Editorial

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Facilitating use of Quality by Design concepts in regulatory submissions

More than 10 years ago, the US FDA announced the Pharmaceutical CGMPs for the 21st century initiative. This initiative was intended to encourage implementation of risk-based approaches that focus both industry and FDA attention on critical areas.

Keywords: control strategy, critical process parameter, critical quality attribute, design space, platform manufacturing, Quality by Design

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In 2008, the Office of Biotechnology Products (OBP) at the US FDA initiated their Quality by Design (QbD) pilot program. The program was designed to define clinically relevant attributes for protein products regulated by the OBP and link them to manufacturing processes. As a supervisor within the OBP, I was fortunate to participate in the review of many of the submissions to the pilot program and comment upon many different approaches from the pharmaceutical/biotechnology industry. Almost without exception, the companies that participated in the OBP pilot program shared with the FDA impressive scientific presentations communicating their efforts to enhance biotechnology product and process understanding. Having recently left the FDA and now being able to look back and reflect, I would like to provide my personal perspective on the current state of QbD implementation as well as provide a few modest proposals to address some of the known regulatory issues.

QbD is defined as *"A systematic approach to product development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"*. This definition, as well as other general concepts related to QbD, can be found in ICH guidance (ICH Q8, Q9, Q10 and Q11; [1–4]). In addition, numerous publications have provided more detailed thoughts on application of QbD concepts to biotechnology product development [5–7].

Practically speaking, regulatory submissions to the OBP based on this guidance and on the OBP pilot program discussions have resulted in modified regulatory approaches, but there has not been a dramatic change or milestone achievement (e.g., as of 2012, the FDA had not yet approved a design space for a biotechnology product). In addition, some regulators have publicly expressed skepticism with respect to the applicability of QbD concepts to biological products [101].

Based on discussions within the OBP pilot program and at public meetings, several common issues have been identified. What follows is a brief overview of specific regulatory issues with some of submissions identified to date.

» Critical quality attributes (CQAs): a common deficiency observed was the inclusion of process capability in the assessment of attribute criticality. Aside from being inconsistent with the definition of CQA as found in ICH Q8, removing process capability from the CQA identification exercise is important to mitigate the risk of inadequate control of an attribute when changes that can influence process capability are made during the product's post-licensure lifecycle management process;

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» Critical process parameters (CPPs): a common deficiency observed was a lack of justification for the parameter ranges that were explored. Setting the ranges too narrowly during development can result in fewer CPPs, but can also result in underappreciating the impact of a parameter on the quality of commercial product. Parameter ranges explored during development should be chosen based on factors including commercial equipment design capability, measurement capability and previous manufacturing history;

» Design space: a common deficiency observed was defining the design space based only on inclusion CPPs. Given the limitations in CPP identification exercises described above, this became a challenge. In addition, most design space experiments are performed at small scale. Many design space proposals included unit operations with known scale dependencies and no intent to confirm or monitor the design space at full scale. To mitigate some of this risk, ICH Q11 stated that: *"…it may be appropriate for an applicant to provide proposals on how movements within a design space will be managed post-approval. These proposals should indicate how process knowledge, control strategy and characterization methods can be deployed to assess product quality following movement within the approved design space"*;

» Platform manufacturing: the concepts of QbD, CQA, CPP and design space were previously defined in ICH Q8 and have been more often applied in the development and manufacture of new molecular entities (sometimes referred to as small molecules). The concept of platform manufacturing was more recently defined in ICH Q11 (finalized in 2012) and has its origin in earlier guidance on monoclonal antibody development [8,9]. Platform manufacturing is defined as *"The approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture other drugs of the same type (e.g., as in the production of monoclonal antibodies using predefined host cell, cell culture and purification processes, for which there already exists considerable experience)."*

/// The Quality by Design program was designed to define clinically relevant attributes for protein products regulated by the Office of Biotechnology Products and link them to manufacturing processes. ///

A common deficiency observed was the unjustified extrapolation of prior knowledge, which was then labeled as platform manufacturing. To be considered platform manufacturing, justification needs to be provided to support the similarity of the prior knowledge as applied to the new drug. In general, utilization of the concept is both an opportunity and a challenge. It is important to understand the limits of this concept and not to underestimate the value of 'case-by-case'.

Aside from these specific issues, there are general issues that both regulators and industry should consider if the promise of QbD is to be realized. Moving forward, regulators need to recognize that the level of review scrutiny and amount of oversight should be proportional to risks to product quality; not the amount of data submitted. In addition, regulators could facilitate progress if they were to promulgate a clear regulatory standard for what constitutes an appropriate control strategy. To identify adequate control strategies, inspectors and regulators have the potential to draw broad lessons by surveying control strategies of already approved products. To the extent possible, these general lessons could be applied during review of new applications.

Moving forward, industry needs to recognize that QbD concepts are inherently regulatory. Applicants can increase the likelihood of the successful implementation of QbD in a regulatory context by providing:

» Well-written summaries of any additional studies supporting enhanced product and process knowledge. Reviewers can be frustrated when confronted with extensive (and sometimes duplicative) data from studies that lack a clear stated purpose;

» Increased use of protocols as described in 21 CFR 601.12(e). As stated in ICH Q11, *"Knowledge gained from commercial manufacturing can be used to further improve process understanding and process performance and to adjust the control strategy to ensure drug*

substance quality." Post-approval adjustments to the control strategy based on improved process understanding need to comply with the overall regulations described in 21 CFR 601.12. Submission of a protocol in the original application describing how this increased knowledge will be used to manage risks associated with specific changes can expedite subsequent regulatory implementation;

» Increased clarity (and detail) within the regulatory filing about what the specific lifecycle management ramifications are with respect to the enhanced process and product knowledge obtained. This could include a better match between the QbD studies/results, known commercial manufacturing capability, and the desired regulatory consequences. Possible examples include:

- If the applicant proposes that the final control strategy will not include lot release testing for a particular CQA, the likelihood of approval of the proposal could be increased if that CQA was included in a process risk assessment and/or process characterization studies;
- If the applicant proposes a design space, the likelihood of approval could be increased if a comprehensive listing of the regulatory consequences for all relevant parameters, including moderate and lower risk parameters, was included. ICH Q11 example 2 provides a possible overall lifecycle management regulatory approach when a design space is proposed.

More than 10 years ago, the FDA announced the Pharmaceutical CGMPs for the 21st century initiative [10]. This initiative was intended to encourage implementation of risk-based approaches that focus both industry and FDA attention on critical areas. The concepts described in ICH guidance and efforts such as the OBP pilot program have laid the framework to facilitate achievement of these goals. Successful resolution of the issues identified here may better align regulatory expectations and facilitate broader implementation of QbD concepts for biopharmaceuticals.

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