Time for a Change – How KASA Impacts Regulatory CMC Submission Strategy

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Planning, assembling, and editing a Chemistry, Manufacturing, and Controls (CMC) dossier is a critical part of every clinical trial application and marketing authorization submission. Every CMC dossier requires the compilation of copious amounts of data from various departments (i.e., Research and Development, Manufacturing, and Quality). Regulatory and technical authors must then summarize these data according to the respective region-specific requirements and facilitate comprehensive and thorough review processes to optimize all content and verify data presentation against source documents. As a final step, the dossier must be formatted, published and packaged in the Electronic Common Technical Document, eCTD, format. Managing this complex process and the corresponding regulatory requirements for both initial applications and lifecycle maintenance can be challenging for sponsors, particularly those embarking on their first major regulatory submission.

The review and evaluation of the CMC dossiers can be equally challenging for the U.S. Food and Drug Administration (FDA) assessors who must review complex CMC text heavy free-style narratives. Further, the FDA repository of product knowledge is not easily accessible to the individual assessors resulting in review of each application in isolation, thereby introducing subjectivity in assessment and regulatory decisions.

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, making lifecycle management challenging.

In a recent FDA webinar, the Office of Pharmaceutical Quality (OPQ) noted, per year, they review about 3,000 Investigational New Drug Applications (INDs), 240 New Drug Applications and Biologic License Applications (NDAs/BLAs), 900 Abbreviated New Drug Applications (ANDAs), and 10,000 supplements, all with data submitted in an unstructured PDF format (i.e., various types of data stored in native formats). Additionally, expectations from industry and demands from congress and the public to speed up the availability of safe and efficacious drugs and emerging advanced drug development technologies are behind FDA's initiative to develop a system to optimize the efficiency and agility of the CMC assessment process and to effectively manage the corresponding data throughout the lifecycle of a product.

To this end, the FDA has developed and launched the Knowledge Aided Assessment and Structured Application (KASA) initiative with an eye towards the adoption of a consistent, harmonized, efficient and agile regulatory review and approval process necessary to support the increasing complexity of leading-edge technology of new drugs.

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The intent of KASA:[1]

- Assure patient focused quality standards and objectivity are given to regulatory evaluations through knowledge management
- Enhance science and risk-based approaches through established rules and algorithms including the use of artificial intelligence (AI) and machine learning (ML)
- Enrich regulatory oversight through life cycle management of products and facilities

This article provides an overview of KASA based on FDA's recent presentations across various forums. The article will trace the path of the program from its inception to its current state, discuss key features, highlight potential benefits to industry and regulators, and provide insights on how drug developers may begin to prepare as the KASA initiative further unfolds.

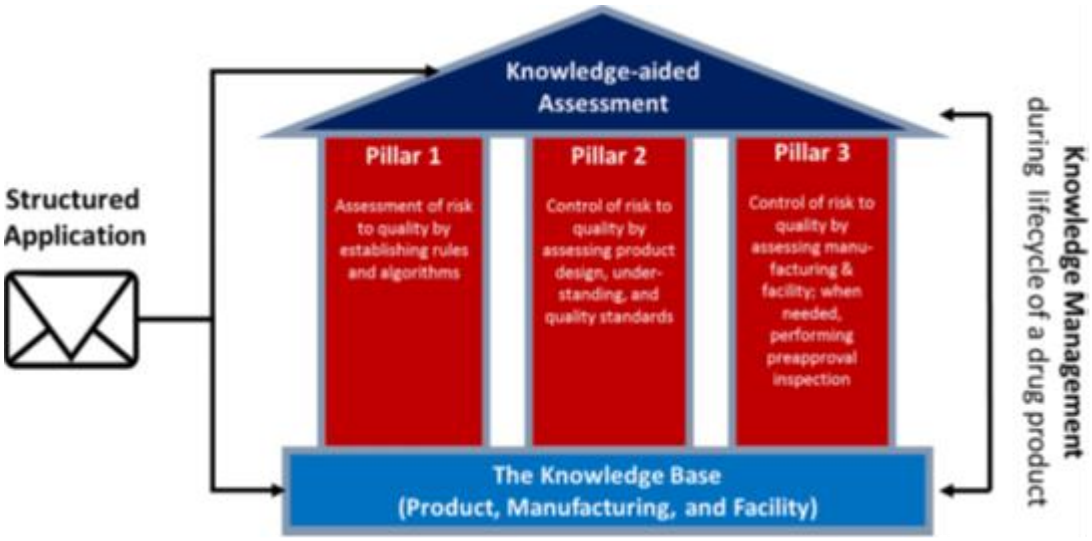
What is KASA?

