

OGD White Paper

Question-Based Review (QbR) for Generic Drugs: An Enhanced Pharmaceutical Quality Assessment System

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Introduction

The Office of Generic Drugs (OGD) is developing a question-based review (QbR) for its Chemistry, Manufacturing, and Controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs) that is focused on critical pharmaceutical quality attributes. The QbR is a concrete and practical implementation of the underlying concepts and principles outlined by the FDA's cGMPs for the 21st Century¹ and PAT² initiatives. It will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment. This white paper discusses 1) what QbR is, 2) why QbR is necessary, 3) how QbR was developed, and 4) what the benefits of QbR are.

What is QbR?

The goal of the CMC review of ANDAs is to ensure that the generic product is appropriately designed (a pharmaceutical equivalent³ to the reference listed drug (RLD)) and that sponsors have methods and controls⁴ in place for the manufacture, processing, and packaging a drug that are adequate for assuring and preserving the identity, strength, quality, and purity of the proposed drug product. In this context, pharmaceutical quality means that consumers will receive a product free from contamination that will reproducibly deliver the therapeutic benefit promised in the label⁵.

The QbR, a general framework for the CMC assessment of ANDAs, incorporates the most important scientific and regulatory review questions that focus on critical pharmaceutical attributes essential for ensuring generic drug product quality. The QbR serves two purposes for the CMC assessment of ANDAs. First, it provides a guide to the reviewer in the evaluation of whether a product is of high quality and in the determination of the level of risk associated with the manufacture and design of the product. Second, it provides transparency to sponsors about the logic that reviewers invoke in their CMC reviews.

Why is QbR Necessary?

The first reason for developing the QbR was the discrepancy between the objectives of FDA's cGMPs for the 21st Century Initiative and current CMC review practices. The cGMP initiative¹ described a "desired state" for pharmaceutical quality in which:

- Product quality and performance are achieved and assured by design of effective and efficient manufacturing processes
- Product specifications are based on mechanistic understanding of how formulation and process factors impact product performance
- Manufacturers have the ability for effect continuous improvement and continuous "real time" assurance of quality
- Regulatory policies and procedures are tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability
- Risk based regulatory scrutiny is associated with the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance, and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.

When one compares these goals to the current CMC review practice, it becomes apparent that in the present system:

- Product quality and performance are predominantly ascertained by end product testing. The present review system places little or no scrutiny on how the design of an effective and efficient manufacturing process can ensure product quality. This also has the effect of not recognizing the many complexities of process scale-up, particularly for complex dosage forms⁶.
- Product specifications are derived empirically based on test data from one batch, which is often not at production scale, mechanistic understanding does not play a significant role in this process. This practice often has the effect of leading to “overly conservative and often irrelevant specifications.”
- The burdensome regulatory requirement of supplements imposed on sponsors for executing minor and incremental changes to manufacturing processes and controls stifles the implementation of continuous improvement of manufacturing processes and strategies for the implementation of continuous "real time" assurance of quality.
- The goal of striving for regulatory consistency among all applicants conflicts with the notion of having regulatory policies and procedures tailored to recognize a particular sponsor’s level of scientific knowledge supporting product applications.
- All products are treated equally without regard to the risk to the consumer. This has the effect of placing too much review time on low-risk products and more significantly, takes away needed resources from the review of high-risk products. Hence, CMC review assessments of complex dosage forms (modified release products, topicals, transdermals) as well as narrow therapeutic index (NTI) drugs,

differ only marginally from those of simple dosage forms (many immediate release solid oral products).

The second reason for developing the QbR is the ever increasing OGD review workload. In the year 2002, OGD received a total of 361 ANDAs. This number increased to 449 in 2003 and to 563 in 2004. This year, 2005, over 700 ANDAs are expected. The increase in ANDAs will also result in a dramatic increase in CMC supplements. Unless there are significant changes to the current policy on CMC supplements the increasing number of supplements will essentially consume all FDA OGD resources. Therefore, it is essential to change our CMC review system to one that can more effectively utilize limited review resources in a more efficient and risk-based manner.

