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# FDA's New Pharmaceutical Quality Initiative: Knowledge-aided Assessment & Structured Applications

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## 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.

## 1. Introduction

The U.S. Food and Drug Administration (FDA) Pharmaceutical Quality for the 21st Century Initiative aims to promote *a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight* (1). Over the years, substantial progress has been made toward this vision, including process analytical technology (PAT) (2), Current Good Manufacturing Practices (CGMPs) for the 21st century (1), Quality by Design (QbD) (3, 4), Emerging Technology (5), continuous manufacturing (6), and six sigma pharmaceutical quality (7).

Meanwhile, FDA's regulatory assessment also evolved from the summary-based review in the 1990s, through the question-based review (8) and risk-based approach (9) in the 2000s, to the integrated quality assessment in 2015 and beyond (10). 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;

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- 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. This paper will describe factors that prompted the development of the KASA system, the vision for KASA, and the benefits it could provide upon its development.

## 2. Current State and Why KASA is Needed

The FDA recognized 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), FDA has experienced a large volume of regulatory drug applications along with, in some cases, shorter assessment timelines.

Apart from the workload, FDA is facing challenges related to the quality assessment itself. First, when a quality assessor picks up a regulatory application, it is not possible to easily locate historical data about similar products, processes, or the facilities. Such a practice has significantly reduced the efficiency of the regulatory assessment and increased the likelihood of inconsistencies. Further, in particularly urgent cases, the FDA may not have readily available up-to-date information to provide timely, thorough, and complete responses, hindering FDA's regulatory oversight.

Second, risk assessment and control can be subjective, leading to inconsistency in regulatory actions and outliers in risk when compared to similar products. In addition, key elements of the quality assessment related to risk and evaluation of control approaches are written in unstructured text that are not readily identifiable in lengthy assessment documents.

Third, the assessment is a freestyle text narrative that often includes exhaustive documentation of information already provided in the application, and the assessments rely heavily on the knowledge and expertise of the assessor. While assessor expertise is highly valued at the FDA, 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 difficulties when comparing products and processes.

The lengthy unstructured text narrative with dispersed information and the lack of efficient knowledge management make it difficult for the FDA to compare relative quality and relative risk across drug products and facilities. This makes it difficult to capture the 'state of quality' for a 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

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late interventions to prevent or address drug shortages or quality failures of marketed drugs. To meet the above challenges, the FDA is developing the KASA system to modernize the quality assessment of drug applications to include structured information. This will promote consistency and enable a much-needed knowledge management tool that will improve efficiency and the overall quality assessment process.

## 3. More About KASA – The What

KASA is a system that captures and manages information about inherent risk and control approaches for product design, manufacturing, and facilities, in a structured format. This is intended to facilitate a concise and consistent quality assessment and largely replace freestyle text. The KASA interface tabulates the following for each critical product quality attribute:

1) Inherent risk to quality
2) Control 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.

The house depicted in Figure 1 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 interconnection between the historical information at the foundation of KASA and the framework of the KASA pillars (risk assessment, control, and communication) ensures all facets of knowledge management to products and processes are captured. 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.

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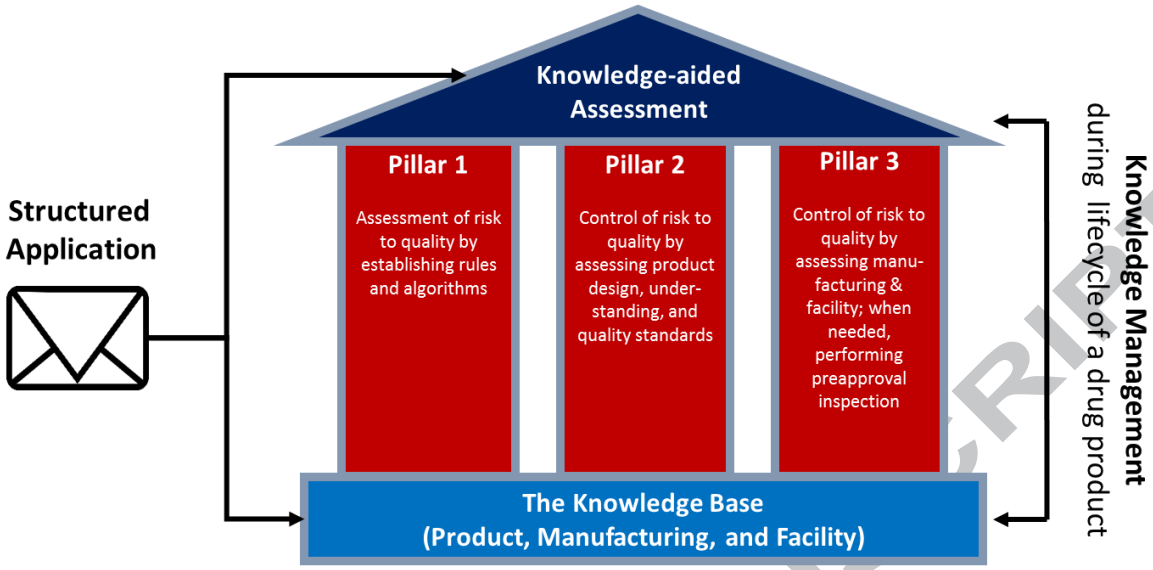


Figure 1. Knowledge-aided Assessment & Structured Application (KASA) system

### 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 modes, 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 and manufacturing 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. The final risk assessment is generally based on the application of the established rules and algorithms of KASA to the information provided in the application and may be further informed by the applicant's risk assessment.

