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Review Article

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

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Abstract

This review paper is about FDA's new pharmaceutical quality initiative: Knowledge-aided assessment & structured applications (KASA). The aim of USFDA is Timely development, assessment, and approval of safe and effective drugs is pivotal for assuring the American public has access to quality medicines. At present, the new drug and generic quality assessment is performed using a written narrative. To modernize the assessment of drug applications, a KASA system has been initiated. KASA could become a system that captures and manages information about a drug product including risk identification, mitigation and communication, and control strategy. It does this through a structured IT framework that could completely replace the current unstructured text-based, narrative assessment.

Keywords: Knowledge-aided assessment & structured applications (KASA), USFDA, Office of Pharmaceutical Quality (OPQ), failure mode, effects and criticality analysis (FMECA)

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1. Introduction

The aim of USFDA Pharmaceutical Quality for 21st century initiatives is to promote a maximally efficient, fast moving, flexible pharmaceutical manufacturing sector.

To achieve that goal some periodical changes has been done by USFDA which are listed here.

- FDA, 2004b.

Reliably produces high quality drugs without extensive regulatory oversight

- FDA, 2004a, FDA, 2004b

Over the years, substantial progress has been made toward this vision, including process analytical technology (PAT), Current Good Manufacturing Practices (CGMPs) for the 21st century.

- FDA, 2009

Quality by Design (QbD)

- FDA, 2017

Emerging Technology

- FDA, 2017

Continuous manufacturing and six sigmas pharmaceutical quality, FDA's regulatory assessment also evolved from FDA 1990s, Summary-based review to FDA, 2007, Question-based review after that FDA, 2015, Risk-based approach in the 2000s to the integrated quality assessment. However, at the same time, the FDA mission has been confronted with challenges toward ensuring efficiency, consistency, and objectivity in its oversight of pharmaceutical quality. To address these challenges and best take advantage of technology advances, the FDA is undertaking the creation of a new system called Knowledge-aided Assessment & Structured Application (KASA). The KASA system is designed to

- 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. The KASA system will promote issue-based quality assessment using structured data and information to improve the efficiency, consistency, and objectivity of regulatory actions. (1,2)

2. Current state and why KASA is needed

The Agency recognizes the need for internal change in response to increasing expectations from the pharmaceutical industry, public demands, and technological advancements to keep pace in the 21st Century. With the reauthorization of the Prescription Drug User Fee Act (PDUFA VI), Biosimilar User Fee Amendments (BsUFA II), and Generic Drug User Fee Amendments (GDUFA II), OPQ has experienced a large volume of regulatory drug applications along with, in some cases, shorter assessment timelines. Apart from the workload, Office of Pharmaceutical Quality (OPQ) faces challenges related to the quality assessment itself, which is still a freestyle text narrative and summarization of information submitted by applicants. This assessment model poses barriers toward best practices for managing quality, lifecycle knowledge sharing, and overall modernization. (3)

Currently, written assessments consist of unstructured text and often have excessive summaries of application data, including tables and other information "copied and pasted" from the actual application. Thus, key elements of the quality assessment such as risk assessments and evaluation of mitigation approaches are often not readily identifiable in these lengthy documents. This results in cumbersome knowledge management and inefficient communications. In addition, assessments rely heavily on the knowledge and expertise of the assessor, which can potentially lead to inconsistencies in assessment. While assessor expertise is highly valued in OPQ, the current approach is hindered by the absence of databases to capture current knowledge that would aide in accessing critical information and making more objective decisions. Coupled with insufficient knowledge management tools, this unstructured text approach can result in inconsistencies and difficulties when comparing products.