How is the QbR Being Developed?

The QbR is being developed based on the following four principles:

- Quality built in by design, development, and manufacture; and confirmed by testing
- Risk-based approach to maximize economy of time, effort, and resources
- Preservation of the best practices of current review system and organization
- Best available science and wide consultation to ensure high quality reviews

The QbR development process began with identification of the essential aspects of the current review process. Then a comparison of the goals of the cGMP initiative to the current review process revealed the key scientific questions that were not being addressed. Once the key questions were recognized, a risk-based approach was used to identify which questions are appropriate for which products. Following this initial phase, there is a time of wide consultation, as shown in the timetable below, with stakeholders and the public before implementation:

January - May 2005	Design and draft QbR by the OGD QbR Committee
May - June 2005	Review by OGD Team Leaders
July 2005	Comments from OGD reviewers and stakeholders
August 2005	Public posting on OGD Web site
Fall 2005	Pilot reviews
Fall 2005 and 2006 science	Reviewer training on quality by design and manufacturing
2006	Transition to new review system
January 2007	Full implementation of new review system

What are the Benefits of QbR?

These driving forces for change have led to the development of a QbR framework that provides 1) for a concrete basis for the implementation of FDA's cGMPs for the 21st Century initiative and 2) for the effective allocation of limited review resources. The QbR review achieves this by incorporating the following four facets into the new QbR CMC review system:

- ***Quality by Design and Performance-Based Specifications Assure Product Quality***

QbR incorporates two new practices into the review to ensure more relevant performance-based specifications. The first practice will include a consideration of a product development report from which reviewers will learn how drug substance and formulation variables affect the performance and stability of the drug product. The second practice will include a critical comparison of the proposed generic drug product and RLD formulations, which will contribute to ensuring the approval of therapeutically equivalent products, particularly in the case of complex dosage forms. Taken together, these new practices will contribute to the goal of establishing product specifications based on a mechanistic understanding of how formulation factors impact product performance.

With respect to manufacturing, the QbR includes a review of the process development report. From the process development report, reviewers learn how the sponsor identifies the critical steps, determines critical process parameters, and establishes appropriate controls to the process, particularly for the more complex dosage forms. This process knowledge helps ensure that after process scale-up, the commercial manufacturing process will reliably produce a product that retains its critical quality attributes. Incorporating process development information into the QbR review will help OGD realize the goal that product quality and performance are achieved and assured by the design of effective and efficient manufacturing processes.

- ***Risk-Based Assessment Facilitates Continuous Improvement and Reduces Supplements***

QbR contains a risk assessment section that can potentially eliminate/downgrade up to 80% of current CMC supplements. This will provide appropriate regulatory relief for supplements of minor and incremental changes to manufacturing processes and controls. By removing these burdensome regulatory requirements, it is anticipated that will facilitate continuous improvement of manufacturing processes and encourage the use of innovative strategies for the implementation of continuous "real time" assurance of quality.

The QbR introduces a simple mechanism whereby some products may be classified in a lower risk category. For these products, sponsors will be granted relaxed post-approval CMC supplement classification. However, this concession is contingent upon the submission of a pharmaceutical development report that demonstrates the sponsor's product and process understanding. Such an approach takes into consideration the sponsor's level of mechanistic understanding and introduces regulatory policies and procedures tailored to recognize the additional knowledge.

- ***Standardized Review Questions Enhance the Quality of CMC Evaluation***

The QbR identifies and incorporates the best practices of the current CMC review system and makes these practices common for the entire office. As such, the new QbR template will provide a standardized method of delivering a comprehensive CMC review. This will require

critical thinking by reviewers and will encourage reviewers to identify only the scientifically important CMC deficiencies in ANDA submissions. QbR ensures that OGD is asking the right questions at the right time and in the most efficient manner.

