U.S. FOOD & DRUG ADMINISTRATION

CDER SBIA Drug Master File (DMF) and Drug Substance Workshop: Opening Remarks

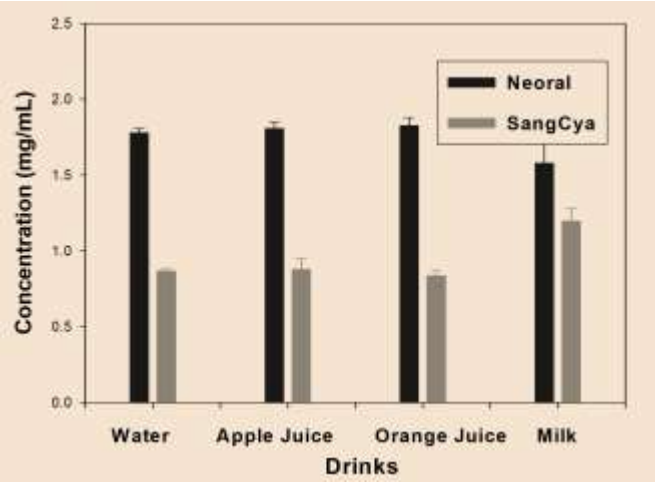
Lawrence Yu, PhD
Director, Office of New Drug Products
CDER | US FDA

SBIA DMF and Drug Substance Workshop – March 3-4, 2021

Pharmaceutical Quality

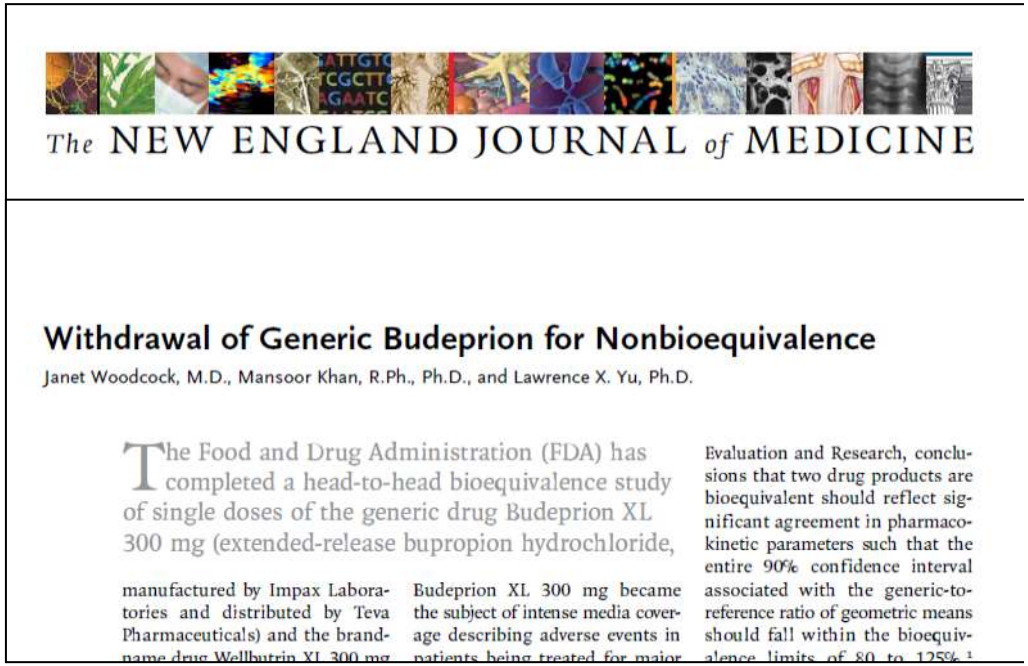
- A quality product of any kind consistently meets the expectations of the user – drugs are no different
- Patients expect safe and effective medicine with every dose they take
- Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects
- It is what gives patients confidence in their next dose of medicine

FDA's Quality Challenges: Cyclosporine Withdrawal in 2000



Drug Label "To make Neoral Oral Solution MODIFIED more palatable, it should be diluted with orange or apple juice…The combination of Neoral solution with milk can be unpalatable…"

