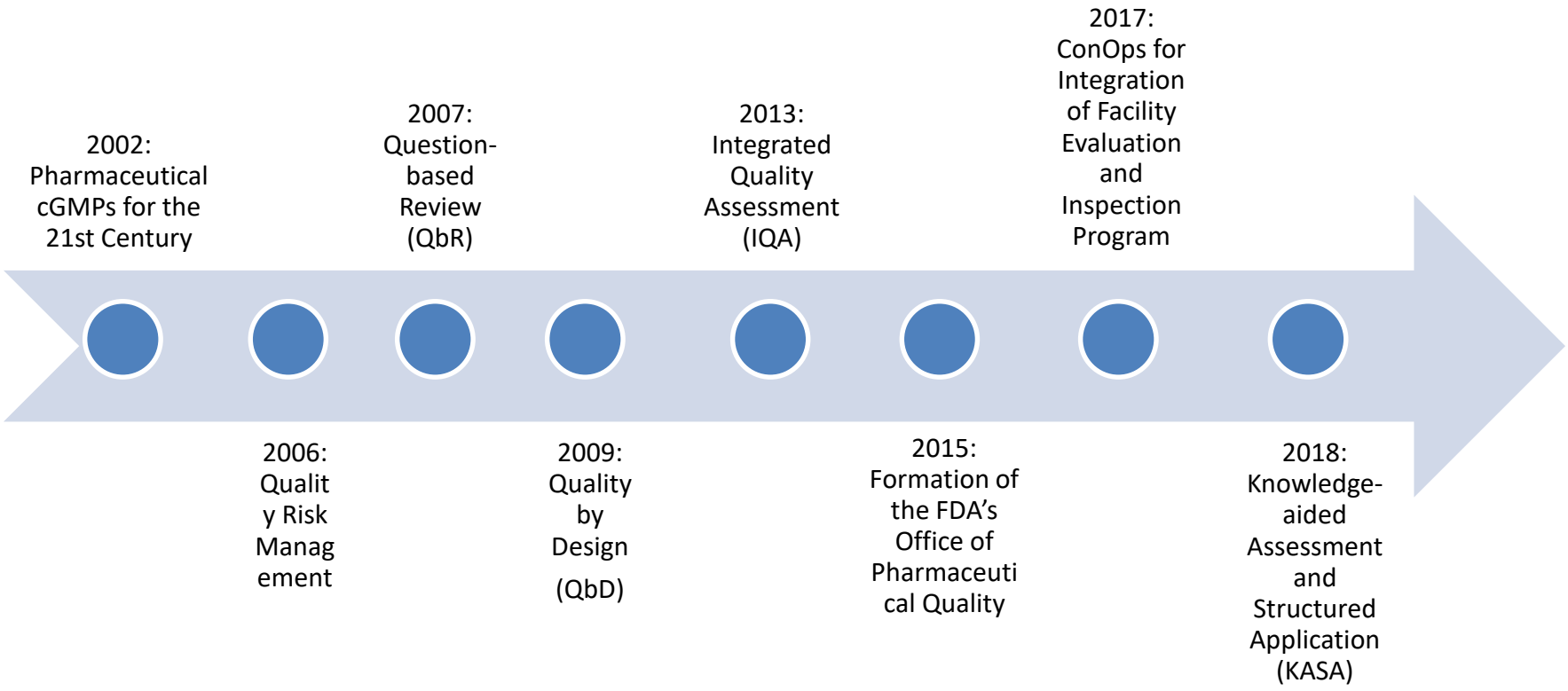
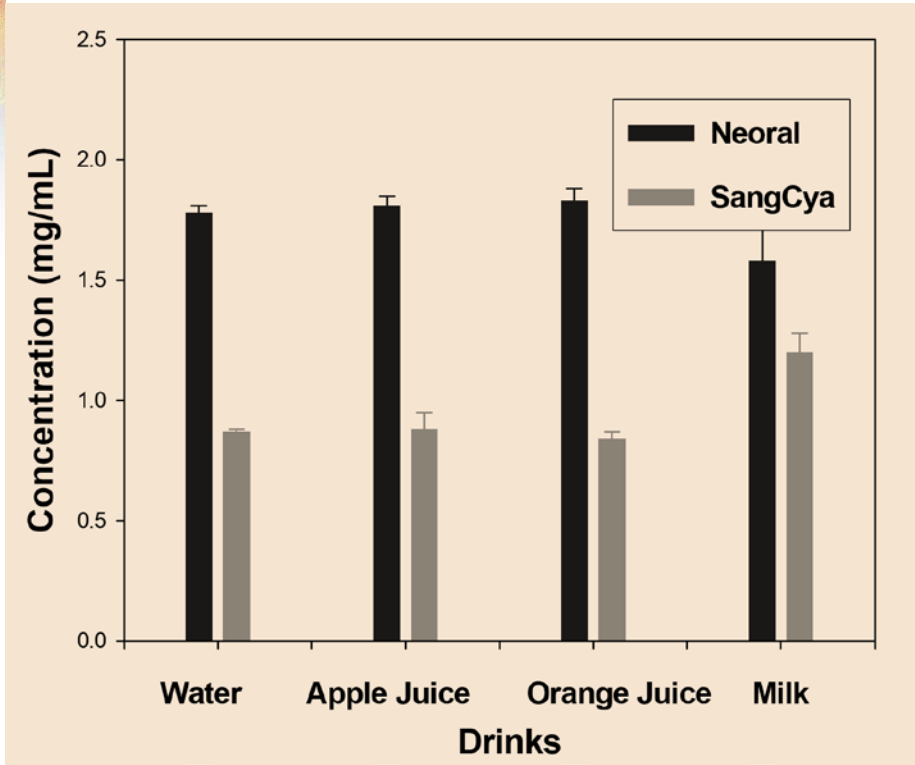
4th PQRI/FDA Conference on Advancing Product Quality, April 9-11, 2019

FDA Quality Assessment Journey



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

2000 Cyclosporine Oral Solution Withdrawal



The NEW ENGLAND JOURNAL of MEDICINE

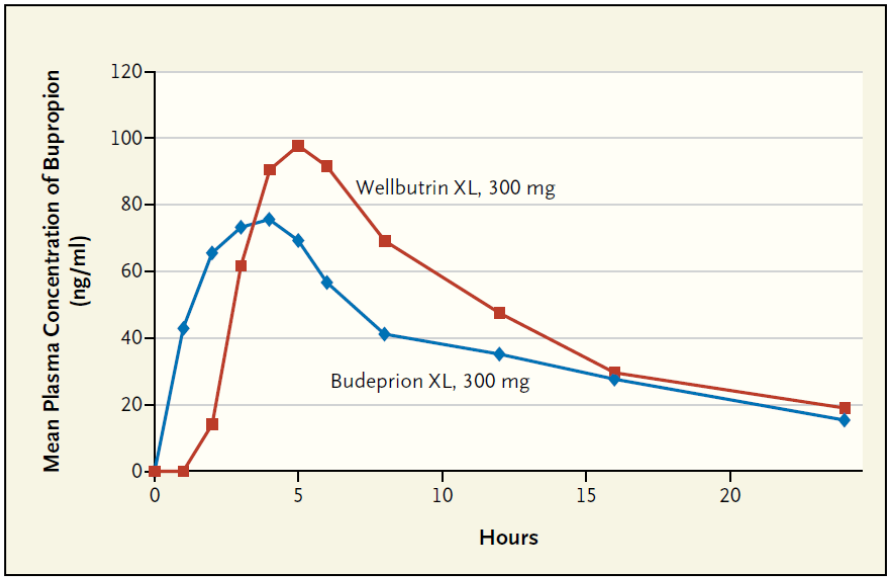
Withdrawal of Generic Budeprion for Nonbioequivalence

Janet Woodcock, M.D., Mansoor Khan, R.Ph., Ph.D., and Lawrence X. Yu, Ph.D.

