# FDA Briefing Document

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

November 2 -3, 2022

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research,
Food and Drug Administration

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# Glossary

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| AC | Advisory Committee |
| CDER | Center for Drug Evaluation and Research |
| CGMP | Current Good Manufacturing Practice |
| FDA | Food and Drug Administration |
| KASA | Knowledge-aided Assessment and Structured |
| OPQ | Office of Pharmaceutical Quality |
| PQS | Pharmaceutical Quality System |
| PSCP | Pharmaceutical Science and Clinical Pharmacology |
| QMM | Quality Management Maturity |

# Memorandum

TO: Members, PSCP

FROM: Michael Kopcha, Ph.D., R.Ph.
Director, Office of Pharmaceutical Quality/CDER/FDA

DATE: October 5, 2022

RE: PSCP Meeting November 2-3, 2022

Dear Committee Members and Invited Guests,

We look forward to your participation in the Pharmaceutical Science and Clinical Pharmacology Advisory Committee (PSCP-AC) meeting on November 2-3, 2022.

This Advisory Committee focuses on important science issues being considered and/or addressed in the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER). As you know, this office is mainly focused on the assessment of the quality of pharmaceutical products. Through your participation and advice on the advisory committee, we develop and finalize our standards for assessing and approving products and setting policy for regulatory decision-making.

This specific meeting will focus on two topics related to OPQ's priority of promoting the availability of quality medicines for the American public. On November 2, 2022, the committee will discuss CDER's Quality Management Maturity (QMM) program. The committee will consider the impact that a QMM program would have on the pharmaceutical industry, drug shortages, and supply chain resiliency. FDA will seek input to determine if the Committee supports the development of a CDER QMM program to incentivize investments in mature quality management practices. On November 3, 2022, as part of CDER's continued effort to provide key updates on modernization of quality assessment, the committee will discuss the next stages of Knowledge-Aided Assessment and Structured Application (KASA). FDA will seek input on the vision and plan to expand KASA over the next five years to include drug substances, all generic dosage forms, new drug and biologics applications, and post-approval changes. Moreover, FDA will seek input regarding the need for advancing digitalization in KASA, including data standardization and mobilization of data from cloud-based servers. Background materials for each of the topics are attached.

We look forward to a very productive meeting in November. We value the opportunity to solicit your assistance in defining and solidifying OPQ's direction in developing sound, scientific responses to emerging issues.

At the start of the meeting on November 2nd, I will outline the goals and objectives for our meeting and I will also update you on ongoing OPQ initiatives and activities.

**Draft Points for Consideration**

**Topic 1 – CDER's Quality Management Maturity Initiative**

QMM is the state attained when drug manufacturers have consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement. CDER has proposed the development of a rating system that will help incentivize drug manufacturers to adopt more mature quality management practices at their facilities.

**Draft Points to Consider for the Committee:**

1. *Should CDER establish a QMM program to incentivize mature quality management practices?*

**Topic 2 – Knowledge-aided Assessment and Structured Application (KASA)**

Timely development, assessment, and approval of safe and effective drugs are pivotal for assuring that the American public has access to quality medicines. The concept of KASA was envisioned in 2016 and discussed at the Pharmaceutical Science and Clinical Pharmacology Advisory Committee (PSCP) meeting on September 20, 2018, as an IT system that modernizes FDA's assessment. Through the development, testing, and implementation of various KASA prototypes, the KASA system has been refined over the course of multiple years. KASA is 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 completely replaces the current unstructured text-based, narrative assessment. At present, quality assessment for generic solid oral dosage forms is performed using KASA. At this meeting, the committee will discuss the vision and plan to expand KASA over the next five years to include drug substances, all generic dosage forms, new drug and biologics applications, and post-approval changes. Moreover, the committee will discuss the need for advancing digitalization in KASA, including data standardization and mobilization of data from cloud-based servers.