The lengthy unstructured text narrative with dispersed information and the lack of efficient knowledge management make it difficult for OPQ to compare relative quality and relative risk across drug products and facilities. This makes it difficult to capture the 'state of quality' for a 9 product at any given time. This becomes especially evident when assessing residual risks with post-marketing quality changes during the drug product lifecycle. These challenges may lead to late interventions in preventing or addressing drug shortages or quality failures of marketed drugs. To meet the above challenges, OPQ is developing the KASA system to modernize the quality assessment of drug applications to include structured information. This promotes consistency and enables a much-needed knowledge management tool that improves efficiency and the overall quality assessment process. (4)

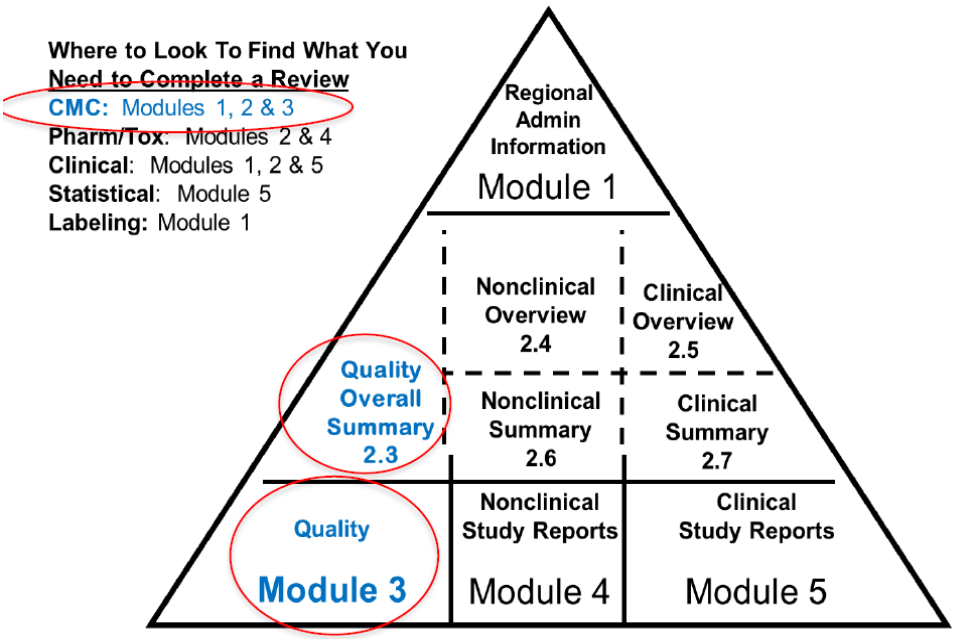

Figure 1. CTD structure for dossier submission

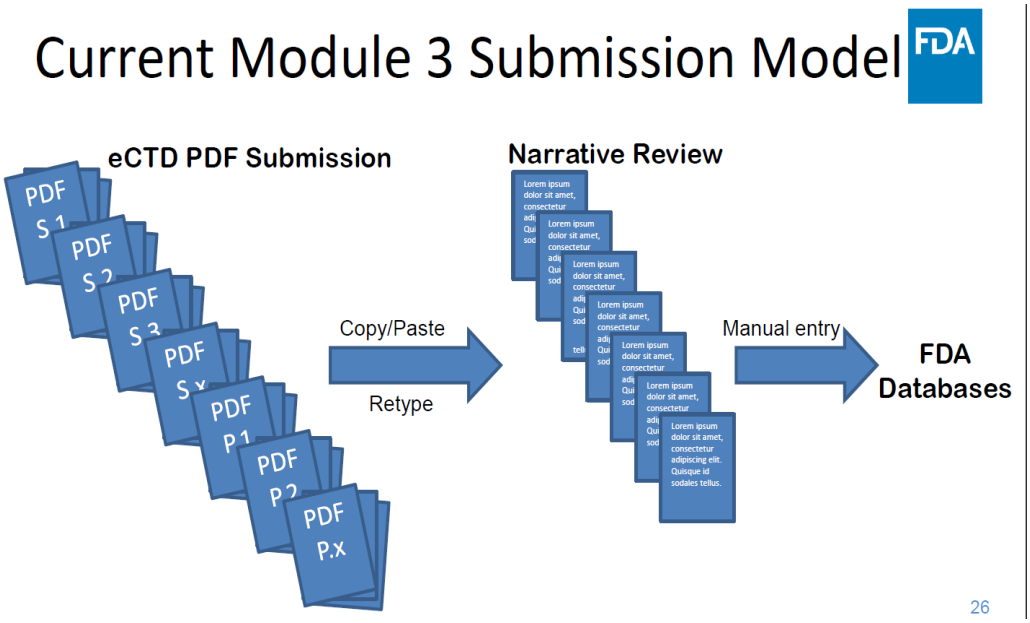

Figure 2. Current submission model without application of KASA

3. More about KASA – The What

KASA is a system that captures and manages information about intrinsic risk and mitigation approaches for product design, manufacturing, and facilities, in a structured template. This is intended to facilitate a concise and consistent quality assessment and largelyreplace freestyle text. The KASA interface tabulates the following for each critical product quality attribute: 1) Inherent risk to quality 2) Mitigation approaches - using a list of generalized structured descriptors related to pharmaceutical design, development, control strategy, and facility implementation 3) A concise summary from the assessor detailing how the generalized approaches are applied in the regulatory application 4) Links to supporting information from the application. (5)