The Food and Drug Administration (FD
completed a head-to-head bioequivale
of single doses of the generic drug Budep
300 mg (extended-release bupropion hydr

manufactured by Impax Labora-
tories and distributed by Teva
Pharmaceuticals) and the brand-
name drug Wellbutrin XL 300 mg

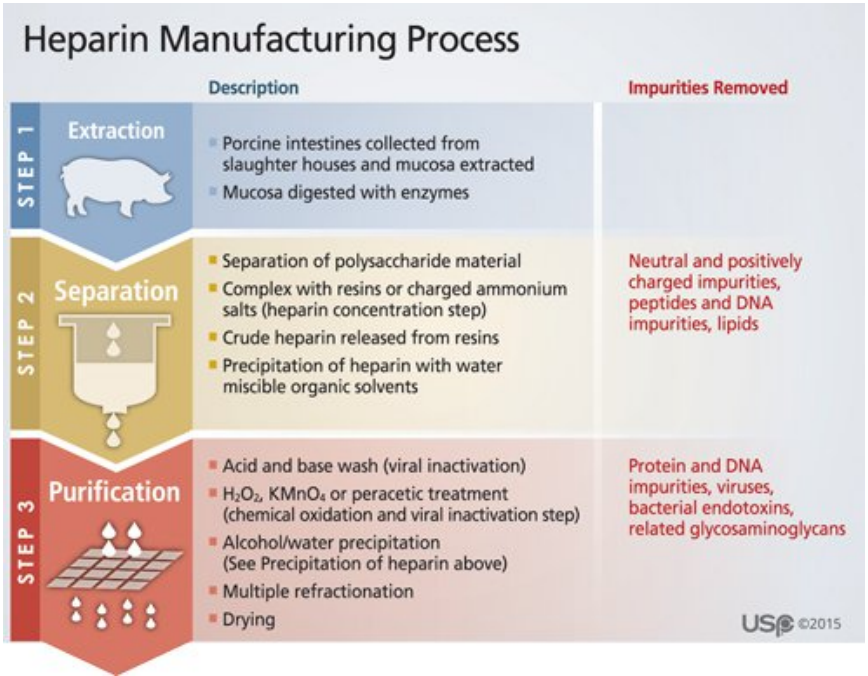
Budeprion XL 300
the subject of intens
age describing adve
patients being treat



Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL) as a Function of Time in 24 Fasting Healthy Volunteers.

2007-2008 Heparin Contamination Outbreak

- A total of 152 adverse reactions associated with heparin were identified in 113 patients from 13 states from November 19, 2007, through January 31, 2008.
- The use of heparin containing a contaminant identified as oversulfated chondroitin sulfate (OSCS) was the cause



FDA Quality Oversight Challenges in Early 2000's

- Quality by Testing (QbT) Approach
  - Review emphasized specifications and testing
  - Specifications derived empirically based on limited batch data
  - Very little emphasis on linking product quality attributes with clinical performance
- Siloed review disciplines related to quality
- Siloed review and inspection functions

Pharmaceutical Quality = Drug Meeting Regulatory Specifications

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

Vision

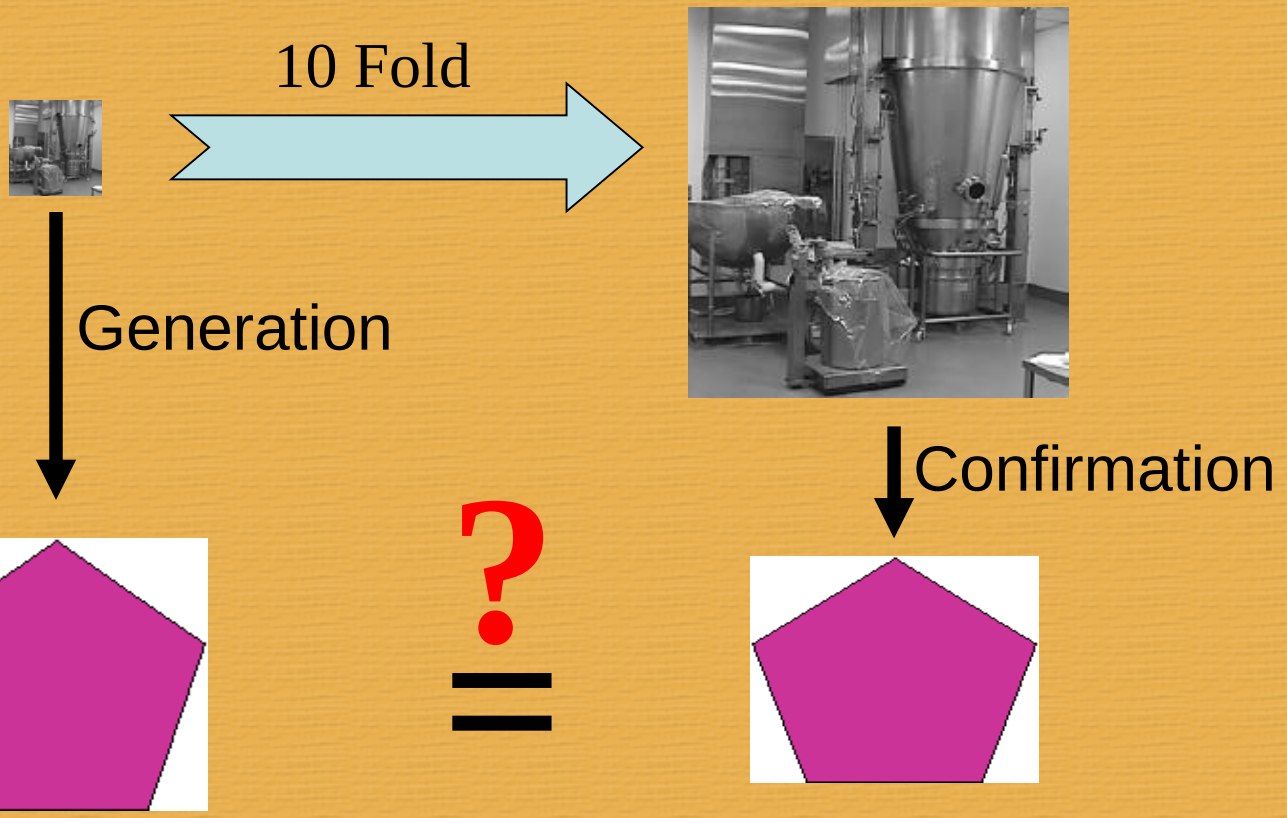
"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight"

-Dr. Janet Woodcock

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

Design Space: Regulatory Challenges (2006 DIA Annual Meeting)



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.