FDA's Quality Challenges: Withdrawal of Budeprion (2006 FDA Approval)



The NEW ENGLAND JOURNAL of MEDICINE

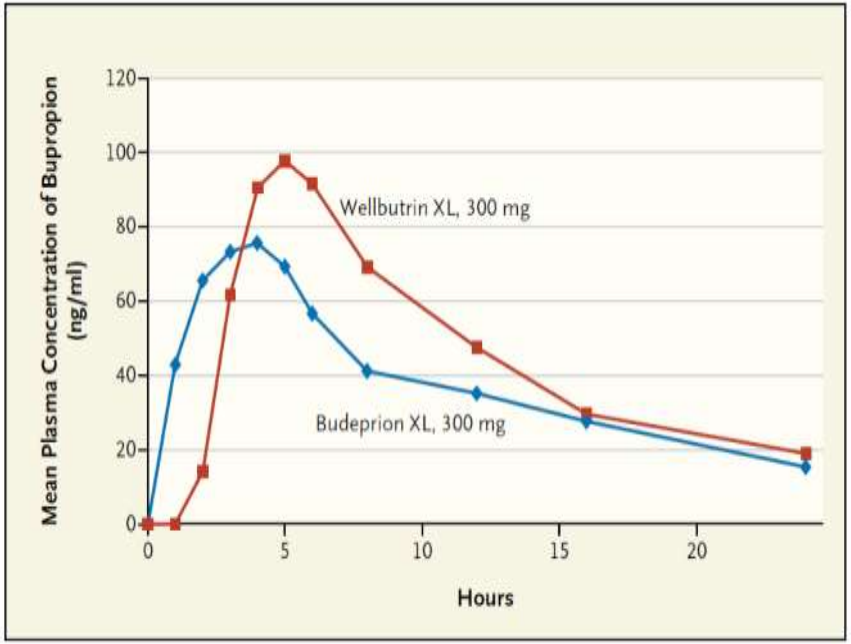
Withdrawal of Generic Budeprion for Nonbioequivalence

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

The Food and Drug Administration (FDA) has completed a head-to-head bioequivalence study of single doses of the generic drug Budeprion XL 300 mg (extended-release bupropion hydrochloride, manufactured by Impax Laboratories and distributed by Teva Pharmaceuticals) and the brand-name drug Wellbutrin XL 300 mg

Budeprion XL 300 mg became the subject of intense media coverage describing adverse events in patients being treated for major

Evaluation and Research, conclusions that two drug products are bioequivalent should reflect significant agreement in pharmacokinetic parameters such that the entire 90% confidence interval associated with the generic-to-reference ratio of geometric means should fall within the bioequivalence limits of 80 to 125%.[1]



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

FDA's Quality Challenges: Heparin Contamination Outbreak in 2007-2008

- 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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System

Takashi Kei Kishimoto, Ph.D., Karthik Viswanathan, Ph.D., Tanmoy Ganguly, Ph.D., Subbiah Elankumaran, Ph.D., Sean Smith, B.S., Kevin Pelzer, Ph.D., Jonathan C. Lansing, Ph.D., Nammalwar Sriranganathan, Ph.D., Ganlin Zhao, M.D., Zoya Galcheva-Gargova, Ph.D., Ali Al-Hakim, Ph.D., Gregory Scott Bailey, B.S., Blair Fraser, Ph.D., Sucharita Roy, Ph.D., Thomas Rogers-Cotrone, M.S., Lucinda Buhse, Ph.D., Mark Whary, Ph.D., James Fox, Ph.D., Moheb Nasr, Ph.D., Gerald J. Dal Pan, M.D., Zachary Shriver, Ph.D., Robert S. Langer, Sc.D., Ganesh Venkataraman, Ph.D., K. Frank Austen, M.D., Janet Woodcock, M.D., and Ram Sasisekharan, Ph.D.

ABSTRACT

BACKGROUND

There is an urgent need to determine whether oversulfated chondroitin sulfate (OSCS), a compound contaminating heparin supplies worldwide, is the cause of the severe anaphylactoid reactions that have occurred after intravenous heparin administration in the United States and Germany.

