The Quality Assessment of Different Application Types – BLAs, NDAs, and ANDAs

Lawrence X. Yu, Ph.D.
Deputy Director, Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

2019 Pharmaceutical Quality Symposium
October 16, 2019

Learning Objectives

- Understand the quality assessment needs of application types – BLAs, NDAs, and ANDAs
- Describe the integrated quality assessment
  - Integrating assessment disciplines
  - Integrating assessment and inspection

New Drug/Biologics License Applications NDAs/BLAs 351(a)

- The goals of NDAs/BLAs 351(a) are to provide enough information to permit FDA assessors to reach the following key decisions:
  - Whether the drug/biologics is safe and effective in its proposed use(s), and whether the benefits outweigh the risks
  - Whether the drug/biologics' proposed labeling (package insert) is appropriate, and what it should contain
  - Whether the methods used in manufacturing the drug/biologics and the controls used to maintain the drug/biologics' quality are adequate to preserve the drug/biologics' identity, strength, quality, and purity

Generic Drug Applications

- A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use, specifically
  - Pharmaceutical Equivalence
    - *Same active ingredient(s), s*ame dosage form, same route of administration, identical in strength or concentration, meet compendial or applicable standards, and may differ in characteristics such as shape, excipients, packaging
  - Bioequivalence

Biosimilar

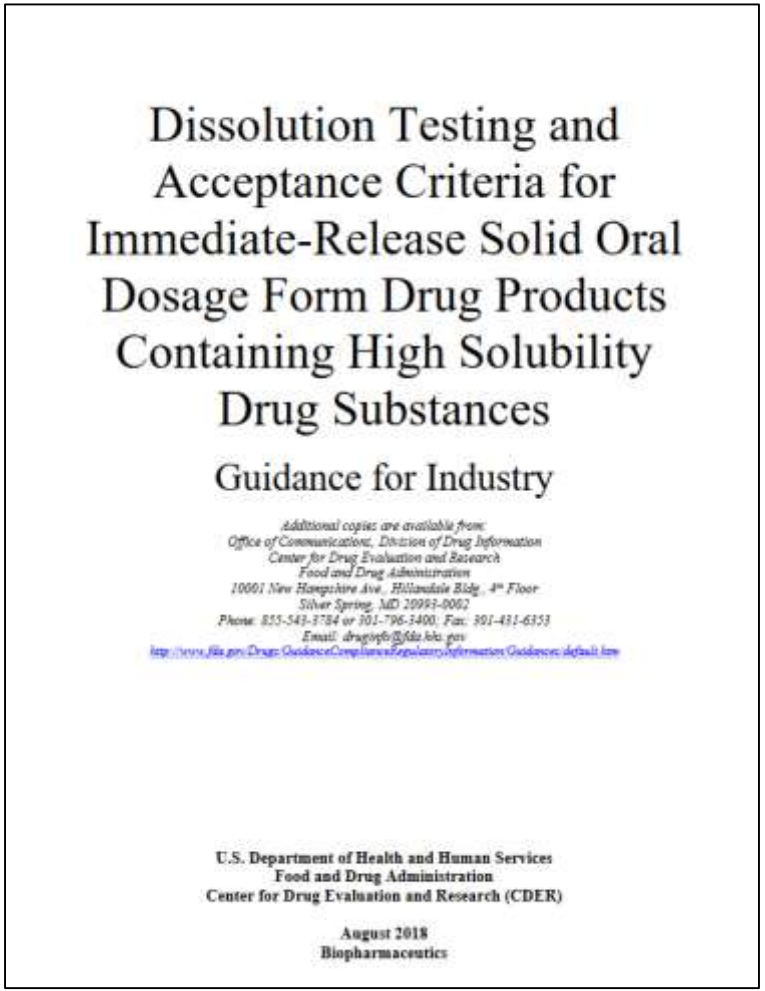
- Biosimilar or Biosimilarity means:
  - that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components
  - there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product

General Requirements for Biosimilar Applications, 351(k)

- A 351(k) application must include information demonstrating that the biological product:
  - Is biosimilar to a reference product
  - Utilizes the same mechanism(s) of action for the proposed condition(s) of use -- but only to the extent the mechanism(s) are known for the reference product
  - Condition(s) of use proposed in labeling have been previously approved for the reference product
  - Has the same route of administration, dosage form, and strength as the reference product
  - Is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biological product continues to be safe, pure, and potent