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

Review Article

Understanding Pharmaceutical Quality by Design

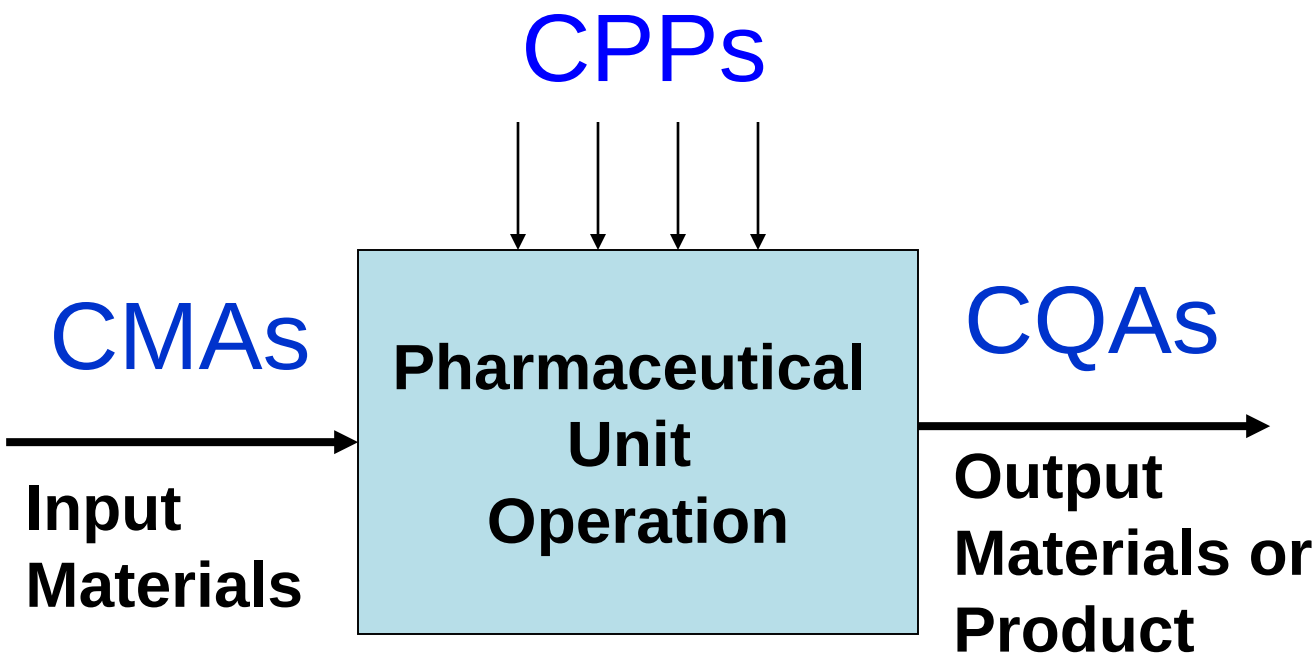
Lawrence X. Yu,[1,6] Gregory Amidon,[2] Mansoor A. Khan,[1] Stephen W. Hoag,[3] James Polli,[3] G. K. Raju,[4,5] and Janet Woodcock[1]

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.

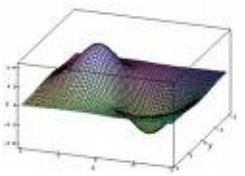
Relationship of CMA, CPP, and CQA



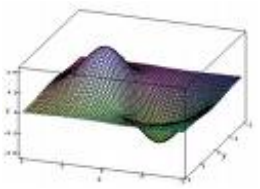
A CQA of an output material may become a CMA if it becomes an input material of another unit operation

Product and Process Understanding: Linking CMAs and CPPs to CQAs

INPUTS (X)