METHODS

Heparin procured from the Food and Drug Administration, consisting of suspect

From Momenta Pharmaceuticals (T.K.K., T.G., S.S., J.C.L., G.Z., Z.G.-G., G.S.B., S.R., Z.S., G.V.), the Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology, Koch Institute for Integrative Cancer Research (K.V., Z.S., R.S.L., G.V., R.S.), and the Massachusetts Institute of Technology (M.W., J.F.) — all in

Product Recalls due to N-nitrosodi-methylamine (NDMA) 2018-Present

The AAPS Journal (2020) 22: 89
DOI: 10.1208/s12248-020-00473-w

Check for updates

Rapid Communication

A Cautionary Tale: Quantitative LC-HRMS Analytical Procedures for the Analysis of *N*-Nitrosodimethylamine in Metformin

Jingyue Yang,[1] Tim Andres Marzan,[1] Wei Ye,[1] Cynthia D. Sommers,[1] Jason D. Rodriguez,[1] and David A. Keire[1,2]

Received 8 June 2020; accepted 20 June 2020; published online 1 July 2020

Abstract. A private testing laboratory reported in a Citizen Petition (CP) to FDA that 16 of 38 metformin drug products they tested had *N*-nitrosodimethyl amine (NDMA) amounts above the allowable intake (AI) of 96 ng/day. Because the FDA had been monitoring drugs for nitrosamines, orthogonal analytical procedures had been developed, validated and applied to detect the following nitrosamines in metformin drug products (if present): (i) NDMA (with a dedicated method) or (ii) NDMA (with a second confirmatory method), *N*-nitroso-diethylamine (NDEA), *N*-ethyl-*N*-nitroso-2-propanamine (NEIPA), *N*-nitroso-diisopropylamine (NDIPA), *N*-nitroso-di-n-propylamine (NDPA), *N*-nitroso-methylphenylamine (NMPA), *N*-nitroso-di-n-butylamine (NDBA) and *N*-nitroso-*N*-methyl-4-aminobutyric acid (NMBA). In contrast to the private laboratory results, FDA testing on

Patients Deserve Quality Medications

From our perspective: Patients deserve quality medications

https://www.fda.gov/drugs/news-events-human-drugs/our-perspective-patients-deserve-quality-medications

Lawrence X. Yu, Ph.D., Acting Director of FDA's Center for Drug Evaluation and Research's Office of Pharmaceutical Science, discusses the important roles of FDA and drug companies in ensuring quality drug products.

Drug quality -- a shared responsibility

Consumers expect and deserve access to safe, effective, high-quality drugs and it's up to both the FDA and manufacturers to make sure that they are available. It is FDA's job to establish standards, conduct pre-marketing reviews and inspections, and perform post-marketing surveillance and investigations to safeguard that all U.S. marketed drugs are safe, effective and of adequate quality. Drug companies have a responsibility to meet these standards to ensure that quality products reach patients.

One quality voice

Failures in drug quality put patients at unnecessary risk. When quality issues arise in manufacturing facilities, product recalls and plant shutdowns can follow, often resulting in drug shortages. By far, the most frequently cited reasons – approximately 65 percent – for drug shortages relate to manufacturing and quality issues. These

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

FDA'S Pharm. Product Quality Journey

- Process Analytical Technology/Emerging Technology Program
- Quality by Design
- Integrated Quality Assessment
- Concept of Operations for Facility Evaluation and Inspection For Human Drugs
- FDA Quality Oversight New Initiative: Knowledge-aided Assessment and Structured Application (KASA)

FDA's Process Analytical Technology

from "Testing Quality in.." to "Building Quality in…"

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)

Pharmaceutical CGMPs
September 2004

Applications of process analytical technology to crystallization processes☆

Lawrence X. Yu[a], Robert A. Lionberger[a], Andre S. Raw[a], Rosario D'Costa[a], Huiquan Wu[b], Ajaz S. Hussain[b,*]

