Disclaimer

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

• Using a 503B supplier:
  • What is the responsibility of the Outsourcing Facility for high quality CSP?
  • What is the responsibility of the hospital pharmacy for high quality CSP?
  • How is a hospital pharmacy to choose a CSP supplier if they must be 503B and few 503B seem acceptable by FDA's 483 reports?

• Using a contract analytical lab
  • What is the responsibility of the lab for compliant test methods?
  • What is the responsibility for the pharmacist for compliant test methods?
  • How might the pharmacist determine if the test method is compliant?
  • What happens if the test fails?

503B – What is the responsibility for high quality CSP?

Follow CGMP-lite as described in

DRAFT Guidance for Industry: Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

FDA’s 503B Draft Guidance

• INTRODUCTION
• BACKGROUND
• CGMPs FOR OUTSOURCING FACILITIES
• REFERENCES
• GLOSSARY

FDA’s 503B Draft Guidance

CGMPs FOR OUTSOURCING FACILITIES
• Facility Design
• Control Systems and Procedures for Maintaining Suitable Facilities
• Environmental and Personnel Monitoring
• Equipment, Containers, and Closures
• Components
• Production and Process Controls
• General Production and Process Controls
• Aseptic Drug Processing
• Release Testing
• Laboratory Controls
• Packaging and Labels
• Quality Assurance Activities/Complaint Handling
### Issue Frequency

<table>
<thead>
<tr>
<th>Issue</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Inadequate/ Improper EM</td>
<td>79.5%</td>
</tr>
<tr>
<td>Lab Testing/ Contract Lab Control</td>
<td>77.0%</td>
</tr>
<tr>
<td>Validation of Sterilization - Media Fills</td>
<td>76.2%</td>
</tr>
<tr>
<td>Inadequate Gowning</td>
<td>72.1%</td>
</tr>
<tr>
<td>SOPs to Prevent Microbial Contamination</td>
<td>67.2%</td>
</tr>
<tr>
<td>Stability Program</td>
<td>63.1%</td>
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<tr>
<td>Inadequate Cleaning/ Disinfection</td>
<td>61.5%</td>
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<tr>
<td>Inadequate Facility / Smoke Studies</td>
<td>58.2%</td>
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<tr>
<td>Control of Equipment</td>
<td>54.9%</td>
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<tr>
<td>Batch Release</td>
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<tr>
<td>Investigations</td>
<td>46.7%</td>
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<tr>
<td>Control of Pyrogenic Contamination</td>
<td>40.2%</td>
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<tr>
<td>QAU Not Effective/ Production SOPs not followed/effective</td>
<td>36.1%</td>
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<tr>
<td>Separation of Clean and Dirty Operations/Storage of Materials</td>
<td>28.7%</td>
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<tr>
<td>Inadequate raw material control</td>
<td>23.0%</td>
</tr>
<tr>
<td>Container Preparation</td>
<td>17.2%</td>
</tr>
<tr>
<td>Labelling Issues</td>
<td>13.9%</td>
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<tr>
<td>SOP/Control of Production</td>
<td>12.3%</td>
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<tr>
<td>Safeguard Against Penicillin/ Cephalosporin Cross Contamination</td>
<td>11.5%</td>
</tr>
<tr>
<td>Records not Available</td>
<td>11.5%</td>
</tr>
<tr>
<td>Personnel not Trained/ Inadequate</td>
<td>10.7%</td>
</tr>
<tr>
<td>Change Control</td>
<td>3.3%</td>
</tr>
<tr>
<td>Obvious Product Contamination (Micro/Particulate)</td>
<td>2.5%</td>
</tr>
</tbody>
</table>
Facility Design

“Certain elements of facility design are considered critical to ensuring the quality of compounded sterile drug products. For example, all processing and controlled areas must be clean and free of visible signs of filth, dirt, mold or mildew, insects, and inappropriate items or debris (see also, § 211.56).”

In addition, specific recommendations are made in this section.
Control Systems and Procedures

“To prevent contamination or mix-ups during the course of sterile and other operations, § 211.42 requires separate or defined areas or other similar control systems for a facility’s operations. Section 211.56 requires that procedures be established and followed that assign responsibility for sanitation and describe in detail the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.”

In addition, specific recommendations are made in this section.

Environmental and Personnel Monitoring

“21 CFR 211.42(c)(10)(iv) requires establishing a system for monitoring environmental conditions in aseptic processing areas, while §§ 211.113(b) and 211.28(a) require personnel sanitation practices and gowning to be both acceptable and qualified for the operations they perform.”

