A Regulatory Perspective on the Quality Overall Summary: Putting the Pieces Together

Abstract

The Quality Overall Summary (QOS) is a summary of all quality-related information provided by applicants to regulators in drug marketing or licensing applications, including New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Biologics License Applications (BLAs) in the United States. It is intended to condense and summarize integral quality information from the submission in a transparent manner. A potentially powerful tool, the QOS could substantially decrease the effort needed by regulators to understand, summarize, collate, and interpret quality-related data in an application. While the QOS holds great promise as a means of promoting effective communication between applicants and regulators, it has the potential to more effectively impact the efficiency and/or quality of regulators' assessments. One approach to make the QOS more effective is the use of a question-based review (QbR) QOS for the assessment of ANDAs. While the QbR-formatted QOS remains a viable option, some applicants outside the generics space are reworking the current QOS framework in their regulatory submissions. As such, there is a corresponding opportunity to improve the overall regulatory utility of the QOS for all application types by making use of key considerations. This document describes key considerations when creating a QOS that: (i) explains product and process development in a patient-focused context, (ii) effectively summarizes the overall control strategy, and (iii) guides the regulator through the submission. Ideally, the regulator should be able to use the QOS to initiate the assessment of potential risk to the patient, and the control of such risk, in the commercially manufactured product. An effective QOS can benefit applicants and regulators by improving communication and transparency, but also emphasizes the direct link of quality to patients by specifically focusing on a product's overall control strategy, potential risk factors related to quality, and other benefit/risk considerations. It is a shared goal to provide the American public with improved access to safe, effective, quality drug products.

I. Introduction

The Quality Overall Summary (QOS) is an element of a drug marketing application that provides a substantially condensed summary of the quality-related data provided in the submission. Regulators can use the QOS to more effectively assess applications and more rapidly comprehend the quality information in the context of patient risk, including the proposed control strategy and any other planned steps to mitigate that risk. Patients benefit from the greater assessment efficiency by having improved access to drugs that are designed and manufactured to consistently and safely fulfill claims in the label.

While the QOS has been effective in certain ways, it has the potential to be an even more effective tool to significantly improve the efficiency and quality of the regulatory assessment and to positively impact all human drug user fee programs. To do this, the QOS needs to effectively describe the product development process in the context of mitigating risk to the patient, provide a clear summary of the overall control strategy as part of risk mitigation or control, and guide the regulator through the fragmented content of the submission. Recently, the concepts of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q12[1] on pharmaceutical product lifecycle management reinvigorated regulatory and industry interest in QOS expectations, especially regarding established conditions and, for NDAs and BLAs, postmarketing commitments.[2] Acknowledging the opportunity to create a more effective tool, some applicants are reworking the current QOS framework in their submissions. This document provides a regulatory perspective of key considerations when an applicant prepares, and a regulatory agency receives, a QOS as part of a drug marketing or licensing application.

In some ways, the lack of harmonization of regulatory expectations for the QOS across different regions of the world has contributed to its underutilization as an effective application assessment tool. Indeed, a proposal on the QOS was endorsed by the U.S. Food and Drug Administration (FDA) as a top quality-related topic at the ICH Assembly Meeting held in June 2017. Aligned expectations for the QOS among

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Final Concept Paper Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

[2] Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products - Guidance for Industry

international regulators may be necessary for the continuous improvement of risk-based, patient-focused regulatory submissions from applicants and the associated assessments from regulatory authorities.

II. Opportunities to Improve the Existing Quality Overall Summary

As described in ICH M4Q,[3] within the Common Technical Document (CTD) framework, the QOS is provided in Module 2, while the larger Body of Data is provided in Module 3 of NDAs, ANDAs, and BLAs.[4] It is very important to note that the QOS, in any form, *does not replace or change* the expected content in Module 3. The QOS is expected to be significantly shorter than Module 3 and is intended to provide the regulator with sufficient information to generally understand the contents of Module 3, including cross-references to specific volumes and page numbers for supporting data. While the QOS has been helpful in communicating certain quality information, there are opportunities to improve its overall effectiveness. Indeed, one such approach to improving its effectiveness has been the question-based review (QbR) for the Chemistry, Manufacturing, and Controls (CMC) evaluation of ANDAs, which focuses on critical pharmaceutical quality attributes.[5] The QbR initiative includes a QbR-based QOS and a corresponding assessment template. Many applicants in the generics space have effectively used a QbR-based QOS and may continue to do so in the future.