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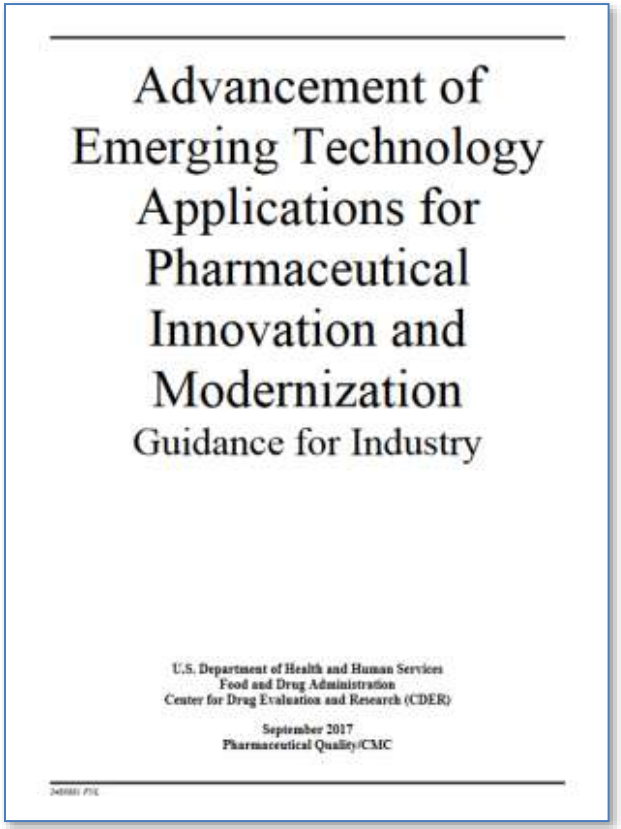
Received 30 April 2003; accepted 6 October 2003

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

Emerging Technology Program (2013)

- Supports industry's development and implementation of innovative approaches in **pharmaceutical design and manufacturing**
- Identifies and **resolves potential scientific and policy issues** related to new approaches
  - Enabled the approval of the first switch from batch to continuous manufacturing process for an approved drug
- A website and Guidance for Industry were posted in 2017



Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization

Guidance for Industry

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

September 2017
Pharmaceutical Quality/CMC

Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

- Approvals of applications utilizing continuous manufacturing (CM)
  - Vertex ORKAMBI (lumacaftor/ivacaftor, 2015)
  - Janssen Prezista (darunavir, 2016)
  - Eli Lilly Verzenio (abemaciclib, 2017)
  - Vertex Symdeko (tezacaftor/ivacaftor and ivacaftor, 2018)
  - Pfizer Daurismo (glasdegib, 2018)
  - Vertex Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor, 2019)
  - API Continuous Manufacturing (2019)
  - Dialysis solutions (2020)
  - Continuous bioprocess (2020)

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 with the adoption of the quality-by-design (QbD) paradigm for pharmaceutical development and the advancement of process analytical technology (PAT) for designing, analyzing, and controlling manufacturing have progressed the scientific and 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 result in poor product quality can lead to drug shortages [3]. Drug shortages are a critical health care issue, affecting individual patients across the USA. Recognizing that shortages commonly begin with a supply disruption related to product

Pharmaceutical 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.

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

Review Article

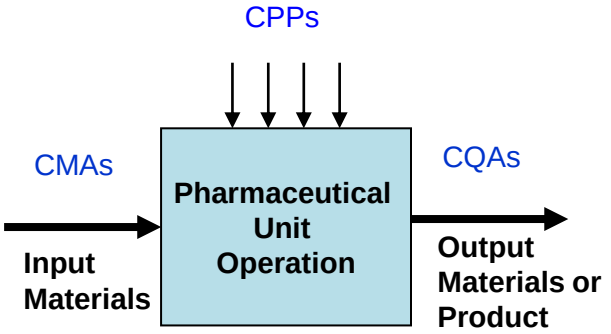
Understanding Pharmaceutical Quality by Design

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.