KASA was conceptualized in 2016 by FDA's OPQ and endorsed by the Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting in 2018. KASA is an information technology (IT) system designed to capture vast amounts of product quality information and organize this information in a structured format before ready access by FDA reviewers across their different divisions. As depicted succinctly in the KASA vision shared by FDA, the knowledge available on the product, manufacturing, and facility forms the basis of their system's algorithm to assess and control quality risks used to review quality applications. The KASA system allows FDA to apply applicant data and capture critical information in a structured pre-defined format.

"KA" stands for knowledge-aided assessment – an integrated set of tools and framework to aid regulatory assessment and knowledge management. "SA" stands for structured application – the content and organization of submission and electronic data standards.

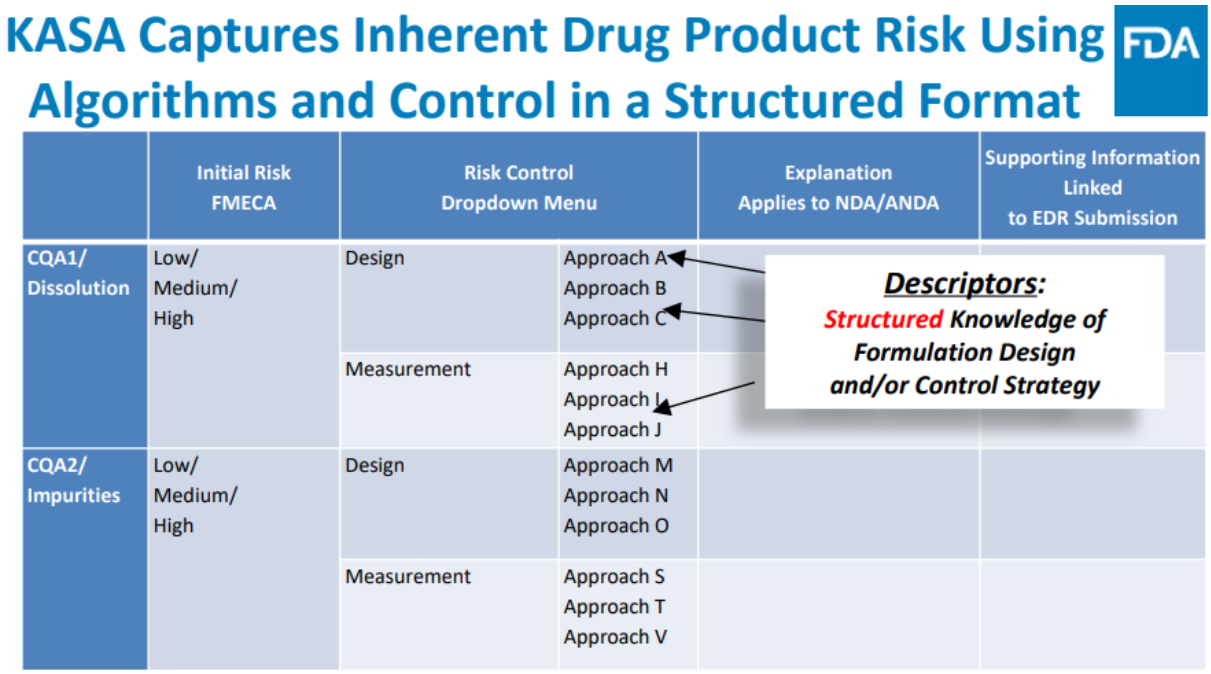
Per FDA's recent workshops, the knowledge-aided assessment part of the KASA system is best described as a three-pillar structure depicted below in Figure 1. The three pillars KA rests upon include drug product assessment, manufacturing integrated assessment, and biopharmaceutics assessment modules.