Patient-centric Quality Standards

- Patient-centric quality standards can be defined as a set of criteria and acceptance ranges to which drug products should conform in order to deliver the therapeutic benefit indicated in the label
  - Patient-centric quality standards can increase flexibility within the pharmaceutical manufacturing sector while maintaining quality by establishing acceptance criteria based on clinical performance, instead of process capability or manufacturing process control
  - Patient-centric quality standards avoid under- or over-discriminating specifications; both of which are contrary to patient needs and interests



Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

Guidance for Industry

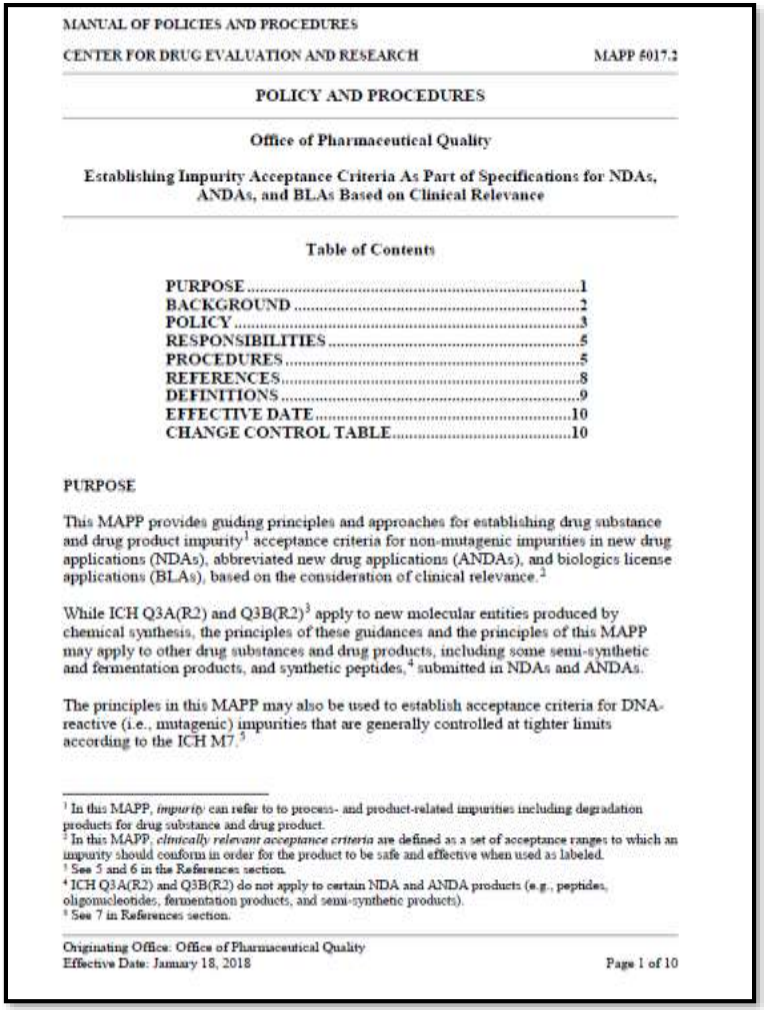
Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Biopharmaceutics

FDA Guidance for Dissolution

- For high solubility drugs, a single point dissolution specification of Q=80% in 30 minutes



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5017.2

POLICY AND PROCEDURES

Office of Pharmaceutical Quality

Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance

Table of Contents

PURPOSE

This MAPP provides guiding principles and approaches for establishing drug substance and drug product impurity[1] acceptance criteria for non-mutagenic impurities in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs), based on the consideration of clinical relevance.[2]

While ICH Q3A(R2) and Q3B(R2)[3] apply to new molecular entities produced by chemical synthesis, the principles of these guidances and the principles of this MAPP may apply to other drug substances and drug products, including some semi-synthetic and fermentation products, and synthetic peptides,[4] submitted in NDAs and ANDAs.