Other applicants, particularly in the new drug space, have realized the potential to improve the effectiveness of their QOS. These applicants are proposing and preparing adjustments, which may be acceptable, provided they are compliant with ICH M4Q. This situation presents an opportunity to address several key issues with the existing QOS framework and to realize several advantages that can be gained from a more effective QOS framework. For example, QOS content could provide regulators with an opportunity to better and more quickly understand a product's overall benefit-risk profile and overall control strategy from a quality perspective, given the indication(s), patient population, and intended use. The QOS could provide an initial orientation to the measures taken to mitigate or control risk to the

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Quality Overall Summary of Module 2 Module 3: Quality M4Q(R1)

[4] Federal regulations require an NDA to contain a summary of the quality-related information in the application (Code of Federal Regulations Title 21, Volume 5, Sec. 314.50(c)). The FDA has adopted through guidance ICH M4Q for NDAs, ANDAs, and BLAs.: Guidance for Industry M4Q: The CTD – Quality and Guidance for Industry Submitting Marketing Applications According to the ICH-CTD Format - General Considerations

[5] Question-Based Review (QbR) for CMC Evaluations of ANDAs

patient. This may substantially decrease the effort needed by the regulator to understand, summarize, collate, and interpret quality data from Module 3 (Fig. 1). Ideally, this would result in more efficient and effective quality assessments. In fact, regulators in multiple regions have used the QOS as a backbone to facilitate risk-based assessment; even, at times, as an initial assessment template. Wider adoption of this practice could be particularly beneficial. In a sense, the QOS could represent an effective and transparent tool to communicate essential aspects of the application. It would fall to the regulator, then, to confirm and follow the risk-based, patient focus of the QOS as a guide to the assessment of the appropriate content provided in Module 3. In the QOS, applicants have an opportunity to clearly convey the patient-focused narrative of their products, which regulators can use in their assessments.

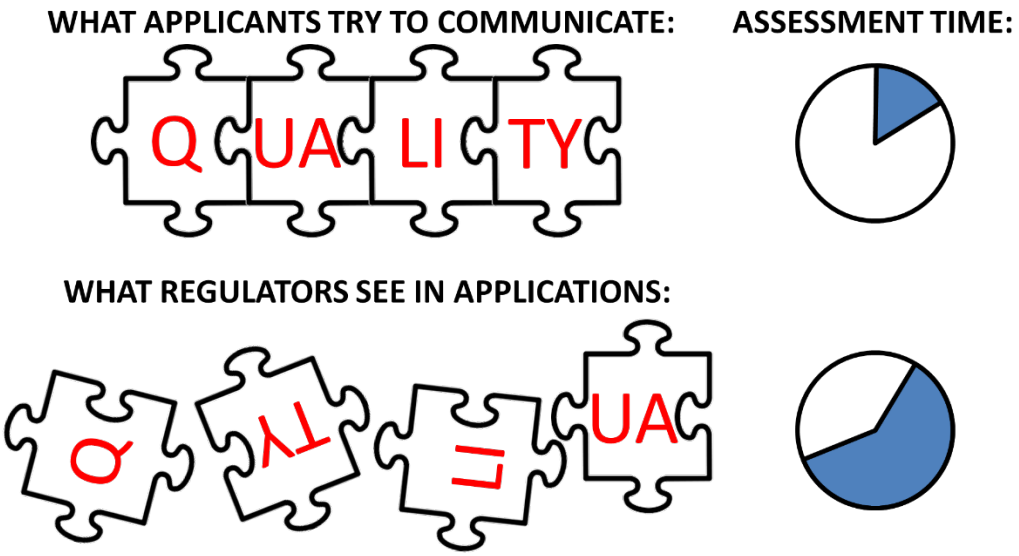

Figure 1. There can be a disconnect between applicants and regulators regarding the communication of quality data and its impact on the assessment. Currently, it takes time and/or communications (e.g., information requests) to fully understand the quality data and its significance in an application.

Better communication through the QOS could be particularly beneficial for any applications with accelerated assessment timelines (e.g., priority, expedited, and breakthrough drug products), or for applications with complex products or processes. In the latter types of applications, there may be a need to clearly explain the extensive development of product or process design, overall control strategy, and selection of analytical methods, in a patient-focused context. There are also clear opportunities to use the QOS to convey established conditions and lifecycle management activities, such as post-approval

commitments for NDAs and BLAs, to ease the burden of implementing and assessing post-approval changes. In the future, when established conditions have been implemented, the QOS would provide an opportunity to communicate a streamlined proposal for established conditions, as well as associated reporting categories for changes to those established conditions.

