Product Quality Microbiology Assessment:
The What and The Where

Marla Stevens-Riley, Ph.D.
Master Microbiology Reviewer
Division of Microbiology Assessment
Office of Process and Facilities
Office of Pharmaceutical Quality
CDER/FDA

Regulatory Education for Industry
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Presentation Overview

- **The What**
  - Product Quality Microbiology defined
  - Mini lesson about product quality microbiology
  - Types of submissions reviewed
- **The Where**
  - Location in Common Technical Document

Product Quality Microbiology Defined

- **What it is:**
  - Microbiology of the manufacturing processes
  - Control of or removal of microbes during manufacturing
  - Part of Chemistry, Manufacturing & Controls (CMC)
  - Combination of microbiology and engineering

Product Quality Microbiology Defined

- **What it is not:**
  - Not clinical microbiology
  - Not evaluation of the efficacy of antimicrobials

Product Quality Microbiology Defined

- **Focus:** Processes that **will be used** for commercial production

- **Not a focus:** Processes and equipment that **were used** for the exhibit batch

Product Quality Microbiology Defined

- **Sterile versus non-sterile drug products**
  - Sterile: no microbes allowed in final product
  - Non-sterile: microbes allowed in final product
  - Sterile vs. non-sterile products:
    - Location, location, location
    - Indication, indication, indication

→If Reference Listed Drug is sterile, then generic drug is sterile

Product Quality Microbiology Defined

- **Sterile products include:**
  - Injectables, ophthalmics, otics, inhalation solutions
  - Sometimes topicals and orals

- **Non-sterile products include:**
  - Orals, nasal sprays, topicals

Product Quality Microbiology Defined

- **Assures there are controls for microbes and by-products**
  - Raw materials, packaging, equipment
  - Manufacturing processes
  - Environment
- **Assures effectiveness of reduction, removal, or destruction**
  - Washing, filtration, heat, radiation, gas
  - Evaluation of validation and process simulations

Mini Lesson

- **Sterile products**
  - Two methods to manufacture a sterile product
    - →Aseptic Processing (aseptic filling)
      - –Components sterilized separately, then brought together
      - –Higher risk
    - →Terminal Sterilization
      - –All components brought together, then sterilized
      - –Lower risk