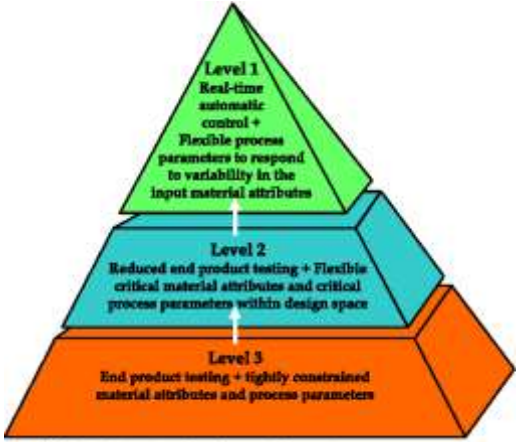


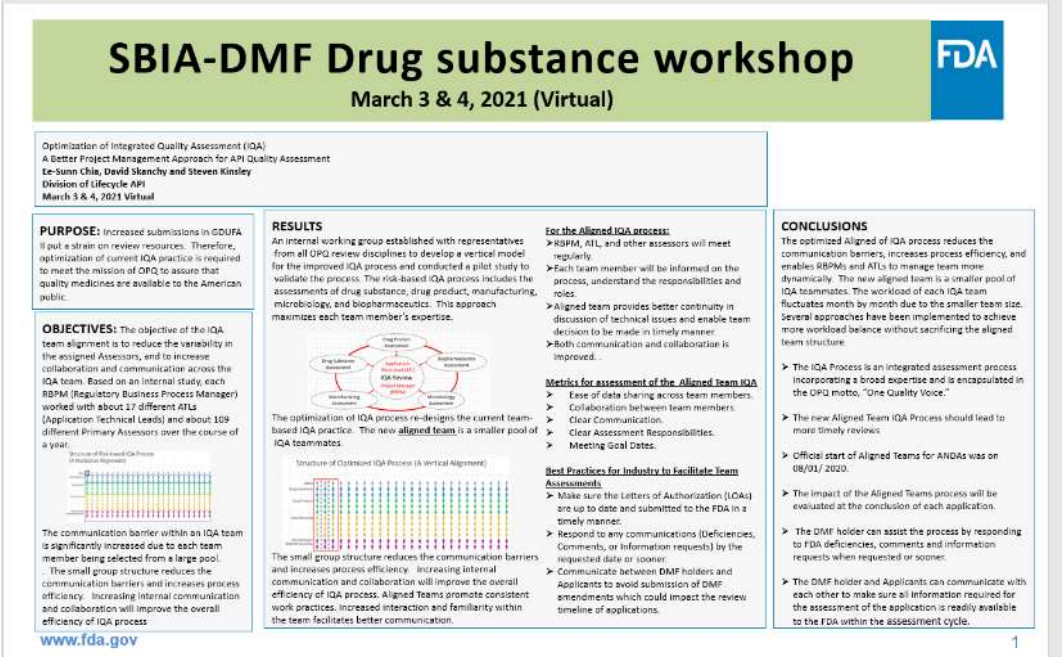
Fig. 3. Control strategy implementation options

Integrated Quality Assessment (IQA): Process Management

Discipline Expert Assessor

Ongoing IQA Improvement Effort

- Ongoing IQA improvement effort helps OPQ to improve the efficiency and effectiveness of quality assessments by removing barriers to communication and trust and enhancing clarity around the process, roles and responsibilities



SBIA-DMF Drug substance workshop

March 3 & 4, 2021 (Virtual)

Optimization of Integrated Quality Assessment (IQA)
A Better Project Management Approach for API Quality Assessment
Ee-Sunn Chia, David Skanchy and Steven Kinsley
Division of Lifecycle API
March 3 & 4, 2021 Virtual

PURPOSE: Increased submissions in GDUFA II put a strain on review resources. Therefore, optimization of current IQA practice is required to meet the mission of OPQ to assure that quality medicines are available to the American public.

OBJECTIVES: The objective of the IQA team alignment is to reduce the variability in the assigned Assessors, and to increase collaboration and communication across the IQA team. Based on an internal study, each RBPM (Regulatory Business Process Manager) worked with about 17 different ATLs (Application Technical Leads) and about 109 different Primary Assessors over the course of a year.