### B. Pillar 2: Risk Control by Assessing Product Design and Understanding, and Quality Standards

The inherent risk identified in Pillar 1 is controlled by design of the product and the use of patient-focused quality standards. Product risk control 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 for the identity, purity, stability, and quality. Product risk assessment includes the product design, intended use, degree of product

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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 constrained to control risks to the product quality (11). 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 control of product risk to be compared across applications and facilities.

Pillar 2 also includes the assessment of the applicants' specifications to determine their acceptability . 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.

### C. Pillar 3: Risk Control by Assessing Manufacturing and Facility, and Performing Approval Inspections

Manufacturing risk control 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, and
3) Process performance and product quality attributes can be adequately and reliably monitored and controlled (11).

Facility risk control, 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 control 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, experience 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 including the proposed established conditions (12), and the firm's known capabilities, there may still be significant risk concerning the ability of the applicant to successfully produce a 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

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facilities named in the manufacturing section of an application can perform and adequately control the proposed operation(s) in conformance to CGMP requirements, as outlined in the FDA Compliance Program Guidance Manual 7346.832 and 7346.843 (13, 14). 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.

### D. Structured Application

Looking toward the future, knowledge-aided assessment would be greatly enhanced if applicants were to submit applications more streamlined in layout with structured data that are aligned 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, such as those initiated for standardization of Pharmaceutical Quality/Chemistry Manufacturing and Control (PQ/CMC) data and terminologies (15), will be made to interface with KASA's structured assessment approach. 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 long-term goal would be a significant step towards modernizing and bringing the overall quality assessment process into the 21st Century.

## 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 its 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 reduce subjectivity of documentation and the time burden for assessors. 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

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allow assessors to focus on high-risk areas and issues. This improves the effectiveness 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.

Finally, by evaluating risks control steps, KASA captures and conveys residual product, manufacturing, and facility risk for each regulatory submission. 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.

## 5. Conclusions

KASA is a new system intended to modernize the quality assessment of regulatory drug applications. KASA represents a concept shift from the 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:

1. assuring patient focused quality standards and the objectivity of regulatory actions through knowledge management;
2. enhancing science- and risk-based regulatory approaches through established rules and algorithms; and
3. enriching regulatory oversight through lifecycle management of products and facilities.

Ultimately the KASA system advances FDA's focus on pharmaceutical *quality*, the foundation for ensuring the safety and efficacy of drugs. It takes the Agency's *quality oversight* one step closer to the FDA overall vision (1) of *a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.*

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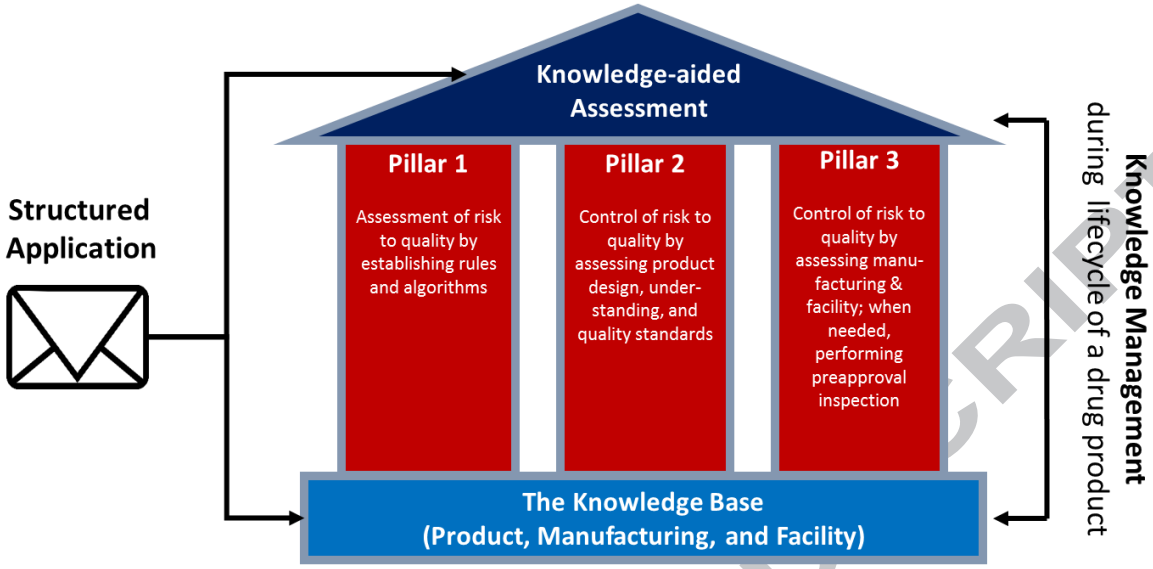


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