Material



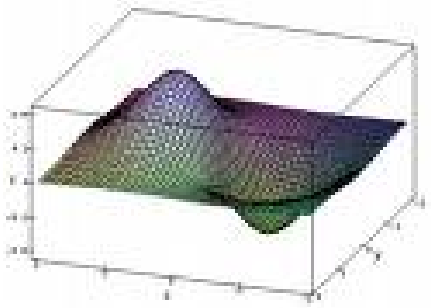
Process

$$Y = f(X)$$

Priori knowledge
Risk Assessment
Mechanistic models
Design of Experiment

Inputs to the process control variability of the Output

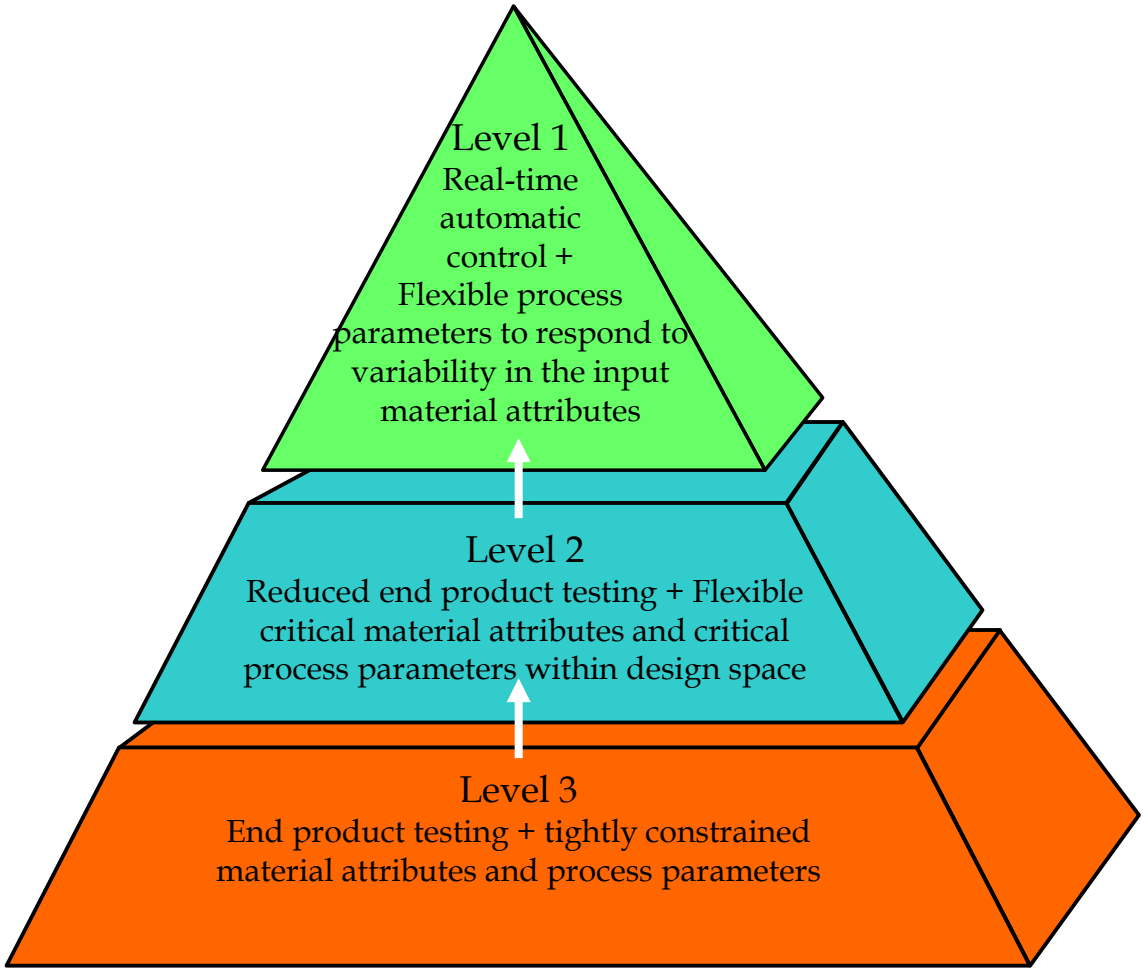
Y



OUTPUT

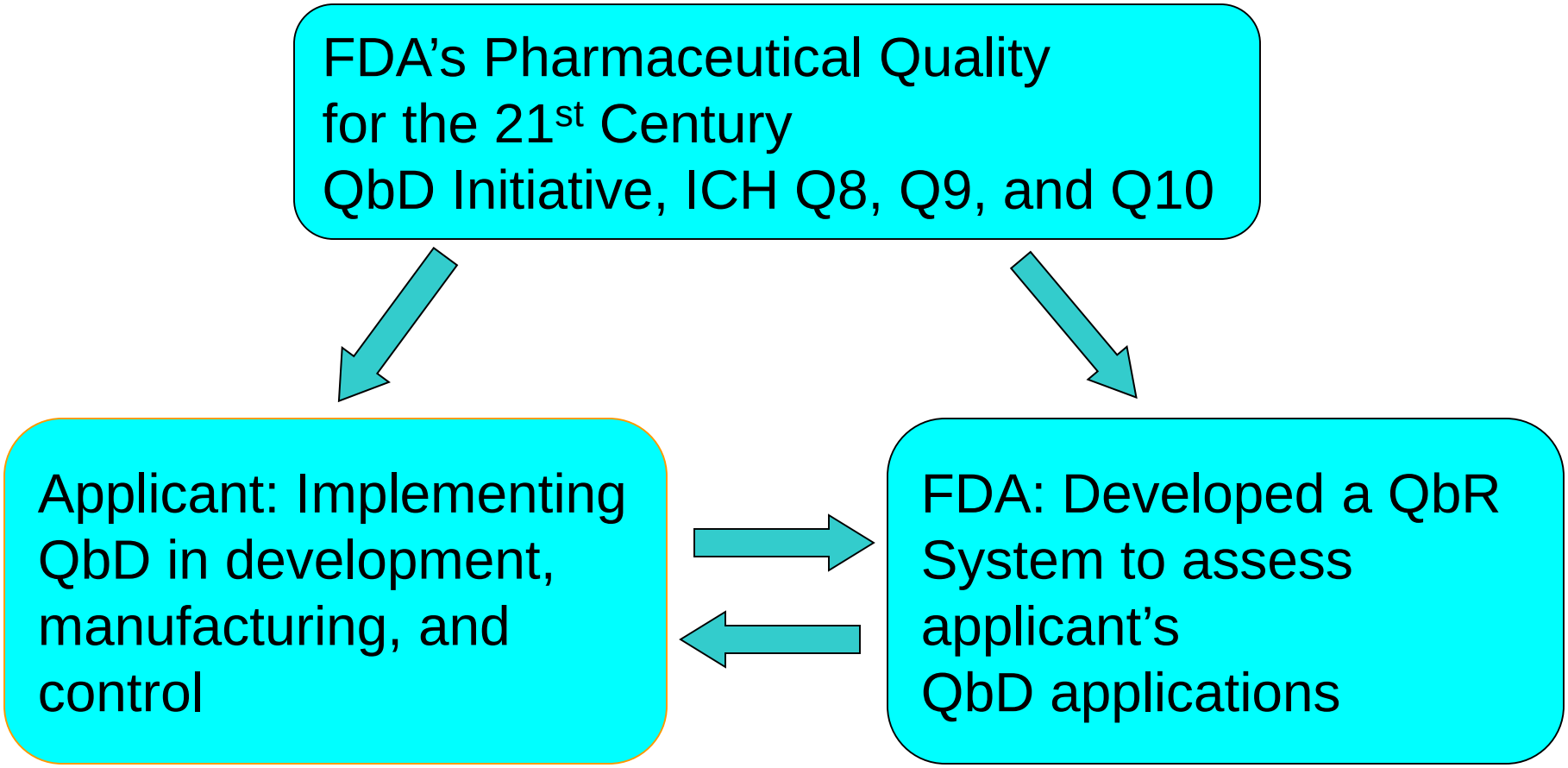
Control Strategy Implementation Options

Enhanced Approach



Traditional Approach

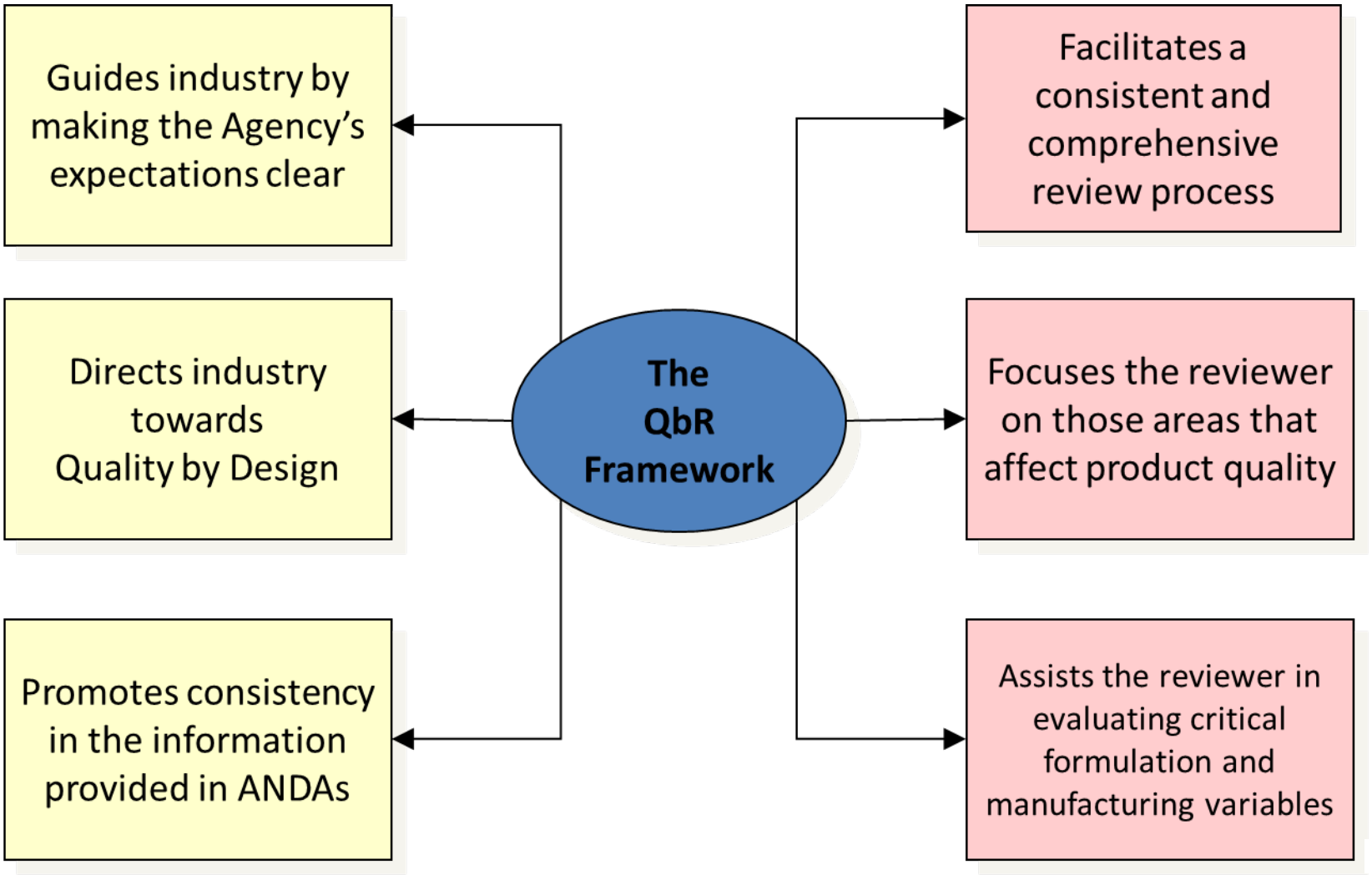
Quality by Design (QbD) and Question-based Review (QbR)



Question-based Review

