Overview of Presentation

- The Recent Events
- GCP and GMP Basics – the 483 Review
  - Reference Documents
  - 483 Review
  - Preparation for the Future
Disclaimer

• I am making this presentation as an independent agent.
• I am not making this presentation as a representative of USP, PDA, ASM, USA, BSA, or any other organization with which I am currently associated.
• The views expressed in this presentation are offered as mine alone.

The Press


http://www.americanpharmaceuticalreview.com/Featured-Articles/135985-GMP-and-Compounding-Pharmacies/
Further Reading


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## Reference Documents

- USP <795> *Pharmaceutical Compounding – Nonsterile Preparations*
- USP <797> *Pharmaceutical Compounding – Sterile Preparations*
- USP <1163> *Quality Assurance in Pharmaceutical Compounding*
- 21 CFR 211 - The Pharma GMPs

## Summary GMP-GCP Comparison

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<th>GMP Topic</th>
<th>21 CFR 211</th>
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Frequent 483 Citations - Current

70 Reports
1/21/14
Stability Program

A lack of data supporting the potency, sterility (or occasionally any data whatsoever) of the preparation that might be stored for over a year.
**Inadequate/Improper Environmental Monitoring**

- Wide range of issues with environmental monitoring (EM) from insufficient frequency, failure to qualify sampling sites, failure to trend data, failure to respond to excursions, etc).

*This area is one of divergence between GCP as described in USP <797> and GMP as the expectations of GMP are designed to address manufacturing facilities, not the traditional compounding pharmacy. It may well be an expectation of "Outsourcing Facilities".*

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**Observation 3**

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

A. Active or passive microbial air monitoring has never been performed in the preparation of injectable or ophthalmic drug products.

B. Microbiological monitoring of operators performing aseptic preparations has not been conducted.

C. Microbiological monitoring of the surfaces within the have not been conducted during or at the end of sterile filling of a batch.

D. Annual certification of the does not include testing for viable and non-viable particulates.

E. There is no established environmental monitoring program.

*From 483 issued 11/22/13*
Validation of Sterilization - Media Fills

Generally citations in this topic involved:

- Terminally sterilized preparations not subjected to a validated sterilization cycle in an autoclave; or
- Aseptic fill operations not validated by a relevant media fill (simulated aseptic fill).

SOPs to Prevent Microbial Contamination Non-existent or Not Followed

Wide range of specific issues such as:

- Failure to have a qualified sanitization (or in some cases any sanitization) program
- Failure control technician exposure to CSP while compounding
- Having procedures but ignoring them in practice

This is clearly both a GCP and GMP issue as there are multiple references in both <795> and <797> to activities designed to control, monitor and minimize microbial contamination.
Inadequate Gowning

• Lack of critical pieces of gowns (hairnet, beard covers, foot covers, etc)
• Having gaps in gowns
• Poor gowning technique
• Poor aseptic technique with gowns.

This GCP concern is covered in USP<797> section “Additional Personnel Requirements – Personnel Cleansing and Garbing”

OBSERVATION 1
Clothing of personnel engaged in the processing of drug products is not appropriate for the duties they perform.

Specifically, cleanroom technicians who engage in aseptic operations do not use sterile lab coats, sterile masks, sterile hair nets, or sterile shoe covers.

From 483 issued 11/20/13
Lab Procedures: Testing/Contract Lab Control

- Poor or non-compliant performance of required testing
  - Potency Testing
  - Sterility Testing
    - Method Suitability
    - Inadequate sample volume
    - Inadequate incubation duration
    - Incorrect incubation temperatures
    - Incorrect growth media
- Poor oversight of testing labs

OBSERVATION 1

Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans and test procedures designed to assure that drug products conformed to appropriate standards of identity, strength, quality and purity.

Specifically,

Your firm has produced and distributed over [Redacted] medication orders of sterile drugs in the past year, for which the following has not been performed on any drug product processed and distributed by your firm:

A. Assay or product identification testing for any sterile injectable or sterile ophthalmic drug product.

B. Sterility Testing for any drug product has not been performed.

C. Endotoxin Testing for any drug product has not been performed.

From 483 issued 11/22/13
Batch Release

Release of sterile product under improper conditions without either potency testing, sterility testing, or perhaps any testing whatsoever to confirm the preparation’s strength, purity, quality or safety.

Inadequate Cleaning/Disinfection

• Manufacturing equipment or the facility cleanliness and the failure of the pharmacy to ensure that there was no carry-over of preparations from one batch to the next
• Failure to confirm that the disinfection of the aseptic area and PEC were actually working.

The GCP requirements for this issue are discussed in USP <797> in the sections “Cleaning and Disinfecting the Compounding Area”
Control of Equipment

Failure of the pharmacy to ensure that the equipment used for compounding was fit for its intended use.

This GCP topic is discussed in the section "Elements of Quality Control – Equipment".

Inadequate Facility / Smoke Studies

These observations dealt with adequacy of design and qualification studies to ensure the facility is meeting expectations for air balance and air flow in aseptic areas.