The house depicted above in Figure 3 represents KASA. The knowledge base represents the house's foundation and encompasses the historical information about the drug product and its manufacturing available to the Agency. Above the foundation are pillars that provide structure and a framework. Each pillar represents a different phase of KASA's development. The following Sections A through C provide details about each pillar of the house, representing noteworthy aspects of development. Section D discusses the long-term vision for structured applications which would greatly enhance the value and significance of the KASA by automating uptake of data into the system. (6)

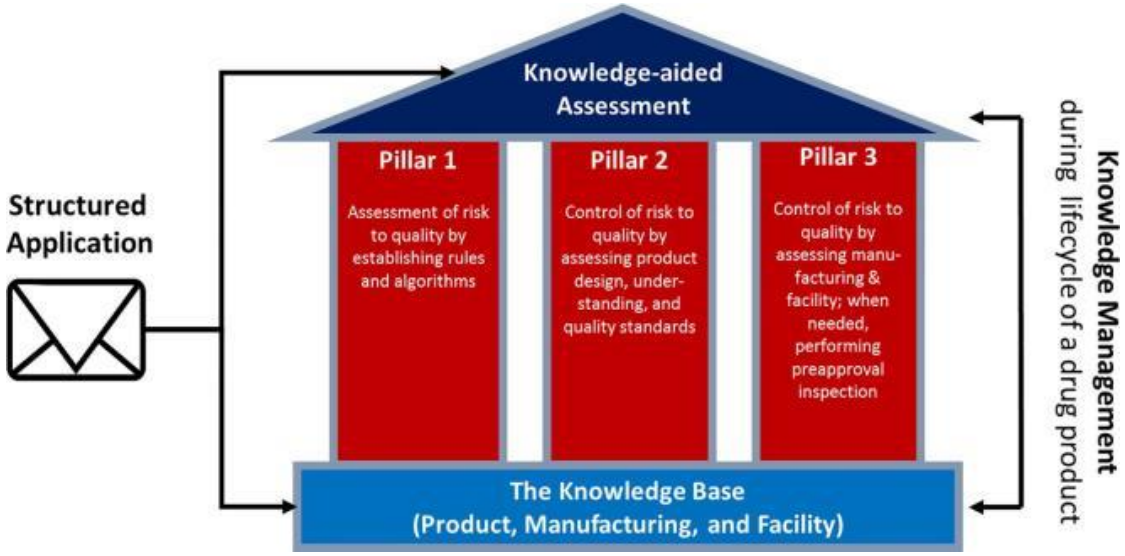

Figure 3. KASA House

A. Pillar 1: Assessment of Risk to Quality by Establishing Rules and Algorithms KASA establishes within its user interface predefined rules and algorithms to estimate the initial inherent product and manufacturing risks. After the assessor enters information in the system based on the application, a failure mode, effects and criticality analysis (FMECA) approach is employed. This is used to objectively and

quantitatively assess and rank risks associated with the failure modes of drug product design and manufacturing. These are the risks that have the greatest chance of causing product failure or unexpected harm to the patient. Product risk considers each critical drug product quality attribute (such as assay/potency, purity, uniformity, dissolution, etc.). Manufacturing risk considers the impact of the proposed material transformation steps on the product quality attributes, and the potential risks involved with implementing the proposed control strategy at the manufacturing site. (7)