III. Putting the Quality Pieces Together

Some applicants have indicated to FDA that they are now preparing novel approaches to the QOS as part of new submissions. FDA is interested in exploring such novel approaches, provided that the QOS is compliant with ICH M4Q, conforms with CTD expectations with no legal obstacles, is suitable for use as a foundation for the assessment document (or as an initial assessment template), and is supported by data cross-referenced in specific volumes and page numbers in Module 3. As discussed above, the QbR-based QOS remains a valid approach for applicants to consider.

As part of any novel QOS in a new regulatory submission, the regulator would like to read the QOS and understand how the submission addresses key considerations, including:

- *Key Consideration 1*: Identifying the main risks to the patient from a product quality perspective. This includes:
    - Identifying specific safety or efficacy concerns that could result from the design of the manufacturing process or product
    - Identifying potential failure modes of the manufacturing process or product

- *Key Consideration 2*: Understanding how the proposed overall control strategy controls and/or mitigates the identified risks to the patient. This includes:
    - Explaining how the submission supports the manufacturer's ability to provide a product that consistently and safely meets labeling claims
    - Explaining how the submission supports commercial manufacturing of the product

- *Key Consideration 3*: Acknowledging potential considerations for the quality assessment of the submission. This includes:

- Highlighting the potential for the submission to warrant regulatory flexibility[6]
- Identifying, if known, any innovative elements of the submission that may present a precedent-setting issue for the quality assessment
- Explaining any pre-application meeting agreements and commitments
- Highlighting the granting of any accelerated review timeline designation
- Providing data summaries that explain key data and findings with adequate cross-references and links to these sections in Module 3
- Providing the regulator with the means to easily locate and access key data in Module 3 and, for NDAs and BLAs, to understand the balance of information provided in the submission, versus that to be gained via post-approval commitments and any planned lifecycle management activities
- Ensuring the information and conclusions in the QOS are consistent with Module 3

The approach to addressing these and other high-level considerations could fall broadly under three domains; ensuring the QOS: (i) is patient-focused, that it identifies the main risks to the patient from a product quality perspective; (ii) effectively summarizes the overall control strategy, and how it mitigates the identified risks to the patient; and (iii) guides the regulator through the submission, acknowledging potential considerations for the quality assessment. In this way, the regulator can be prepared to best assess the applicant's own conclusions about potential risk to the patient, and the control of such, in the commercially manufactured product.

IIIa. Ensuring the QOS is Patient-Focused

The quality standards for a drug product should be proposed in the context of clinical relevance. A patient-focused approach links quality to clinical performance wherever possible. The process and the resulting product should be designed to meet the patient's needs and achieve the intended performance. The proposed quality standards should ensure that the product can reproducibly deliver the therapeutic benefit to the patient, safely, as stated in labeling, whether that benefit has been newly established through

[6] E.g., FDA has various programs that are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of serious or life-threatening conditions. These expedited programs help ensure that therapies for serious conditions are available as soon as it can be concluded that the therapies' benefits justify their risks, taking into account the seriousness of the condition and the availability of alternative treatment. See Guidance for Industry – Expedited Programs for Serious Conditions – Drugs and Biologics

clinical trials or is based on a reference listed drug or reference product. Given the complexity of clinical relevance, the QOS represents an important opportunity to communicate these concepts to regulators. Regulators must always balance risk to product quality - and the associated risk to clinical performance - with availability of drugs to patients, and accept an appropriate level of inherent uncertainty. In considering this uncertainty as part of the approval process, regulators must strike a careful balance between the desire for necessary and ideal amounts of information. Appropriate context, robust connections, and effective collaboration are crucial to this process. Patient-focused quality standards, then, are based on this balanced conversation between applicants and regulators - part of which can occur in the QOS.

A key element of any regulatory submission is the effective communication of potential risks related to product quality and their potential impact on the patient, as discussed in ICH Q9.[7] The QOS provides an opportunity to summarize the benefit and risk considerations, based on patient population and indication. The impact of these considerations on drug development can be clearly stated in the QOS. For example, this could include how the dosage form was selected and how it was designed to deliver the active ingredient to the intended patient population. There is an opportunity to explain how the formulation was designed and manufactured to meet the prescribed dosing regimen or result in the same performance as the reference listed drug or reference product. For any potential risks, there can be an explanation of how they might impact the patient. As described in ICH Q8(R2),[8] the Quality Target Product Profile (QTPP) is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, accounting for safety and efficacy. Meanwhile, Critical Quality Attributes (CQAs) are physical, chemical, biological or microbiological properties or characteristics that should be within appropriate limits, ranges or distributions to ensure the desired product quality. In an application, there should be clear links drawn between the QTPP, the CQAs, and the control strategy for manufacturing the drug.[9] The QOS is one potential venue for clearly communicating these links. Specific safety or efficacy ramifications that could stem from specific product quality issues can be addressed. Any

[7] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Quality Risk Management Q9

[8] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Pharmaceutical Development Q8(R2)

[9] Yu, L.X. et al., Understanding pharmaceutical quality by design, *AAPS J* 2014

areas of uncertainty regarding identified or potential quality issues and patient impact can be described. Further, there is an opportunity to discuss how the provided product quality information supports the proposed labeling (e.g., package insert, carton/container labels, instructions for use, MedGuides).