Figure 1: Three Pillars of the Knowledge-Aided Assessment Component of KASA[1]



Upon feeding the drug applicant's data into FDA's centralized IT repository of information, the data becomes available to all FDA reviewers. Using built-in algorithms, KASA's drug product assessment module captures the inherent drug product risk and control strategies from the applicant's data in a structured format. As illustrated in Figure 2 below, KASA's risk assessment algorithms capture the risks associated with the critical quality attributes (CQAs) of the drug product, such as dissolution profile, impurities profile, and assay. Based on the product design and control strategies adopted by the applicant, the system evaluates the CQAs and categorizes the risk as low, medium or high. The algorithms use failure mode of criticality analysis system encoded in the KASA's IT software to objectively rate the risks. This ranking will alert the assessors to focus more on high-risk areas and less on low-risk areas.

Figure 2: KASA's Risk Assessment Algorithms[2]



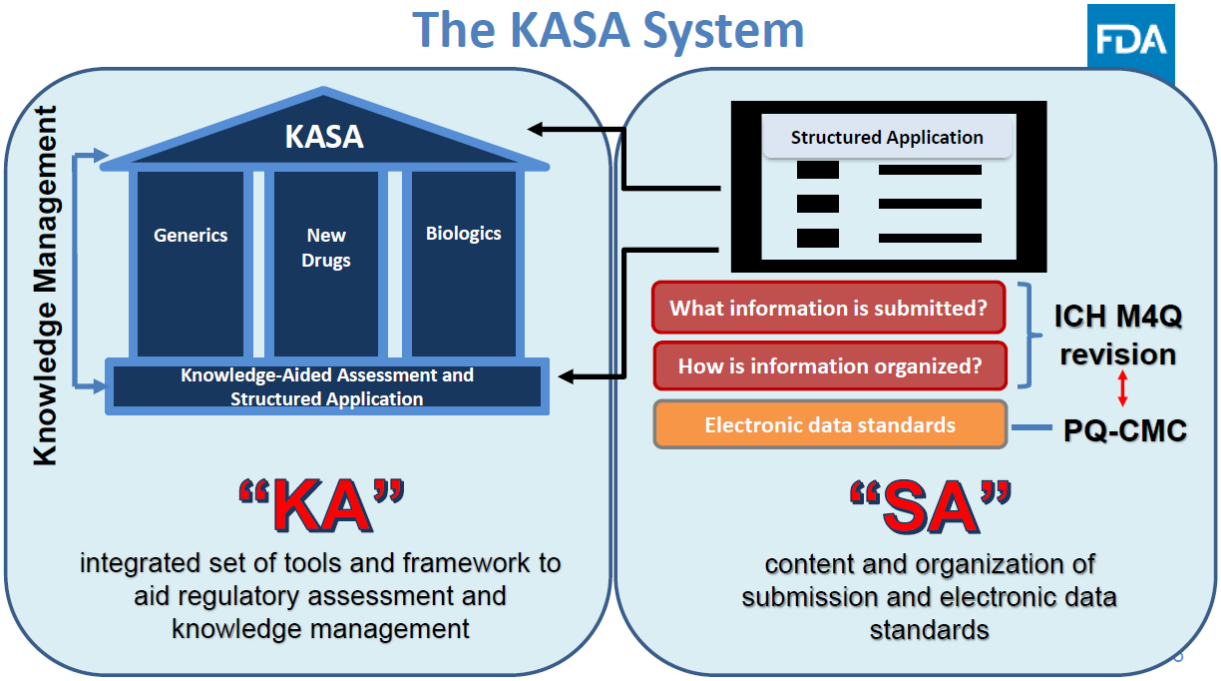
KASA also captures the risk control strategies based on the formulation design, measurements, and control strategies by way of drop-down descriptors. The drop downs are developed based on the fundamental scientific understanding of pharmaceutics and capture the structured knowledge of formulation, design, and control. This in turn enables both consistency in assessment and knowledge management. The assessor can add a short narrative on the specific control strategy that was applied to mitigate the risk, enabling clear and concise risk communication to the applicant. This replaces the earlier method of cutting and pasting long narratives of applicable sections taken from the applicant's pharmaceutical development report.