**Draft Points to Consider for the Committee:**

1. *Do you support the long-term strategy for developing and implementing KASA at FDA and expanding the system from generic drugs to new drugs and biologics assessments?*
2. *In the age of digitalization, what additional actions should the FDA take to realize cloud-based assessment?*

We are looking forward to a very stimulating discussion with the committee on the selected topics. The meeting will be held virtually November 2-3, 2022.

# November 2, 2022

# Topic 1

# CDER's Quality Management Maturity (QMM) Initiative

**Background Information for the FDA Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee**

**November 2, 2022**

**Topic 1: QMM**
**CDER's Quality Management Maturity Initiative**

## 1. Introduction

Pharmaceutical quality is achieved by assuring every dose of a drug on the market is safe, effective, and free of contamination and defects. All drug manufacturing sites must adhere to Current Good Manufacturing Practice (CGMP) requirements, which define the minimum manufacturing standards to legally market drug products in the United States. Compliance with CGMP requirements assures proper design, monitoring, and controls for manufacturing processes and facilities. FDA facility evaluation and surveillance, including facility inspections, provide assurance that sites manufacturing for the U.S. market comply with CGMP.

FDA regularly evaluates manufacturing facilities and acts, if needed, to enforce CGMP requirements. FDA investigators look for deficiencies in meeting CGMPs, but these evaluations do not measure how far a site's pharmaceutical quality system (PQS) rises above these minimum requirements. Simple adherence to CGMP standards does not indicate, for example, that a firm is investing in improvements to prevent supply disruptions.

The ICH Q10 *Pharmaceutical Quality System* guidance augments CGMPs with the concept of an effective pharmaceutical quality system over the lifecycle of a product. ICH Q10 describes activities to manage and continually improve the PQS (the elements), using knowledge management and quality risk management principles (the enablers). The 2019 report *Drug Shortages: Root Causes and Potential Solutions* by the multi-agency Federal Drug Shortages Task Force reported that 62% of drugs that went into shortage between 2013 and 2017 were associated with manufacturing or product quality problems (e.g., substandard manufacturing facilities/processes or quality defects in the finished product). The Drug Shortages Task Force proposed three enduring solutions to the problem of drug shortages; one solution was developing a rating system to incentivize drug manufacturers to invest in quality management maturity (QMM).

QMM is the state attained by having consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement. Gauging QMM requires, in part, determining how well and how thoroughly a manufacturer has implemented the concepts of ICH Q10.

A stronger, more mature quality management system is one that focuses on performance, especially outcomes that affect the patient including reducing complaints, shortages, and quality-related adverse events. Elements of a mature system include vigilant attention to upgrading facilities and equipment, training that promotes superior performance, increased understanding of the product and manufacturing process, and statistical-based monitoring of manufacturing processes and laboratories. QMM provides strong oversight that involves early detection of major variability in any of these areas, which enables senior management to take action to avoid quality failures before patient harm, including drug shortage, occurs.

The 2021 *Biden-Harris Administration 100 Day Supply Chain Review* announced actions the Department of Health and Human Services, under which FDA resides, would take to ensure the U.S. has the pharmaceuticals necessary for economic security, health security, and national defense. One of these actions included QMM:

- *Create robust quality management maturity to ensure consistent and reliable drug manufacturing and quality performance:*
    - *Recognize and reward manufacturers for mature quality systems that focus on continuous improvement, business continuity plans, and early detection of supply chain issues.*

The need for QMM ratings does not, however, indicate that substandard drug products are on the market. Quality management is part of an array of quality. The FDA assesses product quality in regulatory submissions and monitors the quality of drug products in the U.S. market to provide a high level of confidence in the quality of these products. The FDA assesses formulation, process, and facility quality in applications and monitors and inspects manufacturing facilities to assure risks are controlled. This level of control assures quality in drug product batches released to the U.S. market. Mature quality management uses a performance and patient focus to identify areas of improvement and implement changes accordingly.

This type of management gives manufacturers confidence that every batch they make will be acceptable to release to the U.S. market. Mature quality management assures that quality product is on the market at entry and over the product's entire lifecycle: quality issues will not keep the product from being available to patients and consumers. Quality management maturity is an expectation in international guidelines (e.g., ICH Q10), but heretofore not actively evaluated by the FDA. An evaluation of QMM is not currently part of the FDA's assessment, inspection, or surveillance processes; the responsibility for QMM falls solely on the manufacturer.

