cGMP and Potential Directions for the Revision of USP <797>

Scott Sutton, Ph.D.
scott.sutton@microbiologynetwork.com

www.Rx-GCP.com

Disclaimer

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

• Status Check – 483s and 503Bs
• What is the USP?
  • Parts of the USP
  • Specific Interest for Pharmacists
• <797> and Potential Directions
  • Contamination Control
  • Potency and Stability
• Conclusions/Summary

FDA 483 Observations

Based on 126 483 reports on the FDA website (1/4/14)
Common 483 Topics

<table>
<thead>
<tr>
<th>483 Topic</th>
<th>Percentage of Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate/ Improper EM</td>
<td>79.8%</td>
</tr>
<tr>
<td>Validation of Sterilization - Media Fills</td>
<td>77.2%</td>
</tr>
<tr>
<td>Lab Procedures: Testing/ Contract Lab Control</td>
<td>76.3%</td>
</tr>
<tr>
<td>Inadequate Gowning</td>
<td>74.6%</td>
</tr>
<tr>
<td>SOPs to Prevent Microbial Contamination</td>
<td>71.1%</td>
</tr>
<tr>
<td>Stability Program</td>
<td>64.0%</td>
</tr>
<tr>
<td>Inadequate Cleaning/ Disinfection</td>
<td>60.5%</td>
</tr>
<tr>
<td>Inadequate Facility / Smoke Studies</td>
<td>58.8%</td>
</tr>
<tr>
<td>Control of Equipment</td>
<td>56.1%</td>
</tr>
<tr>
<td>Batch Release</td>
<td>55.3%</td>
</tr>
<tr>
<td>Investigations</td>
<td>49.1%</td>
</tr>
<tr>
<td>Control of Pyrogenic Contamination</td>
<td>40.4%</td>
</tr>
<tr>
<td>QAU Not Effective/ Production SOPs not followed/effective</td>
<td>35.1%</td>
</tr>
<tr>
<td>Separation of Clean and Dirty Operations/Storage of Materials</td>
<td>28.1%</td>
</tr>
<tr>
<td>Inadequate raw material control</td>
<td>24.6%</td>
</tr>
</tbody>
</table>

Registered 503B on FDA Site

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm
Overview of Presentation

• Status Check – 483s and 503Bs
• What is the USP?
  • Parts of the USP
  • Specific Interest for Pharmacists
• <797> and Potential Directions
  • Contamination Control
  • Potency and Stability
• Conclusions/Summary

USP 37–NF 32 (2014)

▲ Time-tested, international resource. USP standards are used in more than 130 countries
▲ More than 6,000 monographs
▲ Continuously updated—published annually in a main edition and two Supplements
▲ Available in English (print, online, CD) and Spanish (print)
USP’s Legal Recognition (FD&C Act)

- **SEC. 201.** For the purposes of this chapter -
  - (g)(1) The term "drug" means articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them
  - (j) The term "official compendium" means the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them.

USP’s Legal Recognition: FD&C Act Section 501(b) Adulteration

- A drug or device shall be deemed to be adulterated if it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium.
- Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium...
USP for Compounding Pharmacies

USP provides both general chapters and monographs for compounded preparations. Compounded preparation monographs may include

- Formulas (ingredients and quantities)
- Specific directions to correctly compound the particular preparation
- Packaging and storage information
- Labeling information
- pH
- Beyond-use dates (BUD) based on stability studies
- Detailed assays (majority of monographs)

Standards in USP–NF for compounded preparations may be enforced by both

- States - as pharmacy practice/compounding is traditionally regulated by state boards of pharmacy
- FDA - as compounded preparations remain subject to the adulteration and misbranding provisions of the FD&C Act which require conformance to certain USP–NF standards
USP-NF

USP–NF is a combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). Monographs for drug substances, dosage forms, and compounded preparations are featured in the USP. Monographs for dietary supplements and ingredients appear in a separate section of the USP. Excipient monographs are in the NF.