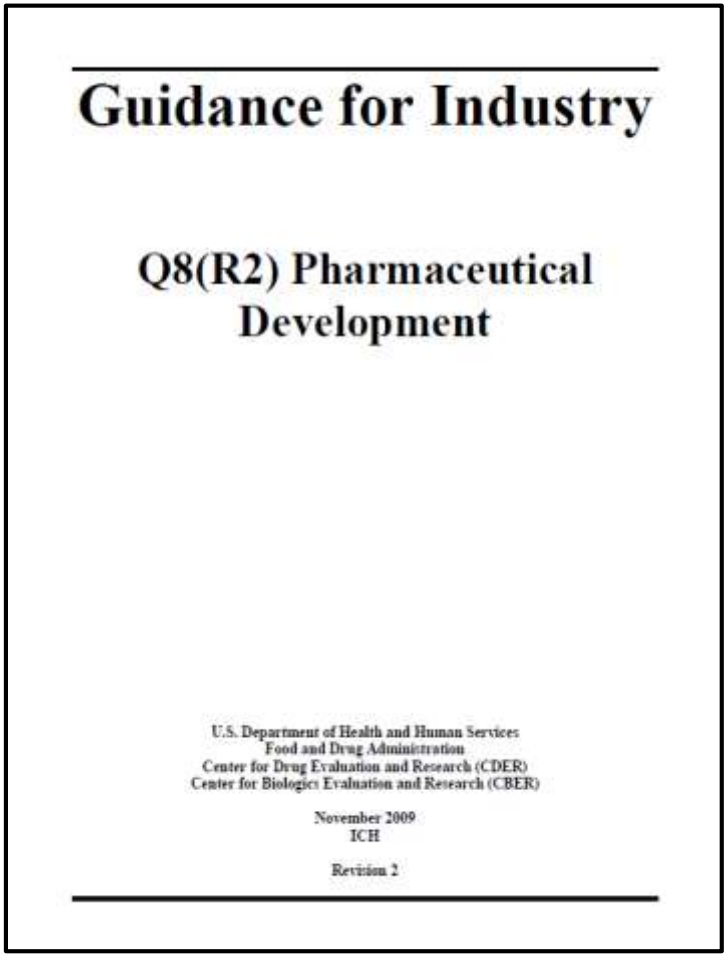
The principles in this MAPP may also be used to establish acceptance criteria for DNA-reactive (i.e., mutagenic) impurities that are generally controlled at tighter limits according to the ICH M7.[5]

[1] In this MAPP, *impurity* can refer to to process- and product-related impurities including degradation products for drug substance and drug product.
[2] In this MAPP, *clinically relevant acceptance criteria* are defined as a set of acceptance ranges to which an impurity should conform in order for the product to be safe and effective when used as labeled.
[3] See 5 and 6 in the References section.
[4] ICH Q3A(R2) and Q3B(R2) do not apply to certain NDA and ANDA products (e.g., peptides, oligonucleotides, fermentation products, and semi-synthetic products).
[5] See 7 in References section.

Originating Office: Office of Pharmaceutical Quality
Effective Date: January 18, 2018 Page 1 of 10

FDA OPQ MAPP on Impurity

- For a specified impurity with a proposed acceptance criterion not more than the qualification threshold, absent other information to support the need for a lower limit, a proposed acceptance criterion up to the ICH Q3A(R2) or Q3B(R2) qualification threshold is generally acceptable...



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

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.

11

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

Review Article

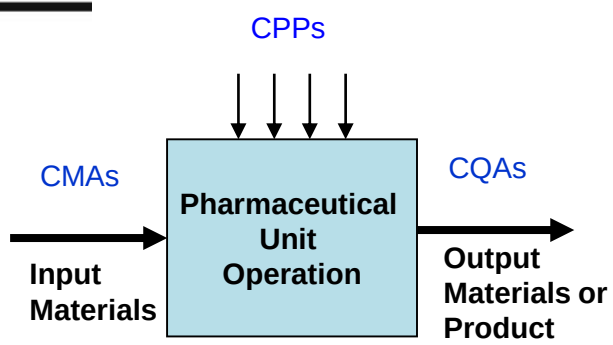
Understanding Pharmaceutical Quality by Design

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.



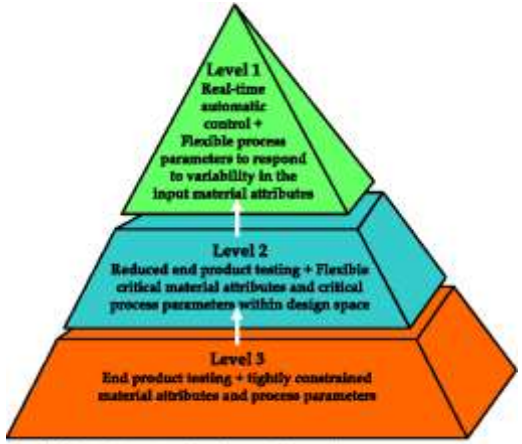


Fig. 3. Control strategy implementation options

FDA's Application Assessment

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

Integrated Quality Assessment (IQA)