A transparent rating system could:

- Inform purchasers about the level of QMM at sites from which they purchase drugs.
- Empower manufacturers to identify ways to improve the effectiveness of their pharmaceutical quality systems, realize regulatory flexibilities described in *ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*, inform selection of contract facilities, and obtain efficiency gains (e.g., speed, throughput, supply timeliness) from investing in quality.
- Provide FDA additional insight into the state of quality for products and facilities and help to identify factors that can lead to supply disruption.

## 2. Benefits of a QMM Ratings Program

A QMM rating system would foster a more robust drug supply chain and greater commitment to quality in pharmaceutical manufacturing. A QMM rating program that overcomes key challenges and includes key elements would provide benefits for all stakeholders as well as the FDA. Minimally, purchasers and payors would get more insight into the supply chain of the drugs they buy or reimburse, pharmaceutical companies would get more insight into the robustness of their supply chains, and patients, pharmacies, and healthcare professionals get improved clinical care via medicine less at risk of quality-driven shortages.

The FDA would benefit from QMM ratings by being more informed about the quality management practices at sites, allowing for better resource allocation decisions (e.g., inspection timing and frequency) and regulatory flexibility (e.g., related to post-approval changes). This is a move away from focusing solely on negative outcomes and one that would move the FDA closer to performance-based regulation. Perhaps most immediately, QMM ratings would ease the process of regulating post-approval changes. The ICH Q12 guidance provides a framework to facilitate post-approval changes in a more predictable and efficient manner, increasing transparency between industry and regulatory authorities, and supporting innovation and continual improvement. In addition to compliance with CGMP requirements, an effective PQS is necessary for firms desiring to use the tools described in ICH Q12. As noted in the FDA's draft guidance *ICH Q12: Implementation Considerations for FDA-Regulated Products*,[1] while the FDA will not require an inspection before an applicant can make use of ICH Q12 principles, the determination of PQS capability will consider, among other things, conformance with ICH Q10, especially regarding change management practices. Clearly, a robust QMM program would enable CDER to more effectively implement ICH Q12.

QMM ratings are a part of an evolution toward performance-based regulatory practice and, as such, they may raise concerns from some. Public transparency is often a necessary driver for industry improvement. Pharmaceutical executives, for example, may not like the fact that a poor QMM rating could affect their stock price. However, public knowledge of facility issues and product recalls already has severe negative consequences to stock price.

In fact, QMM ratings could provide so-called 'good actors' in the industry with less share price volatility. Stakeholders in other industries initially protested the use of transparency and metrics, but now there is general acceptance and recognition of their role in driving quality (e.g., Medicare quality ratings, state reports on cardiac surgery outcomes, and the Physician Payments Sunshine Act). CDER will continue to engage stakeholders during and after the development of the QMM rating program as it has done in 2022 with the May public workshop and this advisory committee meeting.

## 3. Developing a QMM Ratings Program

While a commitment to quality throughout the industry is essential, FDA is uniquely poised to develop a QMM ratings program. FDA conducts robust quality surveillance to track facility and inspection data, quality defect reports (e.g., from MedWatch, consumer complaints, recalls, Field Alert Reports and Biological Product Deviation Reports), and drug sampling and testing results. Not all these data are available to the public. In addition to the need to pay a fee to access private supply chain ratings, some purchasers have indicated their reluctance to use private ratings to drive sourcing decisions without FDA involvement in or backing of those ratings.

CDER has led the formation of an Agency-wide, cross-functional team to develop a QMM rating program. In developing the QMM framework, CDER is considering standardized assessment tools, policy approaches, industry incentives, transparency, and communications. CDER has taken a highly collaborative approach and is considering all impacted stakeholders. Development began by building a foundation of science to assure that the fundamental premise of the program was well-reasoned and supported by objective evidence. CDER also continues to actively engage with stakeholders potentially impacted by a QMM program to better understand their key concerns and consider them in the development of the program.

