KASA to Support Generic Drug Review

FDA expects the new system to advance OPQ's focus on pharmaceutical quality, the foundation for ensuring the safety and efficacy of drugs.

If you have attended recent industry conferences or read FDA news, you must have heard of the KASA a lot. Knowledge-aided Assessment & Structured Application (KASA) is a system that has been developed by FDA to capture and manage information related to a drug product review. FDA plans to use the information about intrinsic risk and mitigation approaches for product design, manufacturing, and facilities, in a structured template. KASA can transform the current unstructured assessment to a structured data and information with an efficient and uniform output.

FDA expects that this will improve consistency, transparency, communication, and objectivity of regulatory actions as well as knowledge management within the Agency. This article reviews and presents the background, the points of discussion and recommendation of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee regarding KASA and the Pharmaceutical Quality/Chemistry Manufacturing and Controls (PQ/CMC) Data Elements and Terminologies initiative.

Why KASA

On September 20, 2018, the Pharmaceutical Science and Clinical Pharmacology Advisory Committee met in the Great Room of Building 31 at the FDA's White Oak Campus. The meeting backgrounder stated the following:

"[T]imely development, assessment, and approval of safe and effective drugs is pivotal for assuring the American public has access to quality medicines. The Office of Pharmaceutical Quality (OPQ) focuses on the quality of drugs, which serves as the foundation for the established parameters of safety and efficacy. OPQ is responsible for the quality assessment of nearly every type of human drug marketing application. At present, the OPQ quality assessment is a written narrative, which results in dense, lengthy documents. In other words, this is a 20th Century approach meant for a time when most regulatory submissions were submitted on paper. OPQ recognizes the need for modernizing the current assessment approach and is in the process of creating a new system."[1]

FDA contends in the advisory committee backgrounder[2] that 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 is necessarily true since the risk assessment and mitigation strategies are now part of the pharmaceutical development section of an application, which is highly structured even though in a text format. Although FDA acknowledges assessor expertise is highly valued in product assessment, the current approach is limited by the absence of databases to capture and in accessing critical information. In addition, this unstructured text approach can result in inconsistencies and difficulties when comparing products.[3]

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.[4] The President's fiscal year 2019 Budget Request included $37.6 million to fund a few initiatives that will help modernize aspects of our generic drug review process. The first initiative will create a new review KASA platform to modernize generic drug review from a text-based to a data-based assessment.[5]

FDA Commissioner Scott Gottlieb, in a June 18, 2018 post wrote the following:

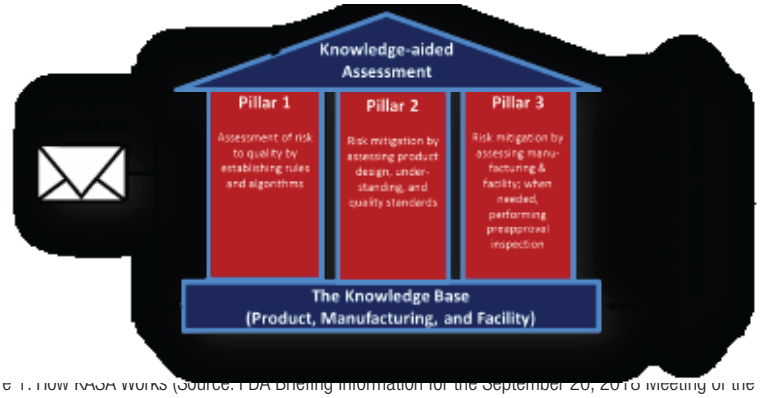

Figure 1: How KASA works (Source: FDA Briefing Information for the September 20, 2018 Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee)

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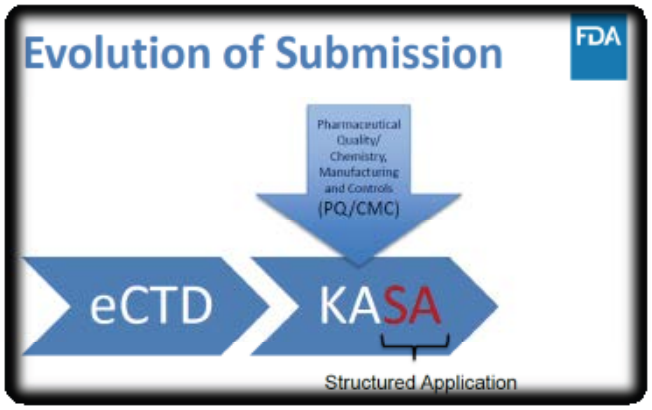

