



Application of cGMPs to Drug Product Microbiology Laboratory Testing and Manufacturing Process Validation

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Disclaimer

- The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA

Presentation Outline

- Role: Div of Microbiology Assessment in CDER
- Identification of sections of 21CFR 211:
 - Microbiological testing requirements for both sterile and nonsterile drugs
 - Drug manufacturing processes, microbiological quality and validation

CDER/OPQ/Office of Process and Facilities/Division of Microbiology Assessment

Functions:

1. Submission Review

- NDA/BLA/ANDAs, Supplements, INDs, DMFs, Mtg Pkgs

2. Subject Matter Expertise

- Facility Inspections
- Incidents (drug contamination, infection outbreaks)
- CDER Policy (guidance/inquiries, outside organizations)
- Input to CDER re: inspectional findings & assessments

§211.167-Special Testing Requirements



- a) For each batch of DP purporting to be sterile:
- There shall be an appropriate laboratory test
 - The test procedures shall be in writing and followed

§211.167 – Sterility Test- FDA Guidance

1. [Sterilization Process Validation Guidance](#)
2. [Aseptic Processing Guidance](#)

§211.167 – Sterility Test- Key Points

- USP <71> is the Compendial Method
- Methods that differ from USP<71> should be demonstrated as equivalent to or better than

§211.167: Sterility Test- Additional Points

- Two methods: Membrane Filtration & Direct Inoculation
- Table 2: Minimum quantity of product to be tested
- Table 3: Minimum number of units to be tested
- Suitability of use of test with product (important)

§211.167: Sterility Test- Additional Points

- Compendial sterility testing is slow (14 days)
- Alternatives to compendial sterility testing
 - Parametric release
 - Rapid microbiological testing methods

§211.167: Sterility Test & Parametric Release

- Only applies to terminally sterilized DP
- Parametric release is defined as a sterility assurance release program where demonstrated control of the sterilization process enables a firm to use defined critical process controls, in lieu of the sterility test, to fulfill the intent of 21 CFR 211.165(a), and 211.167(a).
- [Parametric Release Guidance](#)

§211.167-Special Testing Requirements



- a) For each batch of DP purporting to be pyrogen free:
- There shall be an appropriate laboratory test
 - The test procedures shall be in writing and followed

§211.167: Pyrogens Test-FDA Guidance

1. [Sterilization Process Validation Guidance](#)
2. [Pyrogen and Endotoxins Testing Guidance](#)

§211.167: Pyrogens Test- Key Points

- USP <85> is the Compendial Method
- Methods that differ from USP<85> should be demonstrated as equivalent to or better than

§211.167: Pyrogens Test- Additional Points

- Three methods: Gel Clot, Turbidometric & Chromogenic
- Equation for determination of endotoxin limit
- Equation for determination of MVD of sample
- Suitability of use of test with product (important)

§211.167: Pyrogens Test- Additional Points

- Low Endotoxin Recovery
 - Particular products and formulations
 - *Low Endotoxin Recovery: An FDA Perspective*

Patricia Hughes, et.al. BioPharma Asia, 4/10/15

§211.160(b) Lab Controls- General Requirements



b) Lab controls shall include appropriate specifications...and test procedures to assure:

- The drug product conforms to appropriate quality standard

§211.160(b) Lab Controls- Antimicrobial Effectiveness Test

- Some drug products are labeled “multiple dose”
- Container entered > once for administration
- Drug either includes a preservative or is self-preserving
- USP<51> Antimicrobial Effectiveness Testing
- After initial demonstration of AET, most product batches may be tested for chemical content at release and stability

§211.160(b) AET-FDA Guidance

1. Sterilization Process Validation Guidance

§211.160(b) AET- Key Points

- Product is challenged with a panel of microbes
- Microbe counts measured at intervals to include 28 days
- Table 1: Compendial Product Categories
- Table 2: Challenge Microbe Preparation
- Table 3: Test Acceptance Criteria

§211.160(b) Lab Controls- Viral Testing

- Drug Products derived from biological origin
 - Human or animal tissue/cell lines
- Testing for viruses may be appropriate
- FDA Guidance:

[ICH Q5A Viral Safety Evaluation Guidance](#)

§211.160(b) Lab Controls- Viral Testing Key Points

- Potential sources of viral contamination
- Testing for viruses to qualify cell line
- Testing for viruses in unprocessed bulk
- Recommended viral detection and identification assays

§211.160(b) Lab Controls- Container/Closure Integrity Testing

b) Lab controls shall include appropriate specifications...and test procedures to assure:

- The drug product containers, closures...
...and the drug product conform to
appropriate quality standard

§211.160(b) CCI & FDA Guidance

1. [Sterilization Process Validation Guidance](#)
2. [CCI in Lieu of Sterility Test Guidance](#)