- Question-based Review (QbR) is a general framework for a science and risk-based assessment of product quality
- QbR contains the important scientific and regulatory review questions to:
  - Set regulatory standards relevant to product performance (safety and efficacy)
  - Assess applicants' understanding and control of product and manufacturing

Advantages of the QbR



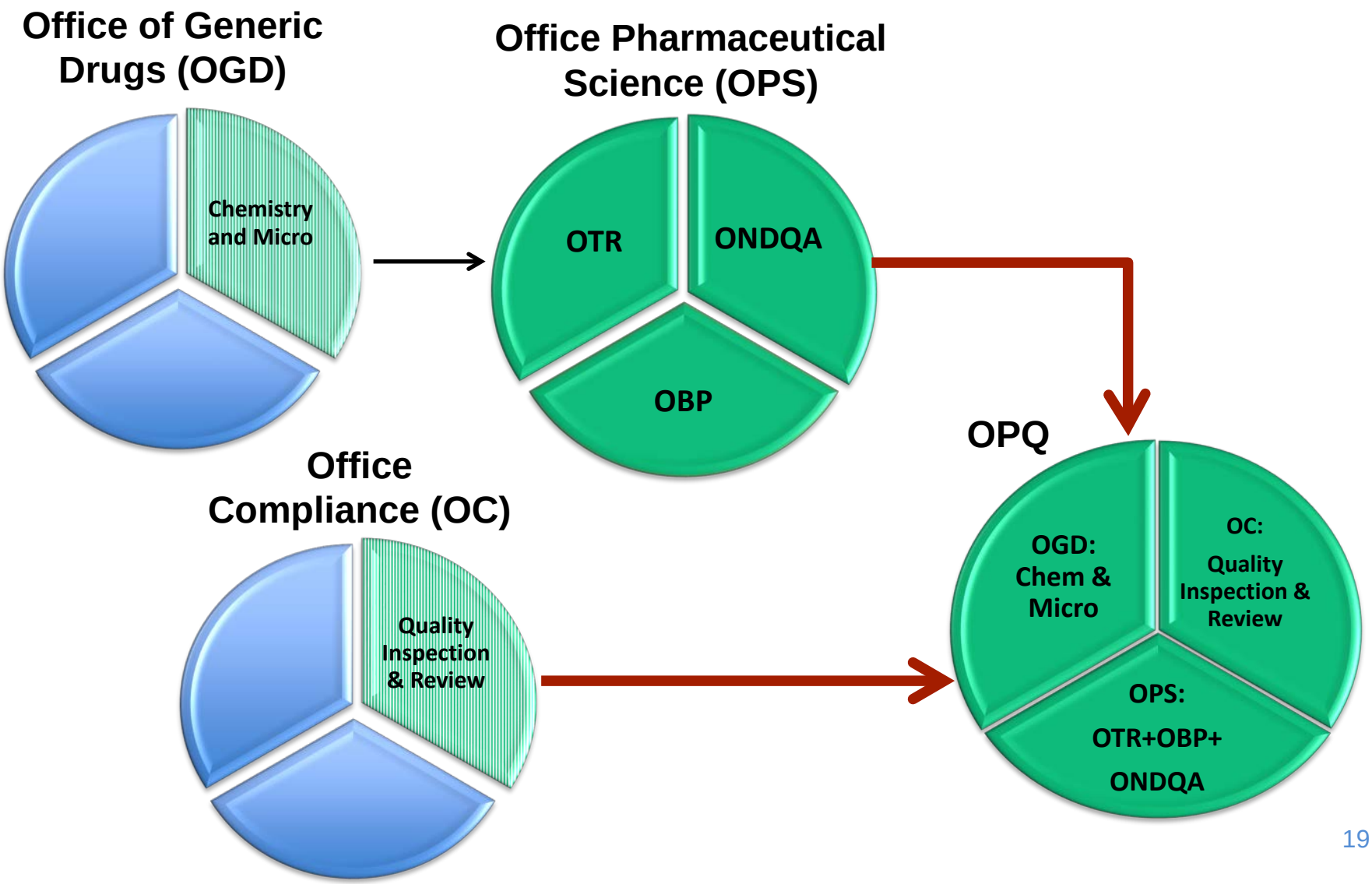
Delivering on the 21st Century Quality Goals

CDER's
Office of Pharmaceutical Quality
(OPQ)