B. Pillar 2: Risk Mitigation by Assessing Product Design and Understanding, and Quality Standards. The inherent risk identified in Pillar 1 is mitigated by design of the product and the use of patient-focused quality standards. Product risk mitigation focuses on the drug substance characteristics and drug product design, understanding, and control. Drug substance characteristics considered when assessing risk include therapeutic index, complexity of manufacturing, and adequacy of control of the identity, purity, stability, and quality. Product risk assessment includes the product design, intended use, degree of product understanding, and product quality control inherent to the critical quality attributes (CQAs). Drug product design determines whether the product is fit for intended use, can meet patients' needs, and maintains its performance through its proposed shelf life. Product understanding is the ability to link input critical material attributes (CMAs) to output CQAs so that input material attributes (e.g., drug substance, excipient, in-process material, primary packaging material) can be appropriately controlled to mitigate risks to the product quality. Within the KASA system, this type of product understanding is captured using drop-down menus with structured descriptors that objectively describe these aspects of product understanding and control strategy. The knowledge captured with such a system enables mitigation of product risk to be compared across applications and facilities. Pillar 2 also includes the assessment of the applicants' specifications and acceptance criteria to determine their acceptability as a part of established conditions. By establishing acceptance criteria based on desired clinical performance, instead of process capability or manufacturing process control, it increases flexibility within the pharmaceutical manufacturing sector while continuing to maintain quality. (8)

C. Pillar 3: Risk Mitigation by Assessing Manufacturing and Facility, and Performing Approval Inspections Manufacturing risk mitigation focuses on design and implementation of the manufacturing process. A manufacturing process is generally considered well understood and controlled when: 1) All critical sources of common cause variability are identified and explained 2) Variability is managed by the process at all scales through successful implementation of the control strategy 3) Process performance and product quality attributes can be adequately and reliably monitored and controlled Facility risk mitigation, or the implementation element of manufacturing risk, focuses on the manufacturer's GMP status and ability to support the control and continued performance of the operations. Determination of risk mitigation leverages the demonstrated capabilities of the manufacturing or testing facilities as it relates to the proposed manufacturing process. It includes evaluation of the facility's recent manufacturing history, knowledge of the facility with the unit operations included in the application, and relevant quality signals for any similar marketed products, including applicable Field Alert Reports (FARs), any associated recalls, regulatory/advisory actions, and available foreign regulatory agency reports. After evaluating development information, the proposed control strategy, and the firm's known capabilities, there may still be significant risk concerning the ability of the applicant to successfully produce the quality product. This remaining risk can be further assessed by performing a pre-approval inspection (PAI) or post-approval inspection (PoAI). The PAI/PoAI assesses whether the facilities named in the manufacturing section of an application can perform and adequately control the proposed operation(s) in conformance to CGMP requirements. Additionally, a PAI evaluates whether the data submitted in the application are reliable, accurate, and complete. Under KASA, manufacturing process design and implementation risks are evaluated and captured using pre-defined descriptors that objectively capture aspects related to manufacturing and facility understanding and control so that objective standards are used to identify the need for PAIs. (9)

D. Structured Application Looking toward the future, knowledge-aided assessment would be greatly enhanced if applicants submit applications more streamlined in layout with structured data that integrates with the assessment system. Regulatory drug applications are currently submitted to FDA in the electronic common technical document (eCTD) format. Despite some benefits, the eCTD poses challenges for FDA assessors because the submitted content does not follow the development flow, contains unstructured data, and varies in the level of granularity provided. Furthermore, the documents are in PDF format so information cannot be easily searched/mined, making lifecycle management challenging. Although KASA is being primarily developed as an assessment tool, it is capable of alleviating problems associated with electronic regulatory drug applications. In the future, it is conceivable that submission structure recommendations will be made to better interface with KASA's structured assessment approach. This would allow applicants to succinctly and consistently summarize steps taken to mitigate inherent risks via development studies, control strategies, and local CGMP facility controls. Under this paradigm, automated tools would be used to populate the KASA template from the structured submission with, for example, specifications and critical process parameter ranges. This would eliminate administrative tasks for the assessor and improve the assessment efficiency by allowing assessors to focus on high risk areas. This longer-term goal would be a significant step towards modernizing and bringing the overall quality assessment process into the 21st Century. (10)

