Question based Review (QbR) for Microbiology

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Presentation Overview

- OGD Division of Microbiology
- Product Quality Microbiology Review
- Description and Development of the Question based Review (QbR) for Microbiology
- Microbiology QbR Benefits
- Microbiology QbR Documents
- Common Industry Micro QbR Inquiries
- References
OGD Division of Microbiology

• We are product quality microbiologists
• Division Director (Acting)-Lynne Ensor, Ph.D.
• Deputy Director (Acting)-CDR Paul Dexter, M.S.
• 3 Team Leaders
• 2 Project Managers
• 12 Microbiology Reviewers
Sterility Assurance of Drug Products

- Product quality microbiology
- Microbiology of sterile and non-sterile products
- We review all drugs labeled as sterile → not just parenteral
- Combination of microbiology & engineering
Focus of Sterility Assurance Review

The product quality microbiology information for a drug product is part of the Chemistry Manufacturing Controls (CMC) information in a submission.
Focus of Sterility Assurance Review

We focus on processes associated with the manufacture of the commercial batch, not the exhibit batch

process validation
Sterility Assurance/Product Quality Microbiology Review

- Terminal sterilization and/or Aseptic processing
- Overall manufacturing operation
- Microbiological monitoring of the environment
- Container closure integrity
- Sterilization/depyrogenation processes
- Specifications for product release and product stability
Current Location of Microbiology Information in a CTD Submission

• Microbiology information is found throughout the CTD submission
  – Module 1: 1.1, 1.2, 1.4, 1.14
  – Module 3: 3.2.P.2, P.2, P.3, P.4, P.5, P.7, P.8
  – Module 3: 3.2.A
  – Module 3: 3.2.R

• Enter stage right: → QbR
QbR for Microbiology Defined

- **Summary** of microbiology information in one location
- Summary narrative of the elements assessed in the microbiology review
- Not a replacement for supporting data
- Chemistry QbR was a template
  - Use of Questions, not statements
  - Placement in Module 2 in the Quality overall Summary (QOS)
Development of QbR for Microbiology

• “Ideal” submission
• Opportunity to update the 1994 Sterilization Guidance
• Incorporated concepts of Quality by Design (QbD)
• FDA “questions” designed for applicants’ “responses”
Microbiology QbR is Created

• Called QbR for Sterility Assurance (QbR-SA)
• Sterile product focus
• Resulting document:
  – Narrative information now consolidated in one location → Module 2
  – Supporting documentation always in Module 3
• FYI: Responses to QbR questions could be placed in a detailed Executive Summary in Module 3
Microbiology QbR Benefits

• Transparent Review Process
  – OGD Website ➔ provides guidance without publishing a guidance

• Clarity ➔ We can communicate our expectations

• Living document

• Fewer deficiencies = less review cycles

• Decrease review time = faster review completion (goal of faster approval time)
Microbiology QbR Benefits

• Means to convey current thinking
  ➔ Labeling concerns-not addressed in 1994 guidance
  – Reconstitution/Dilution Storage
  – Multi-dose vs. single dose
  – Maximum patient dose
  – Pharmacy Bulk Packaging
    • FYI: PBP checklist on OGD Website
    • “Generic Drug Development, Abbreviated New Drug Application (ANDA) Submissions, and Review Information”
Microbiology QbR Benefits

• Potential regulatory relief for supplements
  – Potential downgrading of filing category
  – Potential decrease in or elimination of additional validation studies
  – \( \rightarrow \text{Role of QbD} \)
QbD for Microbiology

- QbD based on process validation and understanding
- More understanding = more QbD
- Design space: variables and parameters
- Sterile product: design space is processes affecting sterility and pyrogenicity
- Ex. TS process for a product
  - parameters and load composition
Microbiology QbR for Terminally Sterilized Products

• Name: QbR-SA-TS
• Status: finalized (Oct 2011)
• Location: FDA.gov website
  –Generic Drugs: Information for Industry
  –Quality by Design (QbD)/Question-based Review (QbR)
Microbiology QbR for Terminally Sterilized Products

Question-Based Review for Sterility Assurance Evaluation of an ANDA

Documents available:

1) Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized Products: Quality Overall Summary Outline


2) Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions

Microbiology QbR Outline

• Module 2.3: Quality Overall Summary
• 2.3.P DRUG PRODUCT
• 2.3.P.2.5 Microbiological Attributes
• Container/Closure and Package integrity
• How was the container/closure system for the drug product validated to function as a barrier to microbial ingress?
• What is the container/closure design space and change control program in terms of validation?
Microbiology QbR FAQ/Expanded

• What is the container/closure design space and change control program in terms of validation?
• Q: What information should be presented in this section?
• A: If the container/closure design space has been established, then describe the design space parameters (e.g. dimensions, composition, and torque range, residual seal force, storage conditions, sterilization/ depyrogenation conditions, etc.) and corresponding acceptance criteria (including limits and ranges) which were validated for container/ closure integrity of the drug product.

• Describe and provide the rationale for any potential changes that may be made within the validated design space, for which no additional validation studies are needed. Describe what criteria must be met for such changes to be considered within the validated design space. Changes made outside the design space would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.

• Q: What if a container/closure design space has not been established?
• A: If a container/closure design space has not been established, then indicate “Not applicable” or “N/A” as the answer to this question.

• Any future changes made after the application has been approved would likely necessitate additional validation studies and should be addressed by a regulatory post-approval change process.
Micro QbR for Aseptically Processed Products

• Name: QbR-SA-AP (draft)
• Status: Draft
• Location: not available yet
• Two documents in draft:
  – Question-based Review (QbR) for Sterility Assurance of Aseptically Manufactured Products: Quality Overall Summary Outline
  – Question-based Review (QbR) for Sterility Assurance of Aseptically Manufactured Products: Frequently Asked Questions
(Draft) Micro QbR for Aseptically Processed Products: Features

• Question and answer format
• Based on 1994 Guidance
• Located in Module 2 QOS
• Relevant questions in the QbR for TS products will be in the QbR for AP products
  – Ex. Container closure system integrity, preservative effectiveness, component sterilization and depyrogenation, control of drug product, stability
(Draft) Micro QbR for Aseptically Processed Products: Features

• Additional questions specific for aseptically processed products:
  – Facility and clean room designs
  – Design of manufacturing process
  – Sterile filtration
  – Environmental monitoring
  – Media fill simulations
  – Hold periods
Micro QbR: Common Industry Inquiries

• If my drug product is aseptically manufactured, can I use the applicable QbR questions for a terminally sterilized product to prepare my submission?

• Can the Micro QbR for TS products be utilized for DMFs?

• The QbR questions are focused on drug product. Can I apply the same questions for drug substance?
Micro QbR: Common Industry Inquiries

• Can Micro QbR questions be used for supplemental applications?

• Is Micro QbR required for ANDA submissions?

• Should separate chemistry QOS and Micro QOS documents be submitted?

• Is Micro QbR applicable to both ANDAs and NDAs?
References

• Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

• Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
References


• **Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers - 2012**
References

• Guidance for Industry: Comparability Protocols – Chemistry, Manufacturing, and Controls Information – Draft 2/03

• Guidance for Industry: Changes to an Approved NDA or ANDA – 2004
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