BIOTECH

Technical Regulatory Topic

USTR 3457

Question Based Review Approach as Part of Quality by Design

Revision Number 0

Revision Date 15-Apr-21

1 Introduction

Drug quality cannot be assured only by finished-product testing, and process validation is required to establish scientific evidence that a process can deliver an effective and safe drug and does so consistently and reproducibly.

Quality by Design (QbD) was advocated by the FDA as part of the Pharmaceutical Quality for the 21st Century – A Risk Based Approach initiative. It was later addressed in the ICH guidelines[1,2,3], the draft Annex 1 of the EU GMP guide[4] and the Chinese Guidelines for the Technology and Application of Sterile Filtration, as a standard approach to build quality into pharmaceutical development at the start of the process.

Risk mitigation is central to Quality by Design (QbD) and Quality Risk Management (QRM), and increasingly, ways are sought to build quality into production steps, to reduce risk to the patient. With respect to aseptic processing, this includes a thorough understanding of the design space for sterile filtration and single-use systems.

1.1 A Question Based Review Format

One way of capturing the aspects of science and risk for product quality is to adopt a Question based Review – Quality Overall Summary (QbR-QOS) approach. QbR gives a structure through which the data collected by applying QbD can be presented. So far this has been used for Abbreviated New Drug Applications (ANDAs), but the list of questions could equally be applied to new drug applications (NDAs).

Indeed, the FDA stated in the 2014 document, Chemistry Review of Question-based-Review (QbR) Submissions that although implemented for ANDAs, the QbR format could also be used as a basis for developing a structured QOS for NDAs[5]. The principles of QbR could also usefully be applied in regions not controlled by the FDA.

Question Based Review Checklist

- How is the product filtered?
- How is filter integrity examined during production? And how is the filter integrity measured, pre-use and post-use?
- How do the filters used during filter validation compare to the filters used during production?
- What parameters were used during filter validation?
- What method was used to determine filter compatibility during filter validation?
- What method was used to determine filter extractables during filter validation?
- What method was used to determine drug adsorption to the filter during filter validation?
- What method was used to determine bacterial retention during filter validation?
- Describe the method used to determine filter integrity during filter validation.

1.2 The Advantages of a Question Based Review Approach

Robert Iser of the FDA in a presentation “Update on Question-based Review” described QbR as “a step in the right direction”[6] as it encourages clear communication and use of similar language. He goes on to say that the use of common quality standards which are consistent with the QbD paradigm and congruent with risk management approaches, encourages justification for choices made throughout the development and manufacture and increases transparency in the applicant’s thought processes.

Benefits to applicants include:

- Clear communication
- Effective quality assessment
- Common quality standards
    - Standardizes submission expectations

- Provides clear expectations
- Provides an opportunity to address critical questions about the product's design, failure risk, and manufacturing controls from both a performance and patient usability perspective.
- Reduces questions from the reviewers during the review cycles
- Use as an internal communication tool

A risk-based approach to quality maximizes economy of time, effort, and resources and the QbR checklist was developed following these principles. The QbR process can be used as part of the risk assessment approach for sterile filter and single-use system validation.

Using the questions in the QbR checklist to review the validation of a drug process and as a starting point to assess risk, whether for an ANDA or NDA could help manufacturers to maximize the assurance of sterility of their process and meet the expectations of the regulators.

For more detailed information on the topic please refer to Pall White Paper USD 3353 "A Risk Based Approach to Validation Studies for Sterilizing Filtration and Single-Use Systems".

2 References

1. ICH. *Q8 (R2) Pharmaceutical Development*. ICH Official Website. [Accessed March 18, 2021] (https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf).

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4. European Commission. *Good Manufacturing Practice (GMP) guidelines, Annex 1: Manufacture of Sterile Medicinal Products*. EudraLex, volume 4. [Accessed 18 March 2021] (https://ec.europa.eu/health/documents/eudralex/vol-4_en).

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6. Iser, Robert. "Update on Question-Based Review (QbR)" (Power-Point Presentation, Regulatory Education for Industry (REdI): Generic Drugs Forum, 2015 April 22). [Accessed March 18, 2021]. https://www.fda.gov/media/91769/download

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USTR 3457
April 2021