The QbR also provides for an efficient review of low-risk products and an in-depth review of more complex dosage forms and NTI drugs. This is achieved by design of questions that can quickly account for common cases and prior knowledge, thereby enabling reviewers to spend little effort on low-risk elements of the review. Conversely, in the case of more complex dosage forms and NTI drugs, the questions will encourage critical thinking and promote a mechanistic understanding of how formulation and manufacturing process variables affect pharmaceutical quality. This approach, which utilizes the pharmaceutical development report, implements the concept of risk-based regulatory scrutiny that considers both the degree of dosage form complexity and therapeutic index, and the level of scientific understanding of how formulation and manufacturing process factors affect product quality. This approach also implements a practical means for dramatically reducing the number of supplements, particularly for low risk products.

- ***QbR-based Quality Overall Summary (QOS) Assists CMC Review and Reduces Review Time***

By having formalized QbR questions, the logic used in drug product quality assessment will be transparent and not arbitrary. This would have the beneficial effect of providing sponsors clear direction to improve the quality of their submissions. Such transparency would likely result in more first-cycle approvals and minimize the inefficient and time consuming process associated with multiple-cycle approvals, particularly in the case of simple drug products.

By having formalized QbR questions and format, OGD can effectively guide both the content as well as the format of the quality overall summary (QOS) that is part of the ICH Common Technical Document (CTD). Therefore, by having a QOS that directly provides answers to the QbR questions, this will eliminate recopying information such as composition, specification, etc., and therefore reduce review time.

Conclusion

The QbR is a concrete and practical implementation of the concepts in the cGMPs for the 21st Century initiative that enhances our current CMC evaluation of pharmaceutical quality in three respects:

1. By directing reviewers to ask the right questions, it enhances their critical analysis with a specific emphasis on quality by design⁷, and thus better enables them to recognize only those deficiencies in CMC information that affect product quality.
2. By encouraging sponsors to share their pharmaceutical development knowledge, it promotes a mechanistic understanding of how formulation and manufacturing process factors affect pharmaceutical quality, and hence leads to more relevant specifications and manufacturing controls.

3. By containing a risk assessment section, it will relate regulatory scrutiny to the level of scientific understanding and dosage form complexity, supporting innovation and continuous improvement. It is anticipated that this will eliminate/downgrade up to 80% of CMC supplements, and thus free up scarce resources.

In conclusion, the proposed QbR will result in reviews that focus on important attributes of drug product quality and encourage reviewers to identify which key specifications and manufacturing controls are necessary to ensure product quality. It will also result in a risk assessment for that product. In the future, the CMC review will provide more information about how the specifications connect to product quality, the risks associated with the manufacture and formulation of this product, and why FDA believes the product can be manufactured consistently.

References

¹ U.S. Food and Drug Administration. "Final Report on Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach." September 2003.
http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm (accessed April 6, 2005).

² Ajaz S. Hussain. "Process Analytical Technology: A First Step in a Journey Towards the Desired State" *The Journal of Process Analytical Technology*. January/February 2005.

³ Pharmaceutical equivalence requires that the generic drug product contain the "same" active ingredient(s) as the RLD, that it be identical in strength, dosage form, route of administration, and that it meet compendial or other applicable standards of strength, quality, purity, and identity.

⁴ In the CMC context, a test can be a control or a part of a control strategy. Opportunities exist to bring forward engineering based (e.g., feedforward and feedback controls) controls to demonstrate the "state of control" and how this may relate to risk mitigation.

⁵ J. Woodcock, "Concept of Pharmaceutical Quality": *American Pharmaceutical Journal Review*, 2004.

⁶ This in part has contributed to prior recommendations for approval of commercial scale manufacturing processes that the sponsor has been unable to implement.

⁷ U.S. Food and Drug Administration. *The PAT Guidance and the Draft ICH Q8 Guidance*