The risk analytics outlined above enable the identification of outliers that facilitates unbiased and objective decisions during application review. Similarly, the integrated assessment of manufacturing modules captures the relevant risks in a structured manner, enabling reviewers to access information on approved manufacturing sites including the sites' demonstrated capabilities with specific dosage forms and current Good Manufacturing Practices (cGMP) history, thereby informing risk categorization for a pending facility assessment application. Additionally, KASA captures biopharmaceutics risk using defined decision tree algorithms.

KASA, for solid oral generics review, was launched in February 2021, and as of November 2022, OPQ assessors have completed 535 drug product assessments, 505 manufacturing integrated assessments and 396 biopharmaceutics assessments.[2] Over the past six years, various Subject Matter Experts (SMEs) across FDA have collaborated and reviewed all stages of development, testing, refinement, and implementation of KASA prototypes.

Figure 3: The KASA System[3]

While the database development described in the previous paragraph and the image presented in Figure 3 supports the KA part of KASA, the SA forms the second half of KASA. SA is supported by two ongoing initiatives namely the revision of Common Technical Document ICH M4Q and FDA's the development of PQ/CMC standards. These initiatives are described in further detail below.



Electronic Standards for Product Quality/Chemistry Manufacturing and Controls (PQ/CMC)

To establish electronic standards for submitting product quality (PQ) and CMC data, FDA initiated the PQ/CMC project. The goals for this project include implementation of structured data standards for PQ/CMC and development of data exchange standards for submitting structured PQ/CMC data to the FDA.[4] This structured and standardized information will be submitted in Module 3 of the Common Technical Document (CTD) as defined by ICH M4.[5]

As per FDA's PQ-CMC website, the scope of the structured submission is intended to only cover certain elements in Quality Modules 3 (and 2.3) that are considered amenable to structuring and would bring value to the quality review process, and not comprehensively cover the entire Module 3.[4] For instance, standardized terminology can be applied to areas where multiple synonymous terms are being used to eliminate confusion, permits use of data analytics(for example - how many assays use Capillary Zone electrophoresis, for what classes of drugs), enables facility risk -assessment. The drop-down menu for the "ingredient role" for PQ-CMC will help sponsor to specify if it is active, inactive, or an adjuvant ingredient.

The submission of structured data in a standardized format is anticipated to increase the efficiency of FDA's review of PQ/CMC data contained in Module 3 of various eCTD submissions to support all phases of clinical development for both novel and generic drugs and biologicals. SMEs from FDA's CDER, Center for Biologics

Evaluation and Research (CBER), and Center for Veterinary Medicine (CVM), have all collaborated in this endeavor. The PQ/CMC team is also partnering with several international collaborators and standards including the European Medicines Agency (EMA), Global Identification of Medicinal Products (IDMP) working group, The Common Technical Document for the Registration of Pharmaceuticals for Human use: Quality – M4Q(R1) (ICHM4Q), and Health level 7 (HL7) in their standardization efforts.[6]

To initiate the first phase of PQ/CMC, the FDA created an open docket and released a Federal Register Notice for public comments on the PQ data elements and terminologies in 2017, 2022, and most recently, on 1 May 2023. FDA is currently seeking public comments for Chapter 2 titled, "Pharmaceutical Quality/Chemistry Manufacturing and Controls (PQ/CMC) Data Elements and Terminologies for the Electronic Submissions of PQ/CMC Data," describing data elements and terminologies covering enhancements to support the solid oral dosage forms component and composition, including multi-layer tablets, capsules, and drug product manufacturing.[7]

FDA plans to maintain Chapter 2 as a living document, periodically adding new chapters, updating and revising data elements and terminologies while retaining the previously published sections.