The communication barrier within an IQA team is significantly increased due to each team member being selected from a large pool. . The small group structure reduces the communication barriers and increases process efficiency. Increasing internal communication and collaboration will improve the overall efficiency of IQA process

RESULTS

An internal working group established with representatives from all OPQ review disciplines to develop a vertical model for the improved IQA process and conducted a pilot study to validate the process. The risk-based IQA process includes the assessments of drug substance, drug product, manufacturing, microbiology, and biopharmaceutics. This approach maximizes each team member's expertise.

The optimization of IQA process re-designs the current team-based IQA practice. The new aligned team is a smaller pool of IQA teammates.

The small group structure reduces the communication barriers and increases process efficiency. Increasing internal communication and collaboration will improve the overall efficiency of IQA process. Aligned Teams promote consistent work practices. Increased interaction and familiarity within the team facilitates better communication.

For the Aligned IQA process:

- RBPM, ATL, and other assessors will meet regularly.
- Each team member will be informed on the process, understand the responsibilities and roles.
- Aligned team provides better continuity in discussion of technical issues and enable team decision to be made in timely manner.
- Both communication and collaboration is improved. .

Metrics for assessment of the Aligned Team IQA

- Ease of data sharing across team members.
- Collaboration between team members.
- Clear Communication.
- Clear Assessment Responsibilities.
- Meeting Goal Dates.

Best Practices for Industry to Facilitate Team Assessments

- Make sure the Letters of Authorization (LOAs) are up to date and submitted to the FDA in a timely manner.
- Respond to any communications (Deficiencies, Comments, or Information requests) by the requested date or sooner.
- Communicate between DMF holders and Applicants to avoid submission of DMF amendments which could impact the review timeline of applications.

CONCLUSIONS

The optimized Aligned of IQA process reduces the communication barriers, increases process efficiency, and enables RBPMs and ATLs to manage team more dynamically. The new aligned team is a smaller pool of IQA teammates. The workload of each IQA team fluctuates month by month due to the smaller team size. Several approaches have been implemented to achieve more workload balance without sacrificing the aligned team structure.

- The IQA Process is an integrated assessment process incorporating a broad expertise and is encapsulated in the OPQ motto, "One Quality Voice."
- The new Aligned Team IQA Process should lead to more timely reviews
- Official start of Aligned Teams for ANDAs was on 08/01/ 2020.
- The impact of the Aligned Teams process will be evaluated at the conclusion of each application.
- The DMF holder can assist the process by responding to FDA deficiencies, comments and information requests when requested or sooner.
- The DMF holder and Applicants can communicate with each other to make sure all information required for the assessment of the application is readily available to the FDA within the assessment cycle.

www.fda.gov 1

Today's Lifecyle API Assessment

- Innovation
  - Lead the development of workload management tool
- Transparency
  - Provide industry transparency on the API review process, review policy, and technical standards to provide better clarity on expectations
- Collaboration
  - Working with field investigators and other discipline experts to perform comprehensive API risk-based quality assessments
- Communication
  - Leverage transparency and understanding so that FDA and industry can improve communication resulting in a more efficient review process for API DMFs and the applications they support
- Engagement
  - Increase industry understanding of the process and technical standards through the talks/posters and multiple opportunities to have questions answered by FDA staff

Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations (2017)

- 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:
  - Pre-Approval Inspection
  - Post-Approval Inspection
  - Surveillance Inspection, and
  - For-Cause Inspection

https://www.fda.gov/drugs/pharmaceutical-quality-resources/integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept-operations

Concept of Operations Highlights

- Improved communication with stakeholders
  - decisional letters and follow-up engagements
- Defined timelines
- Parity between domestic and international functions
- Streamlined work flow
- Clear roles and responsibilities