Parts of USP – 2014 (4 volumes)

Volume 1

• Front Matter
• General Notices
• General Chapters
  • Referee Chapters (<1000)
  • Informational Chapters (>1000)
  • Dietary Supplements Chapters (>2000)
• Reagents, Indicators and Solutions
• Reference Tables
Parts of USP – 2014 (4 volumes)

Volume 2
• USP Monographs A-I

Volume 3
• USP Monographs J-Z

Volume 4
• Dietary Supplements

USP General Notices
• Title and Revision
• Official Status and Legal Recognition
• Conformance to Standards
• Monographs and General Chapters
• Monograph Components
• Testing Practices and Procedures
• Test Results
• Terms and Definitions
• Prescribing and Dispensing
• Preservation, Packaging, Storage and Labeling
For Compounding Pharmacists

- Monographs
- USP Compounding - Specific Chapters
  - USP <795> Pharmaceutical Compounding – Nonsterile Preparations
  - USP <797> Pharmaceutical Compounding – Sterile Preparations
  - USP <1163> Quality Assurance in Pharmaceutical Compounding
- Others

From Front Matter of Volume 1: Guide to General Chapters
cGMP and Potential Revision of <797>

Global
- <795> Pharmaceutical Compounding—Nonsterile Preparations
- <797> Pharmaceutical Compounding—Sterile Preparations
- <823> Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses
- <1160> Pharmaceutical Calculations in Prescription Compounding
- <1163> Quality Assurance in Pharmaceutical Compounding
- <1231> Water for Pharmaceutical Purposes
- <1255> Written Prescription Drug Information—Guidelines

Description
- <1121> Nomenclature

Identification
- <11> USP Reference Standards
- <191> Identification Tests—General
- <197> Spectrophotometric Identification Tests
- <201> Thin-Layer Chromatographic Identification Test
- <521> Chromatography
- <726> Electrophoresis
- <736> Mass Spectrometry
- <761> Nuclear Magnetic Resonance
- <851> Spectrophotometry and Light-Scattering
- <1065> Ion Chromatography
- <1761> Applications of Nuclear Magnetic Resonance Spectroscopy
Overview of Presentation

• Status Check – 483s and 503Bs
• What is the USP?
  • Parts of the USP
  • Specific Interest for Pharmacists
• <797> and Potential Directions
  • Contamination Control
  • Potency and Stability
• Conclusions/Summary
### Summary GMP-GCP Comparison

<table>
<thead>
<tr>
<th>GMP Topic</th>
<th>21 CFR 211</th>
<th>USP &lt;795&gt;</th>
<th>USP &lt;797&gt;</th>
<th>USP &lt;1163&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buildings and Facilities</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Equipment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Personnel</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quality Assurance Unit</td>
<td>X</td>
<td>X (Under QC)</td>
<td>X (Under QA)</td>
<td>X</td>
</tr>
<tr>
<td>Raw Materials</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Control of Components</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Production/Compounding Controls</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Holding and Distribution</td>
<td>X</td>
<td>--</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Records</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Packaging &amp; Labeling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Stability</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>--</td>
</tr>
<tr>
<td>Complaints/Investigations</td>
<td>X</td>
<td>--</td>
<td>X (under Adverse Events)</td>
<td>--</td>
</tr>
<tr>
<td>QC Lab</td>
<td>X</td>
<td>--</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Subcontractor QA</td>
<td>X</td>
<td>--</td>
<td>--</td>
<td>X</td>
</tr>
</tbody>
</table>

### <797> Revision - Major Areas of Opportunity*

- **Clarity**
  - Too many comments and qualifications scattered about the chapter
  - Unclear organization – appendices may modify instruction in test
  - Generally too convoluted
- **Consistency**
  - <797> is inconsistent with other major chapters in USP
    - Contamination Control
    - Stability/Potency

* As seen by the speaker
USP <1115> Bioburden Control of Non-sterile Drug Substances and Products

Nonsterile Product Microbial Influences

- Facility Design & Maintenance
- Tools & Utensils
- In-process Materials
- In-process Monitoring
- Storage Conditions
- Influences From Adjacent Areas
- Seasonal Effects
- Process & Cleaning Water
- Facility Housekeeping & Sanitization
- Nonproduct Contact Equipment
- Validation
- Product & Material Flow
- Personnel Gowns & Hygiene
- Manufacturing & Filling Processes
- Active Pharmaceutical Ingredients
- Raw Materials
- Primary Packaging Components