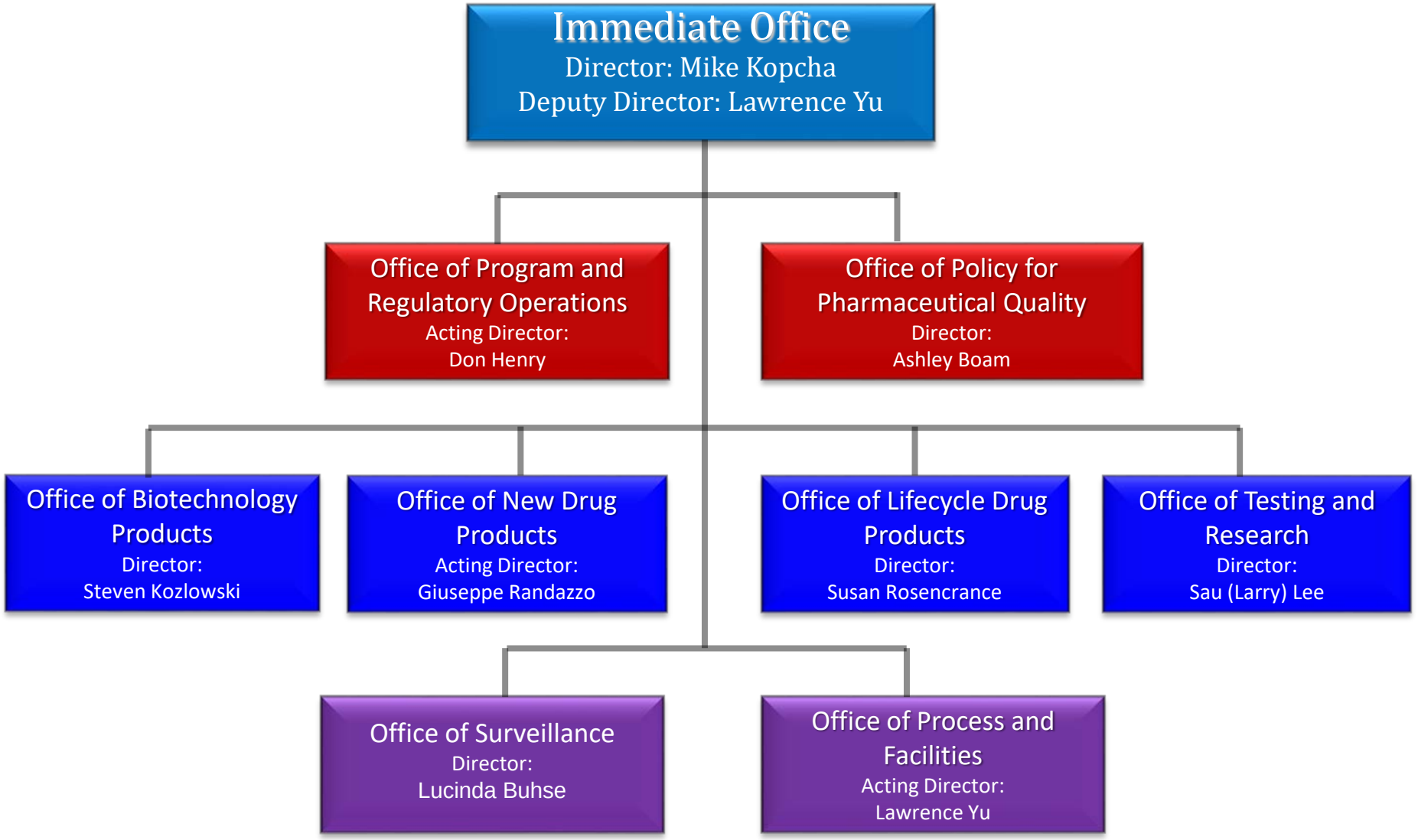
January 11, 2015

Advances FDA's Quality Initiative to the next level

Office of Pharmaceutical Quality Became Official on Jan 11, 2015



FDA OPQ Organization



Mission "Impossible"

- Quality (chemistry) assessment includes:
  - Drug substance
  - Drug product including specialized and complex dosage forms
  - Manufacturing and sterility assurance
    - Scale up and commercial manufacturing
  - Biopharmaceutics

Team-based Integrated Quality Assessment (IQA)

Discipline Reviewers

Technical Advisors

OPQ Laboratories
Policy
Surveillance
Others, as needed

Application Technical Lead (ATL) – oversees the scientific content of the assessment
Business Process Manager (BPM) – manages the process, adhering to the established timelines

Team-based Integrated Quality Assessment (IQA) - Advantages

- Close collaboration and communication among disciplines in a team environment yields better decision making
- Assures the application of uniform quality standards and promotes consistent regulatory practices
- Integration of quality review with inspection results in more informed decision making on facility acceptability and application approvability
- Promotes building an integrated knowledge base

FDA Concept of Operations for Facility Evaluation And Inspection For Human Drugs

On June 6, 2017, the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) have entered into an unprecedented concept of operations (ConOps) agreement to integrate facility evaluations and inspections for human drugs… ConOps will enable CDER and ORA to more effectively manage the growing complexity of the pharmaceutical landscape and to meet new challenges.

New Steps To Strengthen FDA's Inspection And Oversight Of Drug Manufacturing

Posted on **August 31, 2017** by **FDA Voice**

By: Scott Gottlieb, M.D.

Manufacturing of drugs has become increasingly complex and global, requiring us to remodel our oversight of these tasks, to improve FDA's efficiency and reach. As a step toward achieving these goals, FDA previously announced that we're restructuring our field activities, to direct our focus and organization around the programs we regulate, instead of our previous structure, that organized our activities and resources based on geographic regions. This allows us to better align the expertise of our staff and make more efficient use of our resources.

As another key step towards achieving these goals, the FDA's Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) are implementing a new, historic concept of operations agreement to more fully integrate the drug review programs with the facility evaluations and inspections for human drugs. This new collaboration is a model for how we'll modernize other parts of our organization to better achieve our mission.