Knowledge-aided Assessment & Structured Applications (KASA) Initiative

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

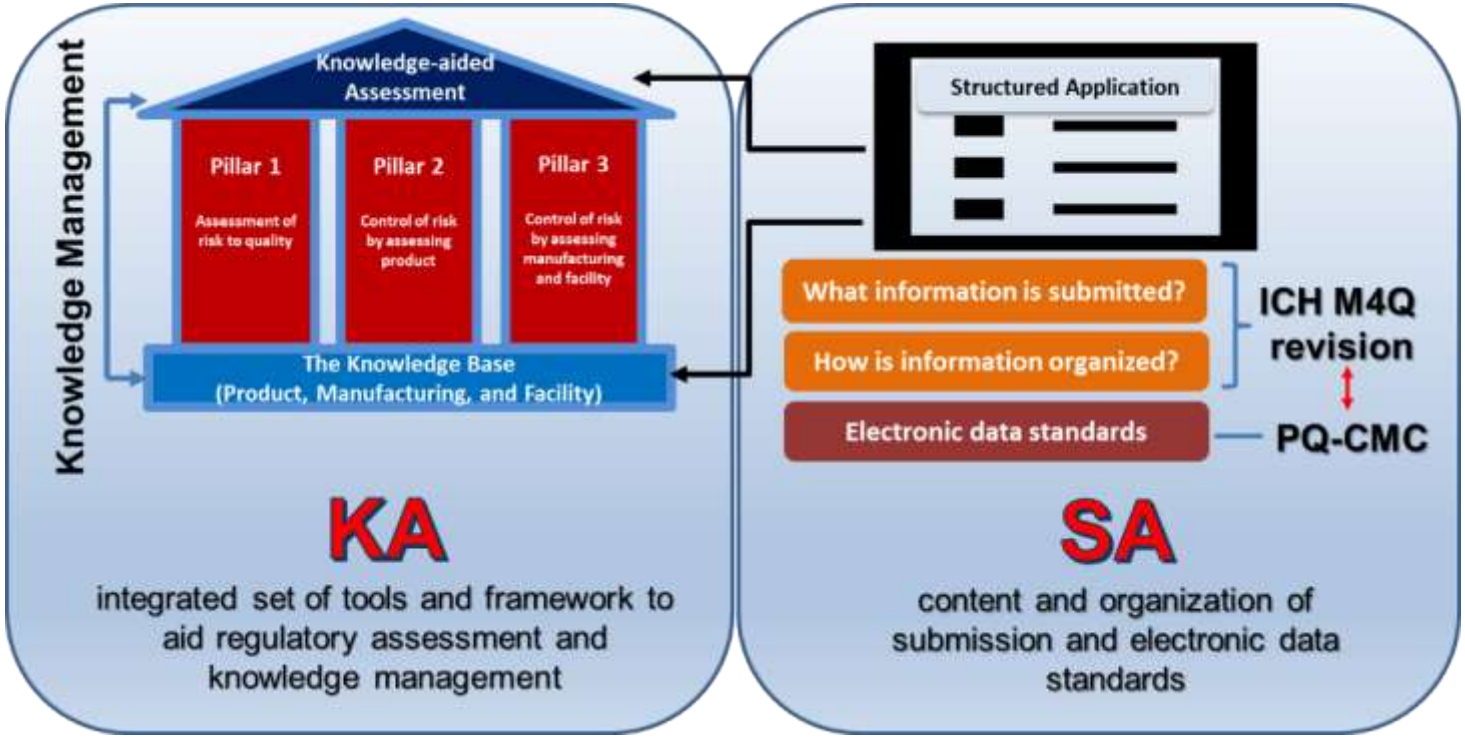
Keywords:
Pharmaceutical quality
Knowledge management
Risk assessment
Risk control
Structured application

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 KASA System: A data-based platform for structured quality assessments and applications that supports knowledge management

KASA: Content Management



Summary

- Patients deserve quality medications
  - Process Analytical Technology/Emerging Technology Program
  - Quality by Design
  - Integrated Quality Assessment
  - Concept of Operations for Facility Evaluation and Inspection For Human Drugs
  - FDA Quality Oversight New Initiative: Knowledge-aided Assessment and Structured Application (KASA)

Thanks

- Our hosts: CDER Small Business & Industry Assistance
- ONDP Lifecycle API Leadership and Staff
- OPQ
- Other CDER Offices
- API assessment is a true team effort!