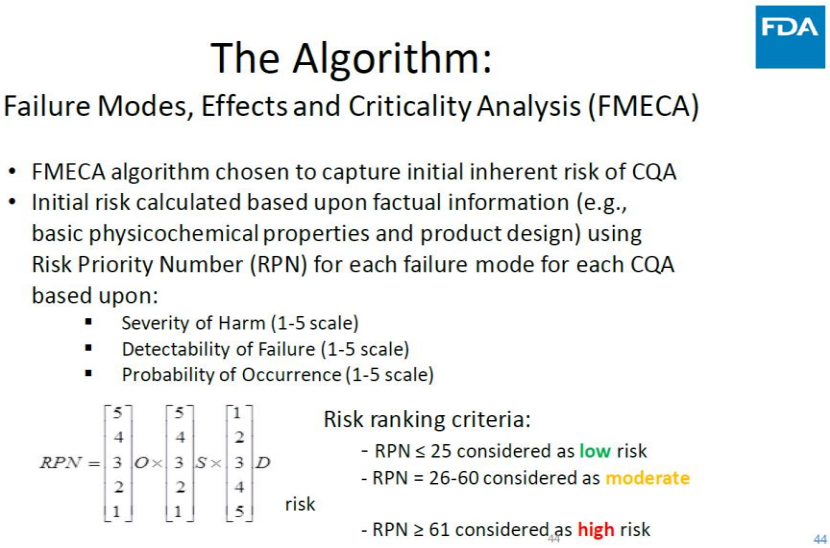

Figure 4. The Algorithm FMECA

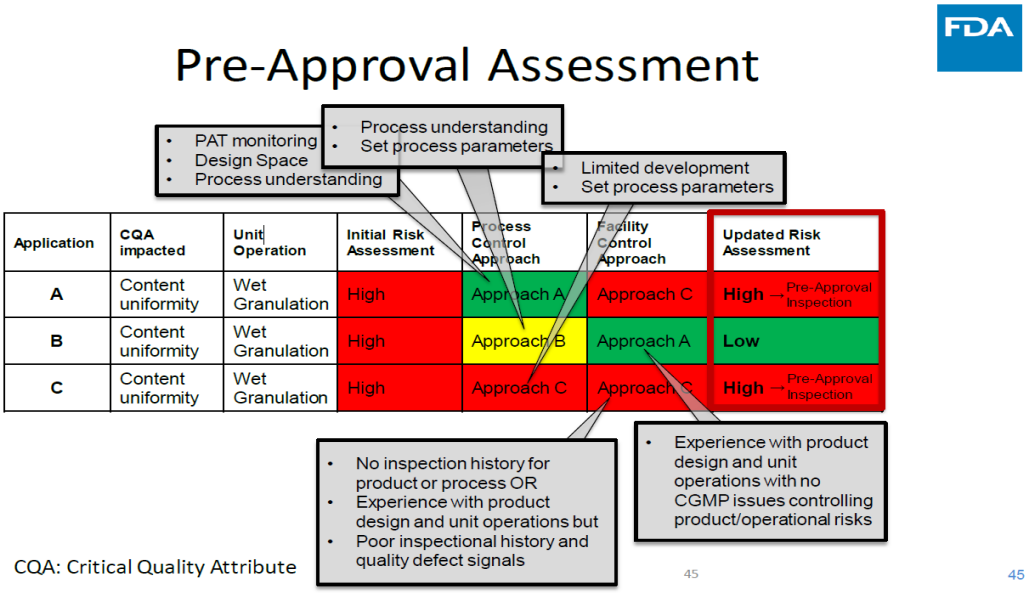

Figure 5. Pre-Approval Assessment

4. Benefits offered by KASA

The KASA system moves regulatory application assessment from the current unstructured text document to an issue-based regulatory and technical assessment using structured data and information with standard formatting, a common vocabulary, and a uniform output. In turn, this improves consistency, transparency, communication, and objectivity of regulatory actions as well as knowledge management within the Agency.