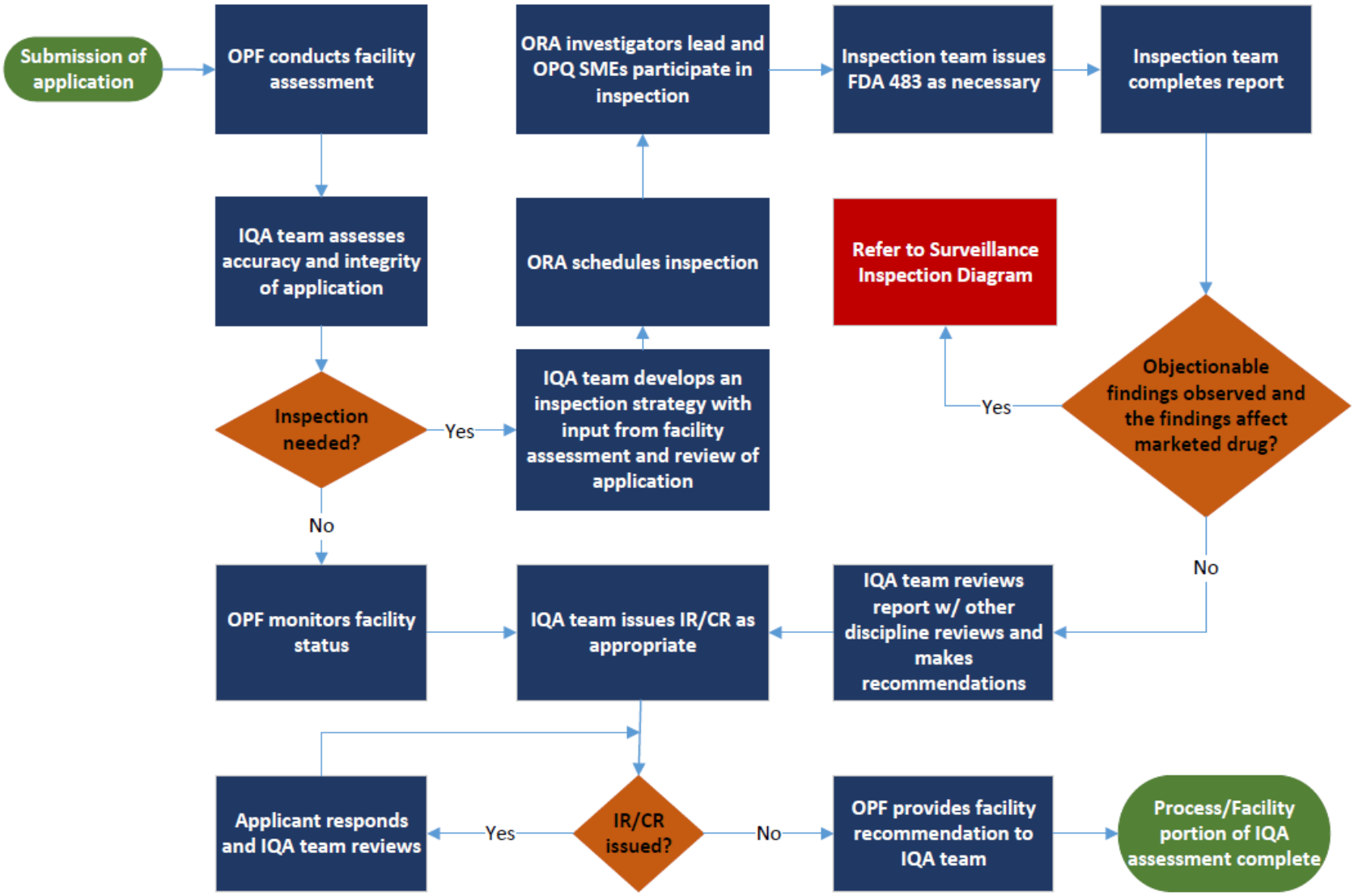
The FDA ConOps Involves the Following Offices:

- Center for Drug Evaluation and Research
  - Office of Pharmaceutical Quality (OPQ)
    - Office of Policy for Pharmaceutical Quality
    - Office of Process and Facilities
    - Office of Surveillance
  - Office of Compliance (OC)
    - Office of Manufacturing Quality (OMQ)
- Office of Regulatory Affairs (ORA)
  - Office of Operations
  - Office of Pharmaceutical Quality Operations
  - Office of Medical Products and Tobacco Operations
  - Office of Policy and Risk Management

Concept of Operations Benefits

- Create and implement a **formalized and streamlined facility evaluation and inspection program** that ensures:
  - Consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision-making for marketing applications across the FDA;
  - Strategic alignment across application functional units by clarifying roles and responsibilities;
  - Improved FDA's operational capacity by enhancing collaboration between various CDER and ORA offices;
  - Enhanced quality and increased access to facility and regulatory decisional information across FDA;
  - Improved timelines for regulatory, advisory, and enforcement actions to protect public health and promote drug quality, safety, and effectiveness.

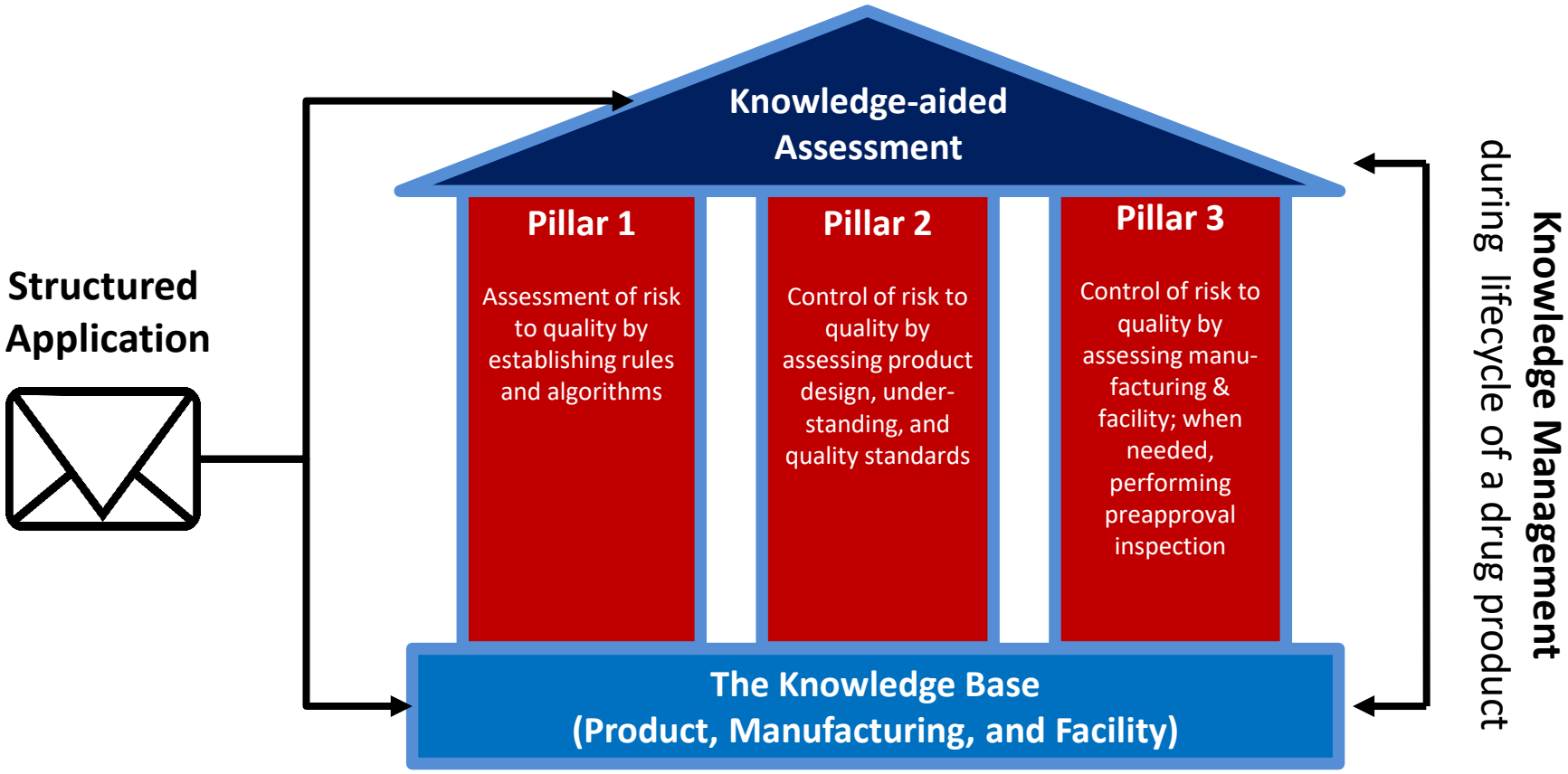
New Pre-Approval Inspection Process: Integration of Review and Inspection