It is envisioned that PQ/CMC will substantially change the submission process and necessitate new business processes and infrastructure for FDA and the applicants. In the coming years, adoption of PQ/CMC for submission will be mandatory under Section 745(a), and hence, it is advised for industry to observe updates from PQ/CMC.[11]

ICH M4Q (R2) Revision

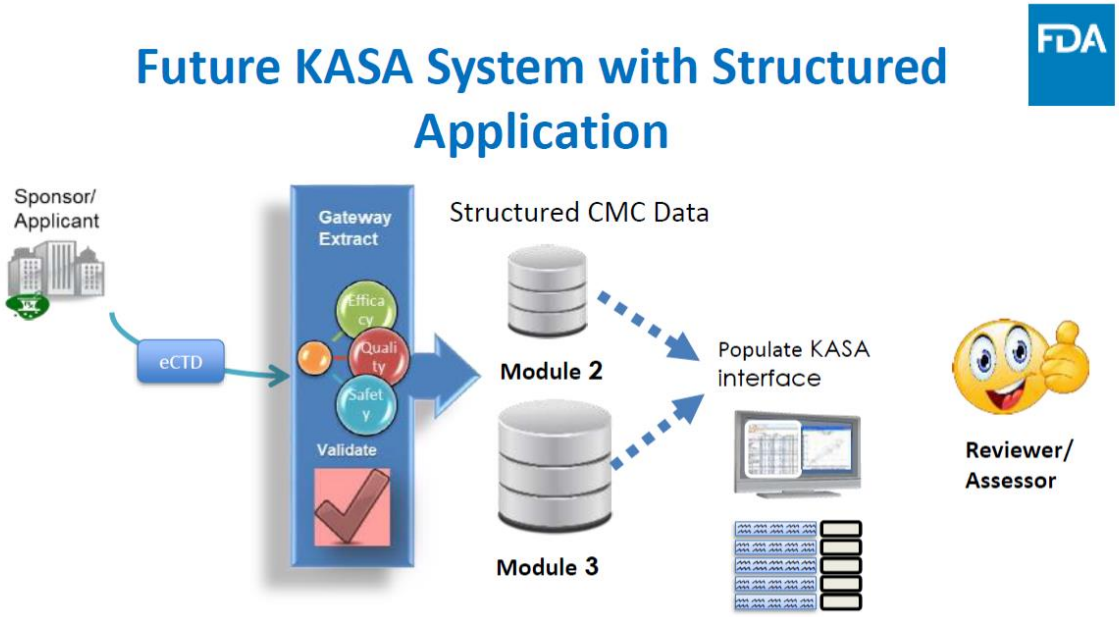
As mentioned in the ICHM4Q-R2 concept paper,[8] M4Q(R1) developed in 2002 is now due for revision. The objective of the revised guideline is to further improve submission, assessment, and lifecycle management efficiency, leverage digital technologies, and accelerate patient and consumer access to pharmaceuticals. This revision is also expected to modernize and optimize CTD quality modules and align with modern quality guidelines presented in ICH Q8-14, encourage global convergence of science-and risk-based regulatory approached in the preparation of dossiers and promote knowledge management.

Further, the revised version is expected to provide guidance on the location of information supporting multicomponent or complex products, such as antibody-drug conjugates, vaccines, advanced therapy medicinal products (ATMPs), cell and gene therapies, tissue engineered products, or other combination products. The concept paper is intended to encourage global convergence of science and risk-based regulatory approaches in the preparation of dossiers. These revisions will support product and process innovation and enrich communication between regulators and applicants. By meeting all these broad and specific objectives, the M4Q(R2) revision will help in elucidating regulatory expectations and supporting efficient assessments, decision making, and actions.

Once implemented, the M4Q(R2) guidance is expected to facilitate and support applicants in the seamless incorporation of the PQ/CMC elements in the quality modules. Structured submissions are expected to seamlessly facilitate KASA's assessment approach.

Further, 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.[9]

Figure 4: The Future KASA System[3]



Further, KASA system supports and feeds OPQ's other critical programs and initiatives such as the QSD (Quality Surveillance Dashboard) and IQA (Integrated Quality Assessment), further described below.