“Environmental monitoring should consist of a well-defined program that evaluates the potential routes of microbial contamination of the human drug that could arise from the air, surfaces, process, operation, and personnel practices. The program should contain an appropriate detection component to verify state of control of the environment.”
Equipment, Containers, and Closures

- Equipment, containers, and closures that come into contact with the drug product must be evaluated to ensure adequacy for intended use
- Equipment, containers, and closures that come into contact with the drug product must be evaluated to ensure adequacy for intended use
- Not necessary to test all incoming if:
  - Supplier certifies sterility and non-pyrogenicity
  - Physical packaging inspected and documented
  - COA confirms sterility and non-pyrogenicity

Components

- Must have appropriate specs for incoming components
- Must be tested upon receipt unless:
  - Approved finished human drug product
  - Purchased directly from FDA registered manufacturer under 510 of FD&C – no alterations or repackaging
  - Label examined and confirmed meets spec
  - Shipment’s package integrity confirmed
Components

• Significant discussion of how to handle components that do not meet previous conditions
• Water is considered a component
• Components must be retested periodically on storage

FDA also provides an alternate approach
“Reducing the Need for Laboratory Testing of Incoming Components”

Production and Process Controls

• General Production and Process Controls
• Aseptic Drug Processing

A significant discussion
Release Testing

“Sections 211.165 and 211.167 require that finished drug products be tested to determine whether they meet final product specifications before their release for distribution. Section 211.22 establishes that the quality control unit is responsible for ensuring that the finished drug product is not released until this testing is conducted and the results confirm that the finished drug product meets specifications. Procedures for final release testing should be established and followed as outlined here.

Appropriate specifications must be established for each drug product (see § 211.160(b)). Specifications must address those attributes necessary to ensure the quality of the finished drug product (see § 211.160(b))...”

In addition, specific recommendations are made in this section.

Laboratory Controls

When testing components, in-process materials, and finished drug products, laboratory controls must be used to ensure the reliability of the tests (§ 211.160). Each laboratory, whether in-house or external to the outsourcing facility, used to conduct testing of components, in-process materials, or finished drug products must employ the following critical aspects of laboratory controls to ensure the quality of sterile drug products compounded by the outsourcing facility (see §§ 211.160, 211.194):"

- Appropriate written procedures for the conduct of each test and document the results
- Have sampling and testing procedures designed to ensure that components, in-process materials, and drug products conform to the specifications set for the drug product
- Use analytical methods and equipment that are suitable for their intended use and are capable of producing valid results; if using a validated or an established compendial test procedure in a specification, the test has been verified and documented to work under the conditions of actual use
Stability/Expiration Dating

“A stability program must be established to assess the stability characteristics of finished drug products, and the results of stability testing must be used to determine appropriate storage conditions and expiration dates (21 CFR 211.166). Stability testing is used to ensure that a drug product will retain its quality (for example, strength) and remain sterile through the labeled expiration date.”

In addition, specific recommendations are made in this section.

Packaging and Labels

Packaging of sterile drugs must be appropriate to the product and capable of ensuring the sterility and integrity of the product until it is administered to a patient (see §§ 211.94, 211.122). Labels must contain required information, and labeling operations must include controls to prevent mix-ups; furthermore, procedures must be developed to ensure these requirements are met (§§ 211.122, 211.125, 211.130, 211.134).

In addition, specific recommendations are made in this section.
Quality Assurance Activities/Complaint Handling

- Quality assurance activities are needed to ensure that procedures are followed and a quality drug product is produced.
- Quality unit must be independent.
- Procedures describing the role and responsibilities of the quality control unit must be established and followed (§ 211.22(d)).
- The quality control unit is responsible for discrepancy and failure investigations and the development and oversight of appropriate corrective actions and preventive actions.

Quality Assurance Activities/Complaint Handling

- The quality control unit has the responsibility to ensure that each batch of finished drug product is sampled and tested to ensure that it meets appropriate specifications for release (see 770 §§ 211.22(a), 211.165(d)).
- The quality control unit must periodically review records of compounding operations to evaluate the quality standards for each drug product to determine the need for changes in specifications or control procedures (§ 211.180(e)).
- The quality control unit is also responsible for evaluating written and oral complaints concerning the quality or purity of, or possible adverse reactions to, a drug product.
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FDA Urges Hospital Pharmacy to Purchase from 503B

- 503B under FDA authority – can enforce higher standards of Quality
- Hospital pharmacies can encourage more compounding pharmacies to register as 503B by market forces


Concerns - Potency


Widespread failure of compounded products for identity, potency or both.
Potency Concerns


Concerns - Contamination

What is the Responsibility of the Hospital Pharmacy?

How to Choose a 503B?