KASA, with access to structured knowledge, will have tools that enable assessors to automatically retrieve historical data and facility information to better inform the regulatory evaluation and decision-making process. KASA will facilitate the assessment of risk using rules and algorithms, which in turn reduces subjectivity of documentation and the time burden. Furthermore, prior to assessment, submitted applications will be checked against KASA informatics to detect any outliers in control strategy and risk attributes as compared to the broader KASA database. The built-in rules and algorithms together with the detection of outliers allow assessors to focus on high-risk areas and issues. This improves the quality and efficiency of the regulatory assessment by semi-automating FDA's quality assessment. Ultimately, this facilitates the introduction of breakthrough therapeutics and low cost, high-quality generic drugs to meet medical needs. (11)

Finally, by evaluating risks and mitigation steps, KASA captures and conveys residual product, manufacturing, and facility risk for each regulatory submission. It will also be instrumental in capturing established conditions. Succinctly identifying the main mitigating factors and residual risk aids the Agency's assessment of post-approval changes and the lifecycle management of drug products. This can help focus post-approval and surveillance inspection resources on the riskiest products or those for which on-site controls are essential for

ensuring critical quality attributes. In this way, the FDA achieves more efficient regulatory oversight by appropriately focusing resources on the high-risk products. (12)

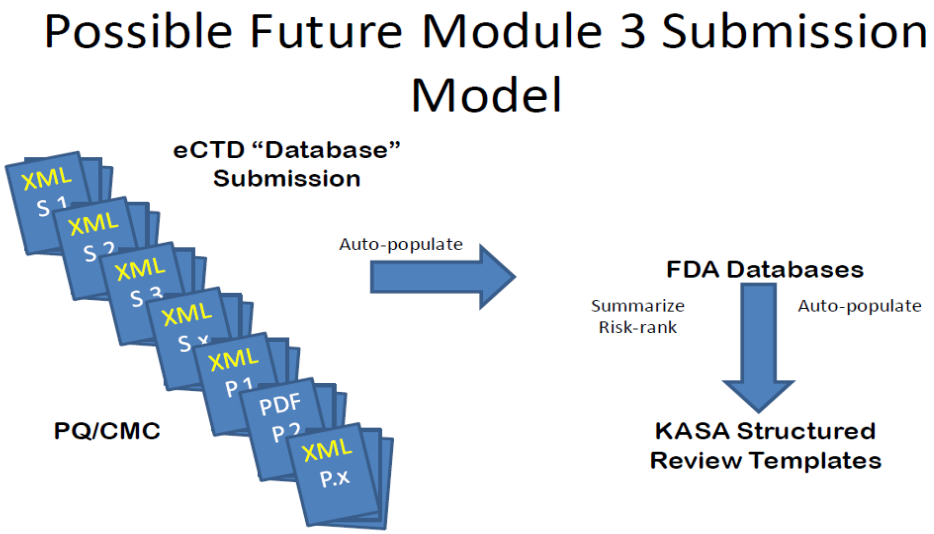

Figure 6. Possible future Module 3 Submission Model

5. Conclusion

Looking back on this project, the overall outcome of results is to be observed. This can be evaluated by looking at how well our objectives were met. KASA is a new system intended to modernize the quality assessment of regulatory drug applications. KASA represents a concept shift from the outdated assessment practices of the past, to a new, more efficient way of handling information and resources. When fully developed and implemented, KASA will contribute to:

- Assuring patient focused quality standards and the objectivity of regulatory actions through knowledge management;
- Enhancing science- and risk-based regulatory approaches through established algorithms;
- Enriching regulatory oversight through lifecycle management of products and facilities.

Ultimately the KASA system advances OPQ's focus on pharmaceutical quality, the foundation for ensuring the safety and efficacy of drugs. It takes the Agency's quality oversight to the next level through modernization.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article

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