The QSD program provides a framework for consistent evaluation of facilities and potential quality signals within a product's life cycle. Through interactive visualizations the FDA users will be able share insights regarding facilities, manufacturing capabilities and product quality issues. Uses analytics for efficient and risk-based assessments. QSD integrates and governs facility and post market product quality data from across multiple systems.

IQA initiative ensures effective and efficient assessment of drug applications by FDA's multiple disciplinary teams, defines business process, operational workload and roles and responsibilities, and establishes internal milestones/timelines to meet user fee commitments.

Anticipated Benefits to FDA and Industry

FDA

As described above the implementation of KASA is expected to facilitate an integrated quality assessment (IQA) and support the quality surveillance dashboard (QSD). The risk-based analytics and structured information enabled by KASA promises to remove bias and make the entire review process more objective and efficient for FDA assessors. The KASA tools enable automatic retrieval of historical data and provide information to enable the reviewer to make informed decisions on a submission. Additionally, KASA provides an increased ability to review emerging data in real time and improved ability to perform analytics and statistical analyses, as necessary.

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.[9]

The many benefits of the implementation of KASA include enhanced risk-based assessment and review of the quality dossier, efficient knowledge management, and seamless product lifecycle management. This is envisioned to enable open and transparent communications between the applicant and FDA. The emerging impact of KASA is reflected in the high number of assessments completed by the OPQ within a short period since KASA launched in 2021.

Industry

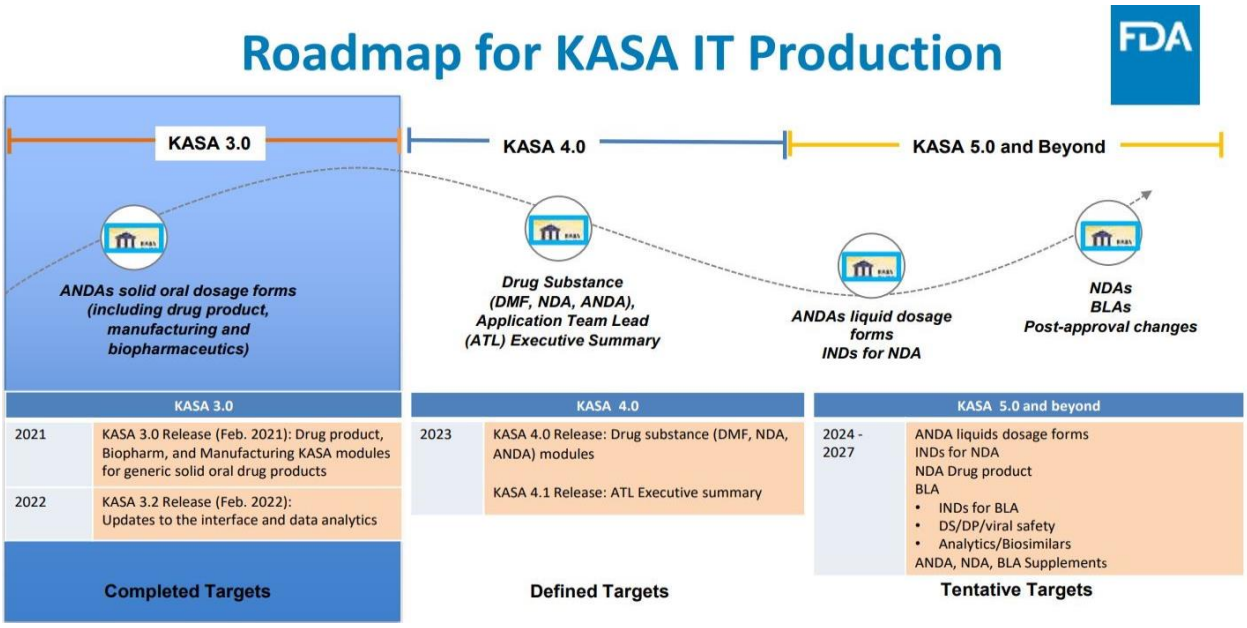
Recent advances in manufacturing technologies (e.g. to align with the ICH Q8 – Q14 quality guidelines) and continued development of complex product modalities (e.g. cell and gene therapies) have increased the burden of compiling a robust and clear CMC module 3 for submission to global health authorities. On top of these demands, there is a critical need to maintain the dossier throughout the development and post-approval process(es) to support CMC changes and to address other dimensions of standard lifecycle maintenance required to ensure continuity of the drug supply to support clinical trials.