Discipline Assessors

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

Integrated Quality Assessment (IQA) - Benefits

- 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 assessment with inspection results in **more informed decision-making** on facility acceptability and application approvability

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

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

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

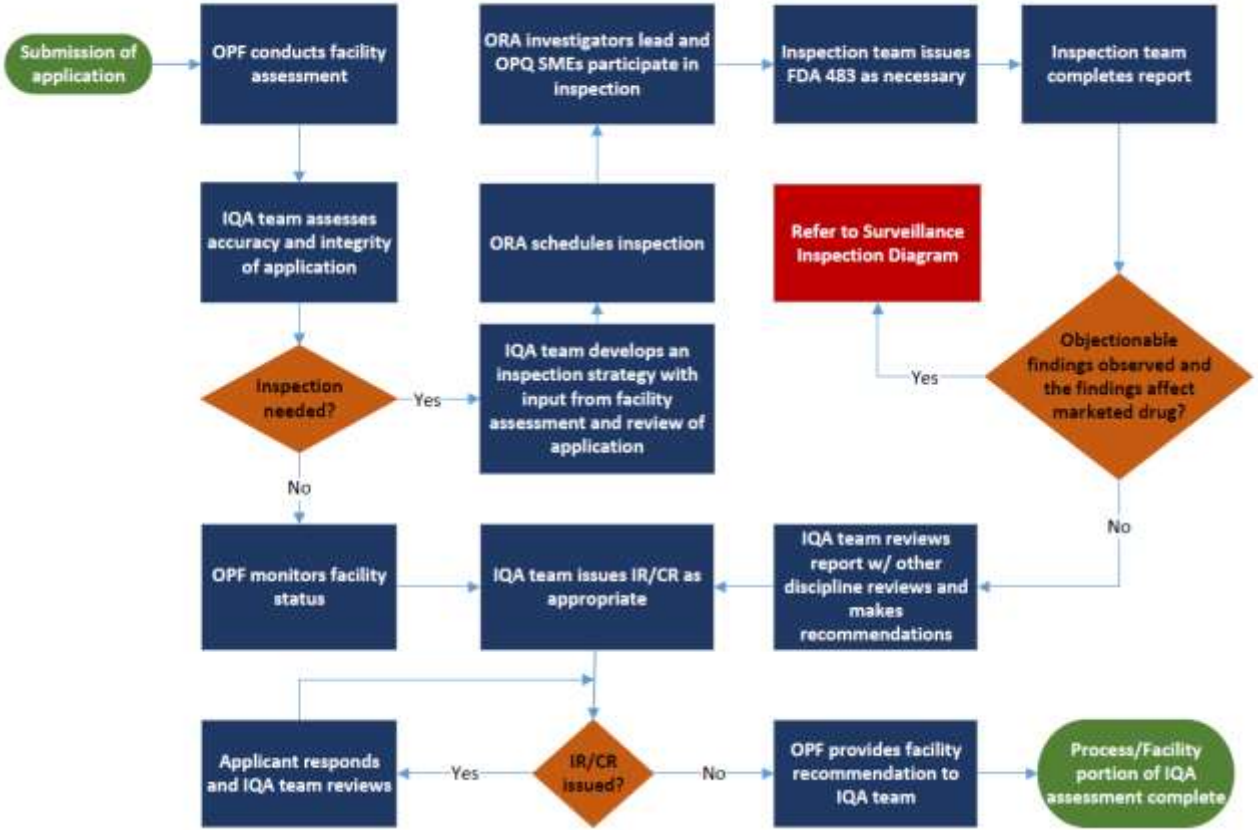
By: Scott Gottlieb, M.D.

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.

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.