Mini Lesson

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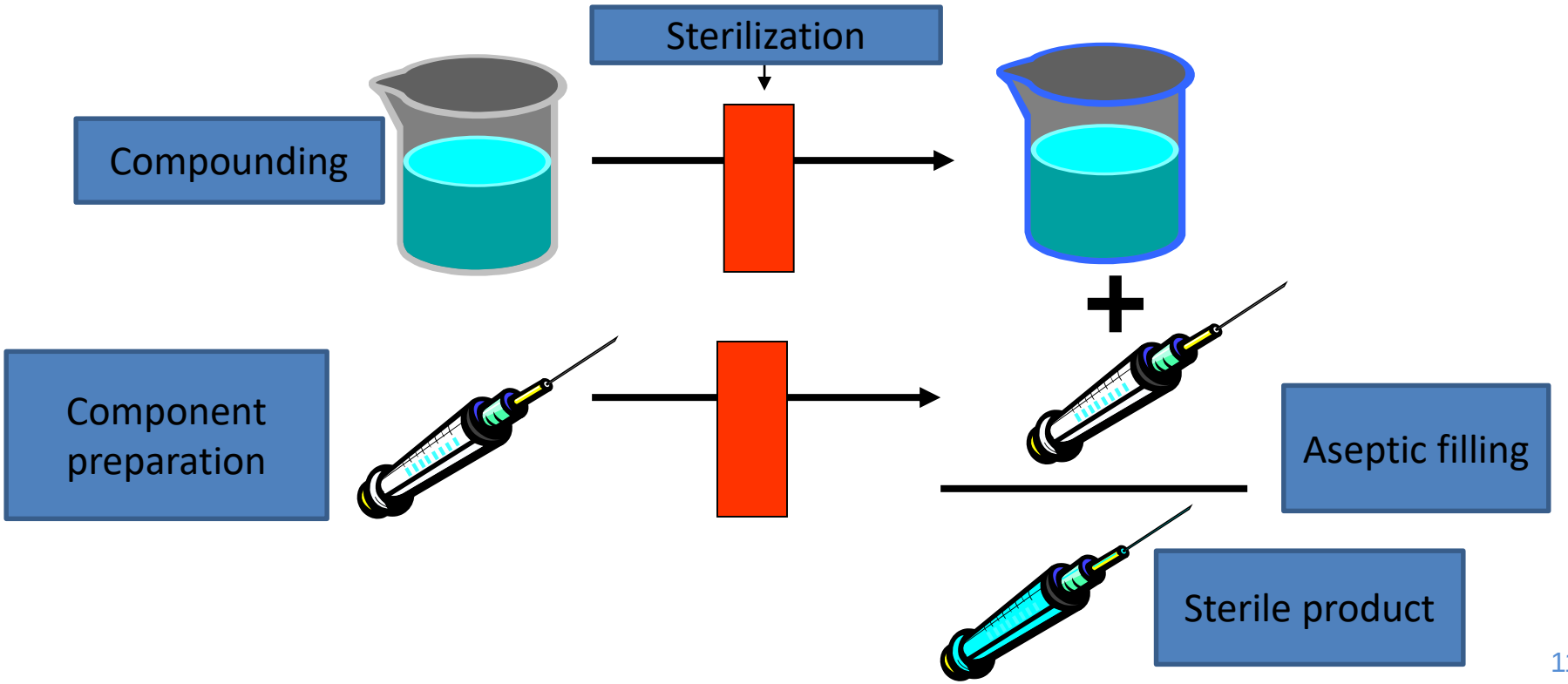
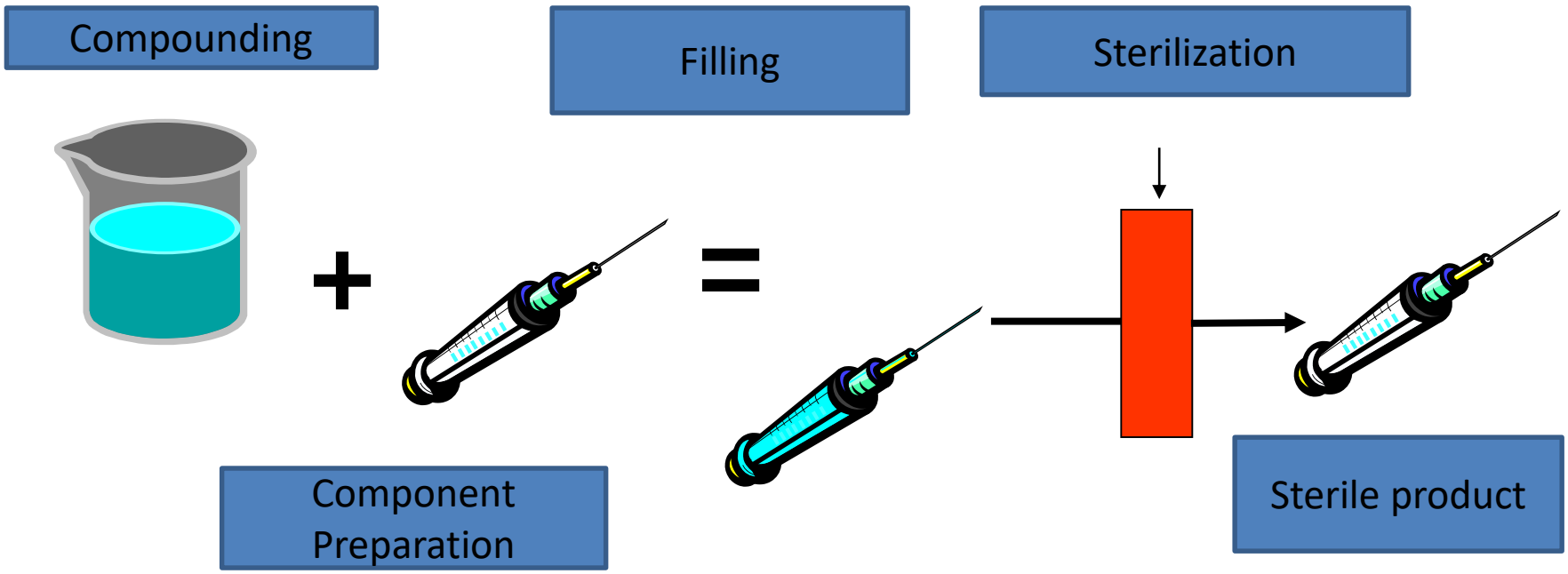
Mini Lesson