In-Process Materials
- Equipment Design
- HVAC
- Personnel Practices & Training
- Equipment Cleaning & Maintenance
Environmental Sampling

This section could be greatly improved:

- Have a strong rationale for where, when and how to sample
- Use the program to establish the state of control of your pharmacy
- Trend the data for information

Water Monitoring:
- Bioburden, TOC, Conductivity

Personnel Monitoring:
- Fingertips, Forearms and Head

Environmental Monitoring:
- Surfaces
- Active Air Bioburden
- Passive Air Bioburden
- Non-viable Air

FDA - Trending

Trend reports should include data generated by location, shift, room, operator, or other parameters. The quality control unit should be responsible for producing specialized data reports (e.g., a search on a particular isolate over a year period) with the goal of investigating results beyond established levels and identifying any appropriate follow-up actions. Significant changes in microbial flora should be considered in the review of the ongoing environmental monitoring data.

Written procedures should define the system whereby the most responsible managers are regularly informed and updated on trends and investigations.

Raw Material and In-process

This area was all but ignored in the current version. Improvements in this discussion could include:

- Incoming chemical identity
- Incoming bioburden
- Incoming pyrogenicity (if relevant)
- In-process bioburden

Facility Concerns

Some topics that might be revised include:

- Conditions for smoke studies
- Maintenance and monitoring of air balance in aseptic suite
- Qualification and maintenance of equipment
Finished Product Testing

There are opportunities for improvements:
- Clarifying requirements for Sterility Testing
- Clarifying requirements for Bacterial Endotoxin Testing
- Clarifying potency testing expectations
Cleaning and Sanitization

Revisions might include enhanced discussions on:
• Qualify an effective cleaning agent to remove chemical residue
• Qualify an effective sanitizer for frequent antimicrobial treatments
• Qualify an effective sporicide for occasional use
• Prepare SOP on how and when to perform different cleaning/sanitization programs.

Procedures

• Additional expectations may be coming in terms of procedures to perform all of above, and to react to excursions
• Clarifying expectations for media fills and how they are intended to model different aseptic processes with interventions
Physical Barriers

- Some discussion of airlocks might appear in response to widespread use of lexan curtains and need for air balance (see also <800>)
- Gowning expectations may be clarified
  - Booties
  - Sterile suit
  - Sterile gloves
  - Sterile googles/mask
  - Sterile hood

Personnel Shedding – Particles per Minute by Activity

Important Consideration

First Air

Water System Maintenance

Additional instruction may be included on:
- Qualification and Maintenance
- Response to excursions in monitoring
- Sanitization and re-qualification
Contamination Control

<table>
<thead>
<tr>
<th>Control</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleaning</td>
<td>Water Monitoring</td>
</tr>
<tr>
<td>Sanitization</td>
<td>Air Monitoring</td>
</tr>
<tr>
<td>Equipment</td>
<td>Turbine Monitoring</td>
</tr>
<tr>
<td>Environmental</td>
<td>Pressure</td>
</tr>
<tr>
<td>Sanitation</td>
<td>Raw Material and Intermediate Monitoring</td>
</tr>
<tr>
<td>Water</td>
<td>Finished Product Testing</td>
</tr>
</tbody>
</table>

FDA 483 Observations

Based on 126 483 reports posted on the FDA web site
Stability and Potency

• Need to control for potency upon release and upon stability
• Revision may include discussion in response to market issues and recent findings.
  • FDA 2006 survey found common potency issues in compounded medications
  • 483 review found little or no support for BUD


Overview of Presentation

• Status Check – 483s and 503Bs
• What is the USP?
  • Parts of the USP
  • Specific Interest for Pharmacists
• <797> and Potential Directions
  • Contamination Control
  • Potency and Stability
• Conclusions/Summary
Conclusions/Summary

• Regulatory landscape for compounding pharmacies is changing
• 503B situation is in flux
• USP provides a wealth of information on best practices
• USP <797> may not be consistent with other USP chapters
• Changes may be coming in USP
  • Contamination Control
  • BUD/Potency

THANK YOU FOR YOUR ATTENTION

QUESTIONS?

Scott Sutton, Ph.D.
scott.sutton@microbiologynetwork.com
+1 585-298-0767 (cell)
http://www.Rx-GCP.com