[1] When final, this guidance will represent FDA's current thinking on this topic.

CDER also launched two pilot programs to support the development of a strategy to objectively rate the QMM of manufacturing sites. A domestic pilot of seven finished dosage form manufacturers ended in 2021 and a second pilot of eight international active pharmaceutical ingredient manufacturers closed in March 2022. The goal of these programs was to gain insight from assessments of a facility's quality management system and other surveillance intelligence to inform the QMM rating system.

One key component of a robust QMM program is the collection and effective use of quality metrics. CDER has long recognized the value of quality metrics for both FDA and industry. FDA's Quality Metrics Program is intended to gather data on certain key metrics to, among other things, incentivize continual improvement and support risk-based scheduling of drug manufacturing facility inspections. As part of a QMM program, for example, quality metrics information could be more routinely submitted to FDA to bolster and support ongoing confidence in the QMM rating of a site.

In moving forward, CDER realizes there are challenges we must address while developing a ratings program:

- Clearly defining the scope and meaning of QMM ratings.
- Relaying the value of these QMM ratings to purchasers so they bear weight on their decision-making.
- Clearly separating QMM appraisals from regulatory compliance.
- Relying on purchasers to understand their own supply chains.
- Ensuring the market rewards products from facilities with higher QMM.
- Determining how to use QMM ratings to enable regulatory flexibility, and
- Addressing potential risks of using QMM ratings in decision-making.

CDER is committed to providing stakeholders with additional information on the QMM program as it develops, including the implementation timeline, how ratings will be shared, and the metrics used to measure the success of the site QMM program that track year-to-year progress in a continual improvement journey.

A QMM program would improve transparency in the market and provide higher-rated manufacturers with a competitive advantage. Manufacturers with higher site QMM focus on continual improvement and are therefore more likely to embrace advanced manufacturing technologies which can improve the capability and robustness of the industry. FDA sees many potential benefits from such a program: manufacturers with higher site QMM could gain recognition in the market; purchasers and payors would receive more insight and confidence into the supply chain of the drugs they buy or reimburse; and patients, pharmacies, and healthcare professionals have access to drugs less at risk of shortage. Most importantly, patients will have more confidence in their next dose of medicine.

# November 3, 2022

# Topic 2

# Knowledge-aided Assessment & Structured Application (KASA): A New Approach that Modernizes FDA's Quality Assessment of Regulatory Drug Applications

**Background Information for the FDA Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee**

**November 3, 2022**

**Topic 2: KASA**
**Knowledge-aided Assessment & Structured Application (KASA): A New Approach that Modernizes FDA's Quality Assessment of Regulatory Drug Applications**

## 1. Introduction

Timely 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 including New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Biologics License Applications (BLAs), including 351(k) applications (i.e., biosimilars). OPQ also performs the quality assessment of Investigational New Drug Applications (INDs) and establishes quality standards for over-the-counter monograph drugs, APIs used in the monograph drugs, and facilities. OPQ quality assessments have historically been based on unstructured text narratives, which precluded knowledge management and resulted in dense, lengthy documents and inconsistent application of regulatory actions. Recognizing the need for modernizing the current assessment approach, OPQ took advantage of modern technology and created a new system named Knowledge-aided Assessment & Structured Applications (KASA).

The KASA system is a data-based platform for structured quality assessments and applications that supports knowledge management. KASA is designed to:

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

The KASA system allows FDA to capture critical assessment information as highly specific structured data in a predefined format which improves the efficiency, consistency, and objectivity of regulatory actions. KASA represents a significant concept shift and revolutionizes FDA's ability to take sound comprehensive regulatory actions. With this advisory committee meeting, FDA will seek input on the vision and plan to expand KASA over the next five years to include drug substances, all generic dosage forms, new drug and biologics applications, and post-approval changes. Moreover, FDA will seek input regarding the need for advancing digitalization in KASA, including data standardization and mobilization of data from cloud-based servers.

