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November 1, 2022

Dockets Management Staff
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2022-N-1777

Pharmaceutical Science and Clinical Pharmacology Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments

To Whom It May Concern,

Biotechnology Innovation Organization (BIO) welcomes the opportunity to comment on the Food and Drug Administration (FDA or Agency) Pharmaceutical Science and Clinical Pharmacology Advisory Committee's efforts related to FDA's Center for Drug Evaluation and Research (CDER) Quality Management Maturity (QMM) program and Knowledge-Aided Assessment and Structured Application (KASA). We appreciate FDA's ongoing commitment to enhancing programs, processes, and systems related to product quality and recognize the importance and benefit that such improvements can bring to both industry and regulators alike, and ultimately, to our patients.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

Quality Management Maturity (QMM) Program

BIO understands that FDA defines QMM as "the state attained when drug manufacturers have consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement". We understand that the Agency has proposed the development of a QMM rating system with the intent to "incentivize drug manufacturers to adopt more mature quality management practices at their facilities". We appreciate the intent to support consistent processes with a focus on regular re-evaluation and enhancement and provide the following recommendations that would help support our understanding of FDA's intent behind proposed QMM ratings and mitigate the potential for unintended consequences.

(1) A QMM program should be voluntary and industry-driven if implemented

First, BIO strongly recommends that any programs related to QMM would be completely voluntary and industry-driven rather than being required and/or led by FDA. Industry would likely have concerns about compliance issues being raised by FDA staff during QMM reviews which

could lead to a lack of transparency and reluctance to participate. Alternative approaches, such as an independent third-party assessment under appropriate confidentiality agreements, would likely alleviate those concerns. We suggest that the Agency also clarifies that sites without a QMM rating system would not be penalized or disadvantaged under a voluntary paradigm as well as additional details about program flexibility in general.

Similarly, we note that FDA's public release of QMM ratings could result in consumer confusion and an inability to distinguish between quality system maturity and product quality. Instead, these values should be held by the independent assessor and the participating sites. The information should only be shared by the participating site to outside parties at their discretion with the ability to be verified by the independent assessors. An unintended consequence of public ratings could be that manufacturers would limit their supplier options, i.e., avoiding low-performing manufacturers with lower margin, high volume foreign producers or patent-protected products without comparable products on the market, to maintain a certain QMM rating which could negatively impact product availability. There could also be additional legal or financial consequences as well as the potential for upward cost pressures on products to balance increased related operating or legal expenses.

We also note concerns that Global Purchasing Organizations (GPOs) might not use QMM ratings as intended. Implementation or use challenges by GPOs should be evaluated with respect to purchasing decisions using QMM ratings. It is generally unclear how FDA intends to influence purchases to consider QMM ratings in a price-driven marketplace.

(2) Any QMM assessment model should be standardized and well-integrated with related programs

Next, we strongly recommend that should the program move forward, the Agency develops a single QMM assessment model that can be deployed in a consistent manner across all FDA Centers in addition to CDER. Having a single model for Quality Management assessment would likely increase industry participation and utility of the program by increasing internal support and avoiding priority conflicts coming from multiple assessments.

Similarly, BIO remains unclear on how CDER would integrate the proposed QM reporting pilot program, as described in recent guidance, into QMM, along with other QMM-related proposals, e.g., Cultural Excellence, Risk Management, etc. We urge FDA to consider how these programs would complement each other to ensure there is no duplication of data being requested between them.

(3) Details about the proposed implementation of a QMM program should be clarified

First, BIO requests more details about FDA's current thinking about potential specific parameters and implementation approaches for the QMM program. We note the importance of close partnership between FDA and sponsors to assure the consistent and timely adoption of such a program in a fit-for purpose manner.

Similarly, BIO requests information about FDA's expected timeline for the development and implementation of a QMM program, as well as details on when such a program might be implemented for domestic and ex-US sites. We would also appreciate clarification on the intended frequency of when sites would be rated and whether there would be flexibility around

this cadence. BIO recommends that participation should enable the potential for reduced inspection frequency, and we request that clear incentives such as this should be communicated.

We recommend that FDA considers how the impact and potential effectiveness of QMM should be assessed over time, and we note the importance of transparency on how FDA will directly correlate QMM effectiveness with performance outcomes. Specifically, we request that FDA provides more details on how the QMM model would reduce drug shortages and improve supply chain resiliency as suggested by the Agency. The Office of Pharmaceutical Quality's (OPQ) White Paper, "Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals" does not address this point. Additional information on the rating system to understand how the QMM rating system would help reduce drug shortages, and how this relates to the overall objective of "having consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement" would be helpful for our members.