Figure 2. Evolution of Submission (Source: Structured Application and Benefits of KASA, Larisa C. Wu, Ph.D., Special Assistant/Chemist, Immediate Office/OPQ/CDER)

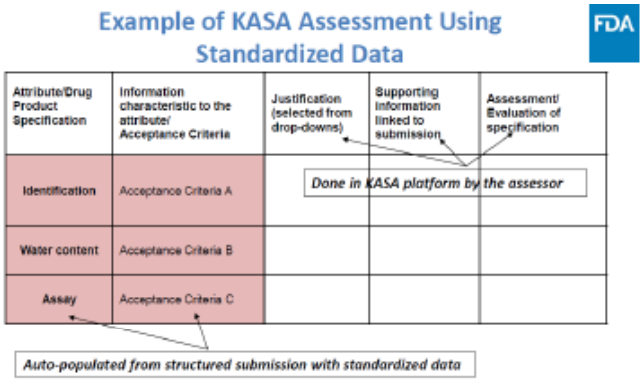

Figure 3. KASA Assessment (Source: Structured Application and Benefits of KASA, Larisa C. Wu, Ph.D., Special Assistant/Chemist, Immediate Office/OPQ/CDER Knowledge-aided Assessment & Structured Application (KASA)" Food and Drug Administration Slides for the September 20, 2018 Meeting of the Pharmaceutical Science and Clinical Pharmacology (PSCP) Advisory Committee)

"We anticipate that the new platform will allow more generic applications to be approved after the first cycle. This will promote timely generic entry and increase overall competition. The new platform will also enable more efficient and robust knowledge management across different aspects of the FDA's review process, helping reviewers capture and manage all of the information about products allowing for more seamless and effective product surveillance based upon quality and risk. This system will benefit both the agency and generic drug sponsors by increasing overall speed and efficiency of the pre- and post-market processes."[6]

How KASA works

FDA somewhat awkwardly illustrates KASA in relation to structured application and knowledge management as a house in *Figure 1*. In a briefing, FDA said, "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."[7] Assessment of risk to quality will be achieved by establishing rules and algorithms; risk mitigation by assessing product design, understanding and quality standards; risk mitigation by assessing manufacturing and facilities, and finally performing preapproval inspection when needed.

According to the new initiative, after the assessor enters information in the system based on the application, a failure modes, effects and criticality analysis (FMECA) approach will be employed. This will be used to objectively and quantitatively assess and rank risks associated with the failure modes of drug product design and manufacturing. The inherent risks identified can be mitigated by design of the product and the use of patient-focused quality standards. Product risk assessment will include the product design, intended use, product understanding, and quality control inherent to the critical quality attributes (CQAs). The initiative will also include the assessment of the applicants' specifications and acceptance criteria to determine their acceptability as a part of established conditions. Risk mitigation will focus on design and implementation of the manufacturing process. Facility and manufacturing risk mitigation will focus on the manufacturer's GMP status and ability to support the control and continued performance of the operations.[8]

Structured application

Having a structured template that completely replaces the current largely narrative-based review will allow for more consistent and predictable entry and analysis of data. Current assessments require manual review of the entire application. KASA will enable automated analysis of some portions of the application, which will save time, and ensure consistency.

Regulatory applications are currently submitted to FDA in the electronic common technical document (eCTD) format. Despite the fact CTD was a result of a harmonization initiative by the international regulatory authorities' community, FDA now argues that the eCTD content does not follow the development flow, contains unstructured data, and varies in the level of granularity provided. The pdf format has its own limitation in terms of data mining, making lifecycle management challenging.[9] This is understandably an issue that has been raised and acknowledged by the industry. Suggestions for alternate formats and platforms have also been made.

