The Question-Based Review (QbR) initiative of the Office of Generic Drugs (OGD) has reached its second full year in 2009. From a human perspective, we can say that QbR has reached “toddlerhood.” And like a true toddler, QbR has come out of its infancy, exploring new ground, trying to define and redefine itself.

As abbreviated new drug applications (ANDA) submitted in the QbR format have become the industry norm and the “growing pains” with the new submission style are waning to some degree, it is an appropriate time to provide the industry with some perspective regarding how these submissions have affected the assessment of generic drugs.

THE ORIGIN OF QBR

Before we evaluate the two-year journey of QbR and weigh in on its future, it may be worthwhile to take a look back as to how it all started. The QbR was chiefly developed by the Office of Generic Drugs (OGD) as a platform to implement the concepts and principles of the US Food and Drug Administration’s current good manufacturing practices (CGMPs) for the 21st Century initiative. It was OGD’s first step toward providing the generic industry with a framework of significant scientific and regulatory questions that focus on sharing, justifying, and building quality into generic drugs. A second driver for developing QbR was the ever increasing workload at OGD. It was expected that by seeking the industry’s response with science-based justification to the critical questions regarding the quality of their drug products, the agency may be able to reduce the number of deficiencies cited and thus reduce the review time.

An OGD white paper published in August of 2005 (1) provided a clear overview of reasons behind the development of QbR. In January of 2006, models of a quality overall summary (QOS) utilizing the QbR format (2) for extended release and immediate release tablets were released on the OGD website to provide direction for the generic industry. Multiple training sessions were offered by OGD throughout 2007, so that more intimate interaction could occur between the regulators and the industry. Also, for further assistance and clarity, a QbR Frequently Asked Questions (3) document was released in 2008.

POSITIVE EFFECTS OF QBR-QOS

Several areas of the ANDA submissions have been positively affected by the QbR-QOS initiative. Many of these changes are consistent with the current quality-by-design (QbD) philosophy of FDA; however, the QbR-QOS is also flexible enough to allow for submissions where QbD strategies are not yet in place. The questions posed in the QbR have allowed the firms to provide justification for choices made throughout the development and manufacture of generic products. A second driver for developing QbR was the ever increasing workload at OGD. It was expected that by seeking the industry’s response with science-based justification to the critical questions regarding the quality of their drug products, the agency may be able to reduce the number of deficiencies cited and thus reduce the review time.

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in assessment. The current QbR-QOS was developed based on the International Conference on Harmonisation (ICH) common technical document (CTD) format and the in-house review practice of the applications submitted to the Office of Generic Drugs.

The QbR questions provide a vehicle for the sponsors to share their wealth of knowledge in product and process development with the agency. QbR has also provided the industry with a platform to use their experience to justify proposed processes and their controls in order to provide better assurance that scale-up from the ANDA exhibit batch size to the routine commercial batch size will be successful. In several cases, the information submitted in the QbR-QOS and the supporting information in Module 3 of the application has adequately justified the choice or elimination of certain excipients from the formulation or the selection of a particular manufacturing process and, in some cases, the design of the drug product that may differ from the innovator product. Identification of critical process parameters (CPP) and critical quality attributes (CQA) in the QbR-QOS and further discussion in Module 3 has also enhanced the reviewer’s assessment of the product and has led to a better understanding by OGD as to the intended design and performance of the proposed product.

**CHALLENGES WITH CURRENT SUBMISSIONS**

The journey of QbR has not been without challenges. The M4Q – CTD Quality (4) states that a summary of the pharmaceutical development is provided in Module 3, Section 3.2.P.2. The questions in the QbR-QOS were drafted in order to provide a snapshot of the summary report in 3.2.P.2. Over the last two years, several drawbacks were identified with the QbR-QOS submissions. One of the major shortcomings of ANDAs submitted during this two-year period is that, albeit adopting the QbR-QOS format, the firms have provided limited product and process development information in Module 3 of the application (body of data) as well as in the QbR-QOS.

On several occasions, firms have provided responses to the questions in QbR-QOS with no supporting information in Module 3. Submissions as these have not added value to the product quality or increased the agency’s confidence in the firm’s ability to manufacture a product with consistent quality at the commercial scale.

In another example, firms have attempted to justify the compatibility of excipients with the active pharmaceutical ingredient by citing successful accelerated stability studies of the exhibit batches. This amounts to reverting to “quality by testing” rather than progressing in the direction of product and process understanding and ultimately “quality by design.” The premise of the excipient-drug substance compatibility studies is to provide justification based on mechanistic understanding of chemical interaction of drug substance, excipients, and the manufacturing process. Thus, justifying excipient compatibility based on end product testing or monitoring changes in physical appearance of a binary mixture does not amount to building quality into the product.