It is also unclear how QMM rating would be aggregated at the product level for a complex supply chain or multiple manufacturing sites.

Finally, we suggest that flexibilities as described by the ICH Q12 guideline, e.g., established conditions, should be available to any manufacturing site with a good GMP record regardless of their participation in a QMM program. In general, we believe that FDA should not delay full implementation of Q12 or any other harmonization guidelines to coincide with the potential initiation of a QMM program.

Knowledge-Aided Assessment and Structured Application (KASA)

BIO understands that FDA continues to refine the KASA system since its implementation and plans to expand it over the next five years to include drug substances, all generic dosage forms, new drug and biologics applications, and post-approval changes, as well as potentially advancing its digitalization. We appreciate the Agency's intent to improve knowledge management and review process efficiency through systems such as KASA and provide the following recommendations to ensure that it functions as intended.

(1) Details about integration of KASA with other domestic and international initiatives should be clarified

BIO appreciates the Agency's intent for KASA to work synergistically with FDA's Pharmaceutical Quality/Chemistry, Manufacturing & Controls (PQ/CMC) Project. Our understanding is that PQ/CMC would define the format by which sponsors will exchange information with FDA which can then be imported into an analytical tool or database like KASA. We note concerns about FDA's implementation timeline of PQ/CMC and potential misalignment with international expectations, and we suggest that structured data submissions should not be mandated before the content and format are fully aligned internationally through the revision of ICH M4Q. We suggest that FDA consider whether all PQ/CMC data elements identified to date are essential inputs for KASA or whether certain variables might be excluded. Identification of key data elements may guide industry's understanding of critical inputs to KASA and the integration with PQ/CMC and ICH M4Q(R2).

In addition, we strongly suggest that KASA should not drive divergence from other harmonized formats and should instead support interoperability of data standards. However, the KASA tool's

relationship with other relevant global initiatives, such as HL7 FHIR exchange standards for regulatory applications and implementation of ISO IDMP data standards, has not been previously communicated. Specifically, we request clarity regarding the expectation for sponsors to implement FHIR-based capabilities with the ability to wrap, deliver, and unpack a FHIR message to the FDA or other global health authorities. Industry also requests clarification on the intent for KASA to be synergistic and/or compatible with the data format standardization requirements outlined by ISO IDMP. Additionally, it is suggested that the Agency consider that KASA (and any future Health Authority-led knowledge management system or data analytics tool) should have the potential to integrate with a global cloud-based information exchange platform to streamline capture of information and data management.

Finally, BIO notes that KASA introduces regional differences for how regulatory CMC information is assessed and parsed, which may create additional heterogeneity in the reviewing process, including questions issued and regulatory interpretation of guidelines and requirements. If KASA or a similar toolset is not implemented on a global and/or harmonized scale, it will have limited benefit for industry in managing global CMC applications and variations in a timely manner. We emphasize that efficiency in regulatory submissions benefits patients worldwide as demonstrated during the pandemic.

(2) Details about processes, parameters, and implementation planning associated with KASA should be clarified

First, BIO strongly suggests that FDA should use a pilot approach in partnership with industry to understand potential benefits, challenges, gaps, and best practices associated with the implementation of KASA. Lessons learned from such a pilot could be analyzed to determine if and how KASA should continue to be expanded and modernized. In general, we request that FDA provides more details on the implementation of KASA in terms of timeframe and elements of a phased rollout.

Next, we acknowledge that KASA was originally developed for generics and note that new modalities or novel manufacturing technologies with limited experience and may be difficult to manage in KASA in the absence of well-defined risk-assessment parameters. Adequate flexibility and/or customization will be needed to accommodate all product presentations and designs. We request additional details on progressing KASA for biologics, combination products, and other modalities.

While KASA utilizes risk-assessment algorithms and established rules to analyze sponsor-provided CMC data, we request transparency about the nature such algorithms and rules, which would clarify to industry which aspects of the CMC application are most essential to KASA.

Conclusion

BIO appreciates this opportunity to submit comments regarding FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee's efforts related to QMM and KASA. As FDA continues to consider such efforts, we would welcome future opportunities to discuss these points.

Sincerely,

Alex May, M.S.
Director, Science & Regulatory
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