## 2. The Why of KASA

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. Historically, assessments in CDER have relied upon freestyle narrative text (Word documents) consisting of: 1) unstructured information; 2) a summarization of application information; and 3) 'copy and paste' data. Such a system can result in inconsistency and ineffectiveness, and it encumbers our ability to share knowledge and efficiently manage FDA's repertoire of approved drug products and facilities. It also hinders our decision-making capabilities because assessors evaluate each application in relative isolation without fully assessing the wealth of information at FDA's disposal.

To meet the above challenges, OPQ developed 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.

## 3. The What of KASA

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. In KASA, the assessors take advantage of digital innovation and assess applications using structured data, advanced analytics, and knowledge management. KASA uses built in risk assessment algorithms to evaluate risks objectively and quantitatively; it uses dropdowns with structured descriptors of risk control approaches. The KASA system also enables computer-aided analyses for a comparison of regulatory standards and quality risk across the repository of FDA approved drug products and facilities. This is intended to facilitate a concise and consistent quality assessment and largely replace freestyle text.

In addition to being primarily developed as an assessment tool, KASA is capable of alleviating problems associated with the submission of electronic regulatory drug applications. We envision the KASA system as a two-part program where KA stands for "knowledge-aided assessment" – an integrated set of tools and framework to aid regulatory assessment and knowledge management, and SA stands for "structured application," including the content and organization of submissions as outlined by the ICH guidance *M4Q The CTD — Quality* and electronic data standards. In the desired future state of KASA, a structured application would include structured standardized data that would be able to auto-populate certain sections in the KASA system, and therefore facilitate the regulatory assessment.

## 4. Structured Application

Looking toward the future, knowledge-aided assessment would be greatly enhanced with the submission of applications 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 its significant 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.

Two ongoing initiatives that will facilitate the "structured application" part of KASA are the revision of ICH M4Q(R1) and pharmaceutical quality electronic data standards. 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 and control strategies. 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.

## 5. 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, has tools that enable assessors to automatically retrieve historical data and facility information to better inform the regulatory evaluation and decision-making process. KASA facilitates the assessment of risk using rules and algorithms, which reduces subjectivity of documentation and the time burden. The built-in rules and algorithms together with the detection of outliers allow assessors to focus on high-risk areas and issues, which improves the quality and efficiency of the regulatory assessment. Finally, by evaluating risks and mitigation 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.

Given the above, FDA's use of KASA is expected to be a win not only for the FDA, but also applicants and patients: more regulatory efficiency, increased consistency between submissions, and faster availability of quality products.

## 6. Where KASA is today

In 2016, OPQ's KASA system was envisioned as a means of modernizing FDA's assessment by taking advantage of the: 1) structured data (as opposed to narrative information); 2) advanced analytics; and 3) knowledge management. This concept of KASA has gone through several iterations through the dedicated work and collaboration of several OPQ and CDER colleagues. Over the years the vision of KASA has been refined through the development, testing, and implementation of KASA prototypes.

In 2020, FDA transferred KASA to the cloud where KASA quality assessments are stored on FDA servers under a FISMA high environment, which is the strictest level of security to ensure protection of confidential information. By moving the quality assessments into the cloud, FDA is thus taking advantage of the flexibility and agility of cloud computing in using structured data to enable efficient knowledge management and data analytics. This major KASA launch (named KASA 3.0) represented a significant step towards the overall modernization of quality assessment. KASA 3.0 is used for the quality assessment of generic solid oral dosage forms and represents a major milestone for KASA development and implementation. OPQ has taken significant steps towards operationalizing KASA which is currently being used by three assessment disciplines (drug product, manufacturing, and biopharmaceutics) for the quality assessment of generics.

OPQ is focused on continuing KASA's development. Following the release of KASA 3.0 for generics, our vision over the next five years includes expanding KASA to drug substances, all generic dosage forms, new drugs, biologics, and post-approval changes.

## 7. Conclusions

KASA is a 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. KASA contributes 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 algorithms;
3. 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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**QMM**

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