FDA maintains a listing of 503B registered facilities at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm

<table>
<thead>
<tr>
<th>Status of 503B Inspection</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Yet Inspected</td>
<td>17</td>
</tr>
<tr>
<td>Inspected – No Findings</td>
<td>2</td>
</tr>
<tr>
<td>Inspected; 483 Not Available</td>
<td>4</td>
</tr>
<tr>
<td>Inspected; 483 Available</td>
<td>33</td>
</tr>
<tr>
<td>Inspected; Warning Letter/Recall</td>
<td>11</td>
</tr>
</tbody>
</table>

56 total
CGMP Based on Historical Lessons

- Scandals in meat industry led to concern over food quality in 1900
- 1901-1906 Vaccine issues resulted in FD&C Act
- 1937 Cough syrup (w/ Diethylene glycol)
- 1938 Further vaccine issues expanded FDA authority and enforcement – inspections
- 1941 Variations in insulin potency led to FD&C amendment on potency
- 1941 Cross contamination of sulfathiazole tablets with phenobarbital led to death of nearly 300
- 1944 – Public health services act – FDA revised manufacturing controls

CGMP Based on Historical Lessons

- 1953 – Revision to FD&C Act Section 704(a)
  - Originally required “first obtain permission” for inspection
  - Now Congress changed to requiring the presentation of credentials and issuance of a notice of inspection "to the owner, operator, or agent in charge"
- 1953 – Creation of FD&C Act Section 704(b) – Form 483
- 1955 – Cutter Incident with Polio Vaccine – Process Control
- 1960’s – Thalidomide; led to effectiveness requirements
- 1972 – Davenport, UK Incident; led to sterility validation/ process control
- 1978 – 21 CFR 210 and 211 finalized
- 1982 – Tylenol; led to tamer-evident closures
CGMP Based on Historical Lessons

• 1984 – Enhancement of punitive fines
• 1989 – L-Tryptophan process modification led to deaths and illness, toxic impurity; led to Change Control requirements
• 1992 – Generic bribery scandal led to enhancement of penalties in generic drug arena
• 2013 – NECC and led to Compounding Quality Act

Take-Home Message

• Pharma manufacturing of sterile products is not easy
• CGMP learnt from school of “hard-knocks”
• CGMP is important
How to choose 503B?

Options

• Buy from cheapest source
• Look at 483 concerns – but these are only “documentation” issues and so are not really important
• Use 483, Warning Letters and recalls as useful documentation for decision-making

483 Reports as Data

• Review Issues
  Check to see if there are Warning Letters or recalls
• Review the Pharmacy’s Response
  • Are they addressing the concerns or claiming to follow <797> rather than CGMP? Are they actually following <797>?
  • Do they have a timeline for addressing the observations?
  • Are they hitting their timeline?
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2013 DRAFT - Contract Manufacturing for Drugs: Quality Agreements

• Owner is responsible for assuring that contractors produce and test drug products, in accord with CGMPs and conditions of approval
• Contractor is responsible for complying with cGMP and other requirements of the Quality Agreement
• Owner is ultimately responsible for approving or rejecting drug products produced by contractors
• Strong Quality Agreement … No “head in the sand” by either party
2013 DRAFT - Contract Manufacturing for Drugs: Quality Agreements

Outline

• Facilities and Equipment
• Materials Management
• Detailed Product-Specific Requirements
• Laboratory Controls
• Documentation
• Change Control
• Use of Sub-contractors
• Knowledge Transfer
• Communication and Information Exchange
• Oversight and Auditing
• Illustrative Scenarios

Contract Labs are Responsible for Competency
Pharmacist is Responsible for the Quality of the CSP

This may require ensuring that the test data are sufficient, accurate and compliant

Contract Labs Must be Audited

- In the past, many labs have claimed “compliance” to USP <71> Sterility testing erroneously
- Currently, a great deal of confusion remains about “compliance”
  - Method Suitability
  - Sample Size
  - Alternate methods
How to Determine if the Lab is Compliant?

- USP Chapter <1117> “Microbiological Best Laboratory Practices”
- FDA. 1993. Guide To Inspections of Microbiological Pharmaceutical Quality Control Laboratories
  http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074914.htm

What Happens if the Test Fails?

- Investigation is required
- Invalidating the lab work can only be done on clear evidence of lab error
- Investigation must include determination of
  - Impact of problem on other CSP
  - Root Cause
  - Corrective Action
  - Execution of Corrective Action
  - Evidence that the Problem is Fixed
Presentation Review

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Microbiology Network

- Consulting
  - Contamination Control/Sterility Assurance
  - Quality Assurance
  - Quality Control
    - Microbiology Lab Operations/Design
    - Microbiology Process/Procedure
    - GCP/CGMP for <797> or GMP compliance
  - Product Development
  - Audits
    - Laboratory Preparation/Contract Lab Qualification
    - Facility Contamination Control
    - FDA Mock Systems Audit of Facility (w/team)

- Training
  - In-house Training
  - Distance Training
THANK YOU FOR YOUR ATTENTION

QUESTIONS?

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