IIIb. Ensuring the QOS Effectively Summarizes the Overall Control Strategy

After establishing the QTPP and CQAs, it is critical to link them to the overall control strategy. This is a key feature of quality risk management and pharmaceutical quality systems. As described in ICH Q10,[10] a control strategy is a planned set of controls derived from current product and process understanding that assures product quality and process performance. These controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. One factor currently limiting the usefulness of the QOS is the lack of effective communication as to how the overall control strategy was designed to address the patient-focused elements identified during drug development (e.g., CQAs). This communication may be more effective with a condensed summary explaining how the control strategy was designed to ensure the desired safety, efficacy and product quality. The summary may include the formulation and its manufacturing, release mechanism, and stability. This information supports the applicant's ability to safely meet labeling claims, either newly established through clinical trials or based on a reference listed drug or reference product. For a generic product, the control strategy can support the ability to manufacture a product that has therapeutic equivalence to a reference listed drug.

Importantly, this summary also provides an opportunity to communicate how the submission supports commercial manufacturing of the product, especially regarding scale-up. This can extend to an explanation as to how the control strategy ensures consistent manufacturing and compliance with regulatory commitments or labeling over the *lifecycle* of the product. The QOS presents an opportunity to also clearly communicate the change management system and a plan for implementing changes post-approval, including a summary of established conditions, reporting categories for post-approval changes, and proposed comparability protocols.

[10] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Pharmaceutical Quality System Q10

IIIc. Ensuring the QOS Guides the Regulator

If the desired outcome of a QOS is a more efficient application assessment and improved patient access to needed drugs, the QOS could serve as an effective guide for the regulator. The QOS provides an opportunity to summarize key aspects of the submission, potential considerations for the regulator, and post-approval commitments for NDAs and BLAs. The QOS can highlight compliance with regulatory requirements or explain a request for regulatory discretion or flexibility. In addition to the cover letter, the QOS is a place to alert the regulator to any accelerated assessment timeline designations or requests. Any requests for regulatory flexibility, especially in the context of patient or indication, or applications granted accelerated assessment timelines, can be justified. The QOS can be an effective means of communicating potential innovative elements or scientific/technical complexities in an application that may require special expertise.

If the applicant is aware of any potential precedent-setting issues, the QOS may be an effective means of alerting the regulator and initiating any necessary policy discussions. These issues should have been covered during development and in pre-application meeting agreements and commitments, which can also be described in the QOS. The QOS should include summaries explaining key data and findings, while providing links and connections to the broader data content in Module 3. Summary tables of key data in the QOS (i.e., batch analysis, in-process controls, stability, drug substance and drug product specifications, comparison to a reference listed drug or reference product) can support regulatory decision-making, control strategy, and post-approval commitments for NDAs and BLAs. As a result of reading the QOS the regulator should be able to easily locate and access all key data in Module 3.

IV. Conclusion

One adaptation of the QOS has been the QbR-formatted QOS for ANDA assessment, which applicants may continue to use for their submissions. However, FDA is aware of, and is generally open to, other QOS options that are compliant with ICH M4Q. In general, effective use of the QOS improves the regulatory assessment process. Again, it is important to note that any QOS framework will negate neither the need for a Module 3 nor the regulator's responsibility to examine Module 3. While it is critical to link the QOS to assessment efficiency and quality, ultimately, the regulator will determine the most effective means of assessing the quality information provided in Modules 2 and 3 of an application. From a

regulatory perspective, it is hoped that any future QOS can play a greater role in application assessment, measurably enhancing assessment efficiency and quality. This can be accomplished by assuring that the QOS is patient-focused, effectively summarizes the overall control strategy, and guides the regulator through the submission. Some potential issues not covered here, but to be considered in further developing and harmonizing the QOS, include ramifications for content in the QOS versus those in Module 3. This includes expectations for QOS content after submission throughout revision and following any regulatory action, and expectations for handling data submitted in Module 3, including post-approval data. While these are potential challenges for applicants and regulators, the ultimate beneficiary of any development regarding the QOS should be the patient. Improvements in application assessment resulting from the QOS, including better communication and increased assessment efficiency and quality, should lead to improved access to safe, effective, quality drug products.