Also, in many submissions, justification of scale up to commercial batch has been insufficient. Without clear rationale and suitable development work for the changes proposed for scale up from the exhibit batch, it becomes difficult for the reviewer to assess if commercial batches will be successful post approval. Lastly, a very serious flaw in QbR-QOS submissions has been inconsistencies in the information provided in the QbR-QOS and the Module 3. These inconsistencies have led to increased review time, on many occasions have led to additional review cycles, and have undermined the benefits of QbR-QOS in terms of reducing the OGD backlog.

**SUMMING UP**

Like many initiatives of its kind, QbR-QOS may be considered a mixed blessing. To date, however, the benefits of QbR far outweigh the issues. At its best, QbR-QOS submissions have provided the reviewer in-depth understanding of the design, the formulation, the process, and the sponsors’ rationale for decisions. It has eliminated transcriptional errors and cut down on the review time by reducing the reviewers’ time that was traditionally spent on fact finding and summarizing ANDA elements. At its worst, the lack of scientific rationale to support the product quality and process in the QbR-QOS and Module 3 has led to additional questions and has delayed the review and subsequently the approval of generic products.

**NEXT STEPS**

Now that we have discussed the “growing pains” of QbR-QOS, the palpable question is what lies ahead for QbR-QOS? The next steps include moving from simply understanding the product and process and a “trial and error” development approach to embracing QbD principles and increased predictability in both the product and the process. Current resources with
respect to QbD recommendations can be found in the ICH Q8 (5) and the draft ICH Q8 (R1) (6) guidance documents, which have been accepted by FDA. In tandem with QbD principles are the ideas of quality risk management, ICH Q9 (7), which may be woven throughout the development strategies. The QbR format can be seen as a platform for QbD principles, and sponsors are encouraged to include the elements recommended in the ICH pharmaceutical development guidances in future pharmaceutical development portions of ANDA submissions. The ICH QbD elements, such as defining a quality target product profile (QTPP), identifying the CQA for the drug product, determining the quality attributes for ingredients in the formulation, selecting an appropriate manufacturing process, and implementing a control strategy based on a comprehensive scientific understanding are clearly the next steps for QbR-QOS submissions.

The QbR platform was designed to allow for seamless transition when QbD principles are put into place by generic drug sponsors. Most of the questions in the QbR-QOS sections 2.3.P.1 and 2.3.P.2 can be utilized to define the QTPP. The questions that specifically deal with design of the product, comparison to the innovator product, choice of the manufacturing process, and critical characteristics of the container closure system all lead to a better understanding of the QTPP of the generic product. Sections 2.3.P.3 and 2.3.P.5 include questions that mesh with the implementation of a robust control strategy that will assist in the assurance that the proposed product performs as intended and conforms to all defined quality attributes after commercialization; and section 2.3.P.4 includes in-depth information with regard to functionality related attributes for the excipients utilized in the formulation.

As ANDA sponsors and OGD become more comfortable with the next steps, inroads can be made to develop guidance and optimize product and process development to implement the enhanced QbD approaches found in ICH Q8 (R1) and many of the risk management strategies found in ICH Q9. This will ensure a more proactive, systematic approach to product and process design versus the traditional reactive, empirical approaches that were commonplace prior to QbD.

We realize that with any change in paradigm, especially one that is still in relatively earlier stages, the concerns on both the sponsor and the regulator sides have not yet fully subsided. We welcome the challenge of working closely with ANDA sponsors to increase the quality of QbR submissions in order to utilize the principles of QbD that will lead to a better understanding of the design for proposed products and processes.

ACKNOWLEDGMENT
The authors wish to acknowledge the following individuals who provided invaluable insight: Lawrence Yu, Ph.D.; Vilayat A. Sayeed, Ph.D.; Sivakumar Vaithilingam, Ph.D.; and Robert Lionberger, Ph.D.

REFERENCES

ARTICLE ACRONYM LISTING
ANDA Abbreviated New Drug Applications
CGMPs Current Good Manufacturing Practices
CTD Common Technical Document
CPP Critical Process Parameters
CQA Critical Quality Attributes
FDA US Food and Drug Administration
ICH International Conference on Harmonisation
OGD Office of Generic Drugs
QbD Quality By Design
QbR Question-Based Review
QOS Quality Overall Summary
QTPP Quality Target Product Profile