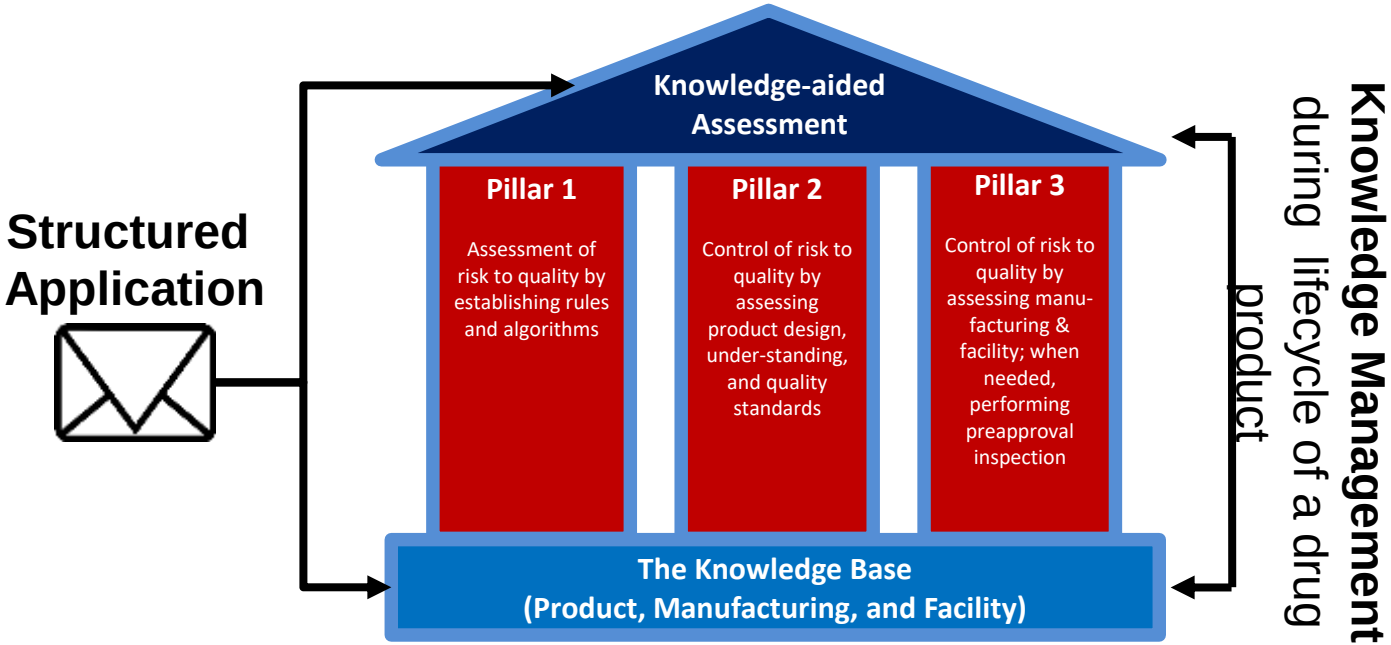
New Pre-Approval Inspection Process: Integration of Assessment and Inspection



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

Knowledge-aided Assessment and Structured Application Initiative



Objectives of KASA System

KASA is designed to:

1. Capture and manage knowledge during the lifecycle of a drug product
2. Establish rules and algorithms to facilitate risk identification, mitigation, and communication for the drug product, manufacturing process, and facilities
3. Perform computer-aided analyses of applications for a comparison of regulatory standards and quality risk across the repository of approved drug products and facilities
4. Provide a structured assessment that radically eliminates text-based narratives and summarization of information from the applications

Unanimous Support

- FDA Advisory Committee Meeting - September 20, 2018
- Ten members from Industry and Academia

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?

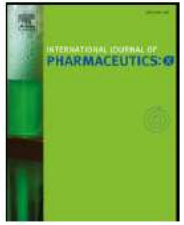
Vote Result: ***YES: 10*** ***NO: 0*** ***ABSTAIN: 0***

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.*

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

Lawrence X. Yu*, Andre Raw, Larisa Wu, Christina Capacci-Daniel, Ying Zhang, Susan Rosencrance*

Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States

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.

Patients Deserve Quality Medications

The Future of Pharmaceutical Quality

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The future of pharmaceutical quality and the path to get there

Lawrence X. Yu*, Michael Kopcha

Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States

6σ

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


Everyone has a role to play
Join us in a commitment to pharmaceutical quality
Together we can give patients improved access to medicine without sacrificing quality

Challenge Questions

1. The following applications **do not** require quality assessment
   a. New Drug Applications
   b. Biological License Applications
   c. Generic Drug Applications
   d. Biosimilar Applications
   e. None of the above

Challenge Questions

2. The Integrated Quality Assessment includes
    a. Drug substance
    b. Drug product
    c. Manufacturing (inspection)
    d. Biopharmaceutics if applicable
    e. All of the above