§211.160(b)-CCI Key Points

- Sterile drug products should maintain a microbial barrier throughout shelf life
- There is no compendial container/closure integrity test
- USP<1207> offers some guidance

§211.160(b)-CCI Additional Points

- Applicants use a variety of methods
- Microbial ingress, dye ingress, others
- Challenge of drug product should include stress of sterilization process
- Include positive and negative controls
- **Demonstrate sensitivity**

§211.165- Testing and Release for Distribution



- Re: Nonsterile drugs
 - b) There shall be appropriate laboratory testing:
 - Drug product required to be free of objectionable organisms

§211.165- Testing and Release for Distribution

- §211.165(b) is the lab determination of:
 - §211.113 Control of microbiological contamination
- Appropriate procedures to prevent objectionable microorganisms in nonsterile drug products

§211.165 & Nonsterile Drugs

- USP<1111>
 - Suggested acceptance criteria for microbial counts based on route of administration
- USP<61>
 - Test method for total microbial counts
- USP<62>
 - Test method for specified microbes

Burkholderia cepacia & aqueous nonsterile DP

PDA Journal of Pharmaceutical Science and Technology



Review

***Burkholderia cepacia*: This Decision Is Overdue**

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Burkholderia cepacia & aqueous nonsterile DP

- Applicants should include a test method for *Burkholderia cepacia* in the release specification

Alternative Microbiological Testing

- Why alternative methods?
 - Conventional methodology takes a long time
- What is needed for adoption of alternative?
 - Demonstration that the alternative method is equal to or better than the compendial test

Alternative Microbiological Testing

- How to demonstrate that the alternative method is equal to or better than the compendial test?
 1. Validate: alternate method works
 2. Demonstrate: suitable for use with product

Alternative Microbiological Testing

- No Existing FDA Guidance
- Potential Useful Resources
 - USP<1223>
 - PDA Technical Report 33

Changing Gears...

Manufacturing Process & Micro Quality

- Drug microbiological quality is built into the manufacturing process, not generated by end product testing
 - Sterilization validation & Quality by Design
- VS
- Sterility/pyrogen testing of finished product are required in CFR

§211.113-Control of Microbiological Contamination

- b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

Manufacturing Process and Sterilization Validation Guidance

- [Sterilization Process Validation Guidance](#)
- [Aseptic Processing Guidance](#)
- PDA TR #1: Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control



Quality by Design for Pharmaceutical Microbiology

Stephen Langille, Ph.D., Lynne Ensor, Ph.D.,
& David Hussong, Ph.D.

FDA

American Pharmaceutical Review
October 2009

Quality By Design and Microbiological Quality

- Drug Product: Critical Quality Atttributes
 - Sterile products: absence of microbes
 - Nonsterile products: free from objectionable microbes

Quality By Design and Microbiological Quality

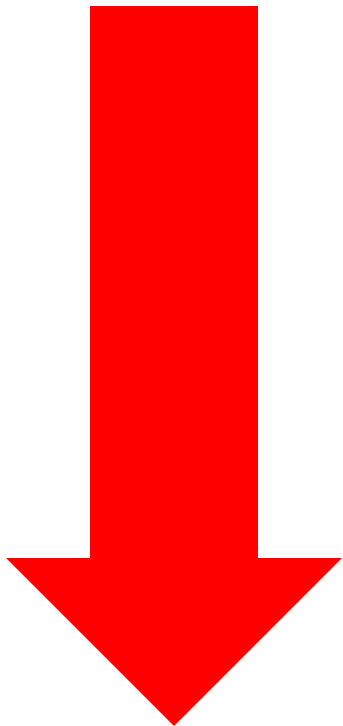
- Drug Product: Critical Quality Atributes
a function of:
- Critical Process Parameters & Critical Control Points
 - Sterilization process, equipment depyrogenation process, bulk solution holding time limits, exposure of aseptic process steps to environment, ...and others

Quality By Design and Microbiological Quality

- Each manufacturing process uses **DIFFERENT** process parameters & critical control points
- Lesser manufacturing processes may introduce micro risk to product quality
- Relationship: level of regulatory review scrutiny with manufacturing process

Sterile Manufacturing Process

Lower Micro Risk



Higher Micro Risk

1. Sterile Filtration/Aseptic Fill
Combined with TS Overkill Cycle
2. TS Overkill Cycle
3. TS with $<$ Overkill Cycle
(bioburden based or product
specific cycles)
4. Sterile Filtration/Aseptic Fill

TS=Terminal Sterilization

Summary Remarks

- 21 CFR Part 211
 - Mandates microbiological quality of drugs
 - Mandates specific microbiological testing
 - Mandates validation of manufacturing processes that impact microbiological quality of drugs



Questions?

Please complete the session survey:

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Thank You

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