USP <797> expects air pressure differentials of 0.02 to 0.05-inch water column between rooms providing physical separation in the aseptic core and that "In situ air pattern analysis via smoke studies should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions" (see section "Facility Design and Environmental Controls").
Investigations

Inadequate response to problems or errors

- In process (for example environmental monitoring excursions)
- Finished product (failure of potency or sterility testing)
- Field complaints

Control of Pyrogenic Contamination

USP <797> addresses this specific topic in “Verification of Compounding Accuracy and Sterility – Depyrogenation by Dry Heat where it is stated “The description of the dry heat depyrogenation cycle and duration for specific load items shall be included in written documentation in the compounding facility. The effectiveness of the dry heat depyrogenation cycle shall be verified using endotoxin challenge vials (ECVs). The bacterial endotoxin test should be performed on the ECVs to verify the cycle is capable of achieving a 3 log reduction in endotoxin.
OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include validation of the sterilization process.

Specifically,
c) The washing and depyrogenation processes for finished product containers (10 ml amber glass vials) have not been validated. Per your firm's procedures, SOP for Cleaning, Sterilizing and Depyrogenation of Vials, city water is used for washing vials instead of purified or sterile water. Depyrogenation processes using an [redacted] have not been validated. Endotoxin burden and challenges, loading configurations, temperature mapping, and heat penetration have not been evaluated to ensure depyrogenation of finished product containers.

From 483 issued 10/2/13
483 Report URLs

- 2013 Pharmacy Inspections and Related Records
  [http://www.fda.gov/AboutFDA/CentersOffices/Office ofGlobalRegulatoryOperationsandPolicy/ORA/ORA ElectronicReadingRoom/ucm340853.htm](http://www.fda.gov/AboutFDA/CentersOffices/Office ofGlobalRegulatoryOperationsandPolicy/ORA/ORA ElectronicReadingRoom/ucm340853.htm)

- Compounding: Inspections, Recalls, and other Actions
  [http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm339771.htm](http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm339771.htm)

Recent FDA Guidances (Draft)

- Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act
- Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
- Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
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Know the Requirements

• USP <797> is central to CSP, but also <795> and <1163>
• Outsourcing Facilities may face a combination of GCP and GMP
  • Review 21 CFR 211
  • Know USP <795>, <797> and <1163>
• Have your facility in a state of control
• Have your processes in a state of control
• Have your testing and stability in line with expectations
Facility Control

- Physical Barriers/Design
  - Storage
  - PEC and Surroundings
- HVAC
- Water
- Cleaning and Sanitization (Separate Activities!)
- Environmental Monitoring
  - Air
  - Surfaces
  - Personnel

Process Control

- Incoming Materials
  - Actives
  - Excipients
  - Water
  - Containers
- Equipment
- Process Steps and Filling Conditions
- Hold Times
  - Process Holds
  - Clean Holds
  - Dirty Holds
Outsourcing Control

- Ensure that outsourcing facility is of acceptable quality
- Are they *REALLY* GCP compliant?

Finished Product / BUD Testing

- Performed in-house
- Contracted
  - You are responsible for the quality of the work you contract – it is your preparation (product)
- Sterility Testing a particular concern

Sterility Testing is Required

1. High Risk CSP produced other than by terminal sterilization by moist heat

2. A High Risk CSP:
   • that are in multiple dose vials for administration to multiple patients, or
   • that are exposed longer than 12 hours at 2-8°C or longer than 6 hours at >8°C.

3. Any CSP stored BUD before use.

For all risk categories of CSP the control measures (facility qualification, sterilization method, personnel gowning, PEC, etc) must be in place and appropriate. If any are not – even the sterility test is not sufficient to release CSP, even within BUD.

Sterility Testing

• Two separate tests
  • Membrane Filtration
  • Direct Transfer
• 20 Units, 2 media & temperatures
• Requires Growth
  • Incubation period - 14 days

Membrane Filtration

• Filter required amount of product through two filters
• Neutralize/Rinse
  • 3 100 mL volumes suggested
  • Formulations for dilution fluids suggested
• One filter into Soybean Casein Digest Broth (SCDB or TSB) – incubate at 20-25°C for 14 days
• One filter into Fluid Thioglycollate Medium (FTM) – incubate at 30-35°C for 14 days

Direct Inoculation

• Place required amount of product into sufficient recovery medium (with neutralizers?)
  • Soybean Casein Digest Broth (SCDB or TSB) – incubate at 20-25°C for 14 days
  • Fluid Thioglycollate Medium (FTM) – incubate at 30-35°C for 14 days
Method Suitability Test

Can we neutralize any antimicrobial properties of the medication?

Use specified challenge organisms
Use specified total amounts of products

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This Webinar’s Sponsor

Q.I. medical, inc

Q.I. Medical makes unique products for pharmacists and nurses who handle sterile solutions.

Their focus is on devices, test kits, and accessories that improve aseptic technique.

Applications include environmental monitoring, technique and process validation, microbial and endotoxin contamination testing, filtration, and needleless dispensing.

http://www.qimedical.com/

Upcoming Webinars

• February 27th - USP and Compounding Pharmacies
• March 27th - Compounding Pharmacies and the Sterility Test
• April 24th - Compounding Pharmacies and Contract Testing Lab.
• May 22nd - Compounding Pharmacies and the Bacterial Endotoxin Test
THANK YOU FOR YOUR ATTENTION

QUESTIONS?

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