Sterilization
Compounding
Component preparation
Aseptic filling
Sterile product

Mini Lesson


Compounding
Filling
Sterilization
+
=
Component Preparation
Sterile product

Submissions Reviewed

- **Applications**
  - ANDAs, NDAs, BLAs, INDs
  - Originals, amendments, supplements
  - Drug Master Files
  - Meeting packages
  - Controlled correspondence (generics only)
  - Inquiries

Location of Information

- **Module 1-Regional**
  - 1.1 Forms
  - 1.2 Cover letter
  - 1.4 References
    - Letter of Authorization for DMFs!!!

Location of Information

- **Module 1-Regional**
  - 1.14.1 Draft Labeling
    - Container label: Dose
    - Package insert:
      - Reconstitution and/or dilution and storage
      - Pharmacy Bulk Package information
      - Patient dosage and administration

Location of Information

- **Module 2-CTD Summaries**
  - 2.3 Quality Overall Summary
    - Optional
    - Question-based Review for terminally sterilized products
    - Question-based Review for aseptically processed products

Location of Information

- **Module 3.2.P. Drug Product**
  - P.1 Description and Composition of Drug Product
    - Components
    - Container closure system
  - P.2 Pharmaceutical Development
    - P.2.5 Microbiological Attributes
      - Antimicrobial effectiveness testing
      - Container closure integrity testing

Location of Information

- **Module 3.2.P.3 Manufacture**
  - P.3.1 Manufacturers
    - Manufacture for commercial production
    - Testing for release and stability
  - P.3.3 Description of the Manufacturing Process and Process Controls
    - Commercial production

Location of Information

- **Module 3.2.P.3 Manufacture**
  - P.3.5 Process Validation
    - Validation studies for proposed commercial production processes
      - Sterilization
      - Depyrogenation
      - Process simulations

→ Validation assures that you can do what you say you will do

Location of Information

- **Module 3.2.P.5 Control of Drug Product**
  - P.5.1 Specification
    - All sterile products: Sterility Test (USP <71>)
    - All sterile injectable products: Sterility Test and Endotoxins Test (USP <85>)
  - P.5.2 Analytical Procedures
  - P.5.3 Validation of Analytical Procedures

Location of Information

- **Module 3.2.P.8 Stability**
  - P.8.1 Stability Summary and the Conclusion
  - P.8.2 Post-approval Stability Protocol and Stability Commitment
    - Sterility Test (or Container Closure Integrity)
    - Antimicrobial Effectiveness Test (USP <51>)
  - P.8.3 Stability Data

Location of Information

- **3.2 Regional Information**
  - R.1 Executed batch records
  - R.2 Comparability protocol
- **A.2 Adventitious Agents Safety Evaluation**
  - BSE/TSE documentation
  - Viral clearance studies

References

- MaPP 5040.1: *Product Quality Microbiology Information in the Common Technical Document-Quality (CTD-Q)*

https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/default.htm

- Guidance for Industry: *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064983.htm

References

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

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM276168.pdf

- *Question-based Review (QbR) for Sterility Assurance of Aseptically Processed Products: Quality Overall Summary Outline*

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm

Thank You

Marla Stevens-Riley, Ph.D.

marla.stevens-riley@fda.hhs.gov

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