Some of the CMC heavy lifting required to meet these challenges may be reduced or lightened, at least theoretically, based on recent KASA initiatives. Further, harmonizing CMC standards, adopting the structured information standards advocated by PQ/CMC, and the upcoming revision and updates of ICH M4Q(R2) may increase visibility into the way CMC modules will be presented and reviewed. This will enable more efficient and speedy communications between the applicants and reviewers, and thus, faster availability of quality products.

Evolution of KASA

For over six years, FDA SMEs across all levels developed, tested, implemented, and refined various prototypes of the KASA platform. In 2020, the KASA IT infrastructure was transferred to the cloud where KASA quality assessments are now stored on FDA servers under a Federal Information Security Management Act (FISMA) high environment – the strictest level of security to ensure protection of confidential information. Cloud-based assessments provide the agency with the flexibility and agility of cloud computing in using structured data to enable efficient knowledge management and data analytics. As noted earlier, KASA for solid oral generics was launched in February 2021 – a major milestone in FDA's KASA journey.

Figure 5: Roadmap for KASA IT Production[2]



As presented in the roadmap for KASA IT production Figure 5, building on the success of KASA 3.0 released for oral solid generics in 2021, OPQ continues to develop KASA further to include assessment of drug substance information submitted in Drug Master Files (DMFs), ANDAs and NDAs. The drug substance review is supported by the submission of Form 3938 for DMFs which enables the agency to review the contact and facility information in a structured format, improving efficiency and accuracy, as well as by the submission of SD (structured data) files for chemical structures.[3, 10]

KASA systems will be extended by the review of all generic dosage forms, new drugs, biologics and post-approval changes over the next five years with the inclusion of unique elements and additional analytical tools applicable to each modality (i.e., microbiological controls for parenteral drugs and inclusion of viral clearance/adventitious agents testing modules for biologicals manufactured in animal origin cell lines).

During the recently held Pharmaceutical Quality Symposium on October 31, 2023, the Agency updated that the KASA for IND prototype is currently undergoing pilot testing to optimize its modules for various assessment needs. Additionally, KASA for DS interface and enhancements (NDA, DMF and ANDA) have now been released on CDER IT platform.

How Industry May Prepare

A general understanding of how the agency is building KASA (e.g. using risk-based algorithms and descriptors) is essential for applicants to consider during future CMC-specific product development. More specifically, applicants should use the principles of KASA to guide iterative risk product-specific risk assessments, to develop necessary controls and mitigation strategies, and to compile and present them in a manner that facilitates open and transparent communications and review efficiency.

Applicants are encouraged to review Chapter 2 of the PQ/CMC data standards and terminologies released for public comments in May 2023. In the coming years, adoption of PQ/CMC for submission will be mandatory under Section 745(a), and hence, it is advised for industry to observe updates from PQ/CMC.[11]

Additionally, the first draft of M4Q(R2) is anticipated to be released for public review as per the current work plan and this document will provide applicants with insights on the revised structure of the quality modules that will pave the way for efficient assessment.

Conclusion

In conclusion, FDA's KASA initiative is intended to address the demands of an increasingly complex product development landscape. As novel manufacturing and analytical tools continue to emerge, FDA is faced with an accelerating pace of drug development mirrored by a rapidly expanding scope of product modalities. These advances place clear challenges on OPQ review staff to apply necessary resources and to implement appropriate standards to ensure review and approval processes that are efficient and robust.

By leveraging modern data analytics and IT tools, KASA offers a unique opportunity to enhance knowledge management, ensure consistency in decision making, and facilitate efficiency of quality modules review. These outcomes are critical to the drug developers and to FDA by way of fair and risk-based assessments which enables safe and efficacious drugs to be delivered to patients expeditiously.

Questions about KASA? Connect with Halloran.

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