In her presentation at the September 20, 2018 Advisory Committee meeting Larisa Wu of FDA suggested that "a structured application that communicates with the KASA interface would serve as the ultimate enhancement to the system."[10] She illustrated the evolution of submissions, as seen in *Figure 2*. Dr. Wu also said that Pharmaceutical Quality/Chemistry, Manufacturing, and Controls (PQ/CMC) is a stepping stone toward structured submissions.[11] Although KASA is being primarily developed as an assessment tool, it is likely to enhance the quality of application and ease of review due to inclusion of structured datasets (*Figure 3*).

To support future electronic acquisition and use of submitted information, FDA undertook a project to identify and prioritize PQ/CMC information that would benefit from a structured submission approach. This would be part of an application submitted in the Common Technical Document as defined by the International Council for Harmonization's (ICH):

"The goals of this project were (a) to identify types of PQ/CMC information that are available in applications, information that is important to evaluate an application, information categories and elements that are

common across the various application types, and (b) to provide recommendations for standardization of the categories and data types necessary for application review. This initiative will align, where comparable elements exist, with substance and product identifiers described by the International Organization of Standardization for the Identification of Medicinal Products (ISO IDMP) standards. For consistency of product quality data across FDA centers, the draft standardized data elements and terminologies were created by an Agency workgroup comprised of Subject Matter Experts (SMEs) from the Center for Drug Evaluation and Research (CDER), the Center for Veterinary Medicine (CVM), and the Center for Biologics Evaluation and Research (CBER)."[12]

The docket provides draft data elements and terminologies associated with PQ/CMC subject areas and scoped to some of what is currently submitted in Module 3 of the electronic Common Technical Document (eCTD) submission but is not intended to be comprehensive in covering all eCTD product quality information. FDA has developed limited structured data elements and supporting terminologies for PQ/CMC and has recently engaged in discussions with standard-setting bodies to codify these data elements into a data exchange specification for the submission of PQ/CMC data. The working group recommended that review of these elements and definitions should be conducted by personnel in pharmaceutical companies who will be able to determine if the element definitions and controlled terminologies are understandable and meaningful.[13] The circulated draft document provides a first set of key data elements and terminologies associated with PQ/CMC subject areas and uses Global Substance Registration System (G-SRS), Data Universal Numbering System (DUNS), Structured Product Labeling (SPL), Unified Code for Units of Measure (UCUM) and other data fields are to be coded based on HL7 (Health Level 7).[14]

On July 11, 2017 FDA published a notice in the Federal Register requesting comment on the draft standardized Pharmaceutical Quality/Chemistry Manufacturing and Control (PQ/CMC) data elements and terminologies for the electronic submission of PQ/CMC data. The establishment of standardized pharmaceutical quality data elements and terminologies will provide opportunities for FDA and industry to transform PQ/CMC submission data into a readily useable electronic format. As a result, these established data elements and terminologies will improve the efficiency and quality of the drug review process. The Agency is seeking comment on the accuracy, suitability, and appropriateness of these data elements and terminologies for submission of PQ/CMC data.[15]

By September 11, 2017 when the comment period closed, there were 12 comments made by various pharmaceutical organizations including Pharmaceutical Research and Manufacturers of America (PhRMA).[16] Interestingly, there were no comments from Association for Accessible Medicines (AAM) that represents the generic and biosimilar industry.

Advancing to the next level

KASA is a latest system intended to modernize the quality assessment of regulatory drug applications. During 2017, OPQ developed and piloted a dashboard interface for quality risks for critical quality attributes and corresponding mitigation and control strategies for drug substance and drug product. In addition, a computer-aided interface to emphasize lifecycle knowledge management and standardization of ANDA quality assessment has been designed.[17]

Although a lot of the details of the KASA infrastructure are still unknown, the concept and some of the tools are being tested by FDA. When fully developed and implemented, FDA expects KASA to advance OPQ's focus on pharmaceutical quality, the foundation for ensuring the safety and efficacy of drugs. PQRI recently announced that at 4th PQRI/FDA Conference on Advancing Product Quality on April 9-11 in Rockville, MD, FDA will launch its KASA initiative. FDA hopes that all these initiatives will take the Agency's quality oversight to the next level. **CP**

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