FDA Quality Oversight Progress

- Quality by Design
- Integrated Quality Assessment
  - Integrating review disciplines
  - Integrating review and inspection
- FDA Quality Oversight New Initiative: Knowledge-aided Assessment and Structured Application (KASA)

Knowledge-aided Assessment and Structured Application (KASA)



Purpose of KASA

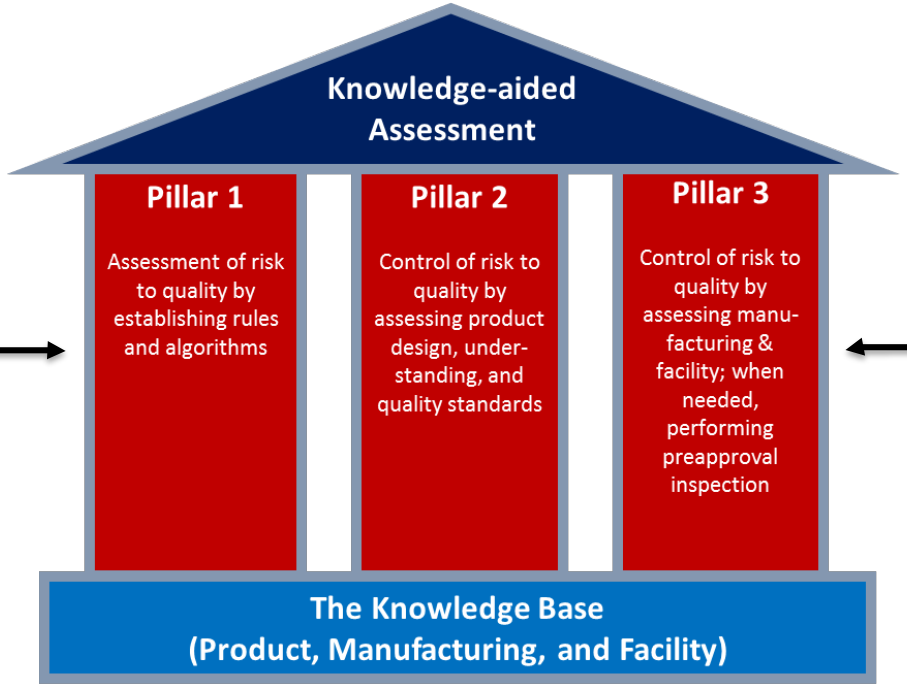
- Capture and manage knowledge during the lifecycle of a drug product;
- Establish rules and algorithms for risk assessment, control, and communication;
- Perform computer-aided analyses of applications to compare regulatory standards and quality risks across applications and facilities; and
- Provide a structured assessment that minimizes text-based narratives and summarization of provided information.

FDA Advisory Committee Meeting, September 20, 2018

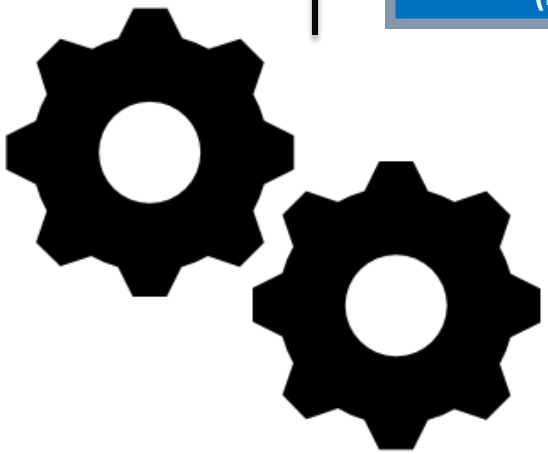
VOTE: Relating to the KASA initiative, should the FDA consider the enhancement of submission format to improve the efficiency and consistency of regulatory quality assessment?

Vote Result: ***YES: 10*** ***NO: 0*** ***ABSTAIN: 0***

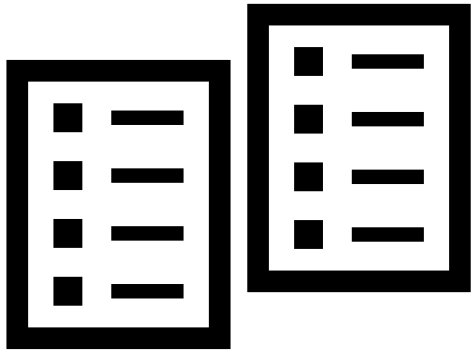
Committee Discussion: *The committee unanimously agreed that, relating to the KASA initiative, the FDA should consider enhancement of submission format to improve the efficiency and consistency of regulatory quality assessment under the KASA initiative. Several members stated that this would increase communication while making submissions from industry easier and more transparent. Brand and generic industry representatives on the committee also agreed that KASA would be good for industry and FDA. Members encouraged a flexible design, so data is searchable, easily transposable and exportable for further analysis. Please see the transcript for details of the Committee discussion.*



KASA



Retrospective information



Prospective information structured as per PQ-CMC

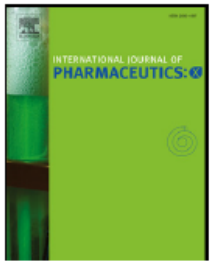
4th PQRI/FDA Conference
April 11 10-11:30 AM, 2019

- Introducing FDA'S New Initiative: KASA (Knowledge-aided Assessment and Structured Application)
  - Moderator: Lawrence Yu
  - Presenters: Susan Rosencrance, Andre Raw, Derek Smith, and Mary Ann Slack
  - Panelists: Susan Rosencrance, Sharmista Chatterjee, Mahesh Ramanadham, Paul Seo, Larisa Wu, Ramesh Sood, Geoffrey Wu

Contents lists available at ScienceDirect

International Journal of Pharmaceutics: X

journal homepage: www.journals.elsevier.com/international-journal-of-pharmaceutics-x



FDA's new pharmaceutical quality initiative: Knowledge-aided assessment & structured applications

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ARTICLE INFO

Keywords:
Pharmaceutical quality
Knowledge management
Risk assessment
Risk control
Structured application

ABSTRACT

This paper describes a new FDA's pharmaceutical quality assessment system: Knowledge-aided Assessment & Structured Application (KASA). The KASA system is designed to: 1) capture and manage knowledge during the lifecycle of a drug product; 2) establish rules and algorithms for risk assessment, control, and communication; 3) perform computer-aided analyses of applications to compare regulatory standards and quality risks across applications and facilities; and 4) provide a structured assessment that minimizes text-based narratives and summarization of provided information. When fully developed and implemented, KASA will enrich the effectiveness, efficiency, and consistency of regulatory quality oversight through lifecycle management of products and facilities, and information sharing in a standardized and structured format. Ultimately, KASA will advance FDA's focus on pharmaceutical *quality*, the foundation for ensuring the safety and efficacy of drugs.

The Future of Pharmaceutical Quality

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