Applying United States Pharmacopeia (USP) Chapter <797> Standards to Procurement Strategies for Coping with Drug Shortages
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Top 4 Things to Know for CE
1. Make sure your BADGE IS SCANNED each time you enter a session to record your attendance.
2. Carry your Evaluation Packet with you to EVERY session.
3. Pharmacists, Pharmacy Technicians and Nurses need to track their hours on the Statement of Continuing Education Form as they go (the 2-page triplicate form, so press firmly!).
4. FOR CE: At your last session, total the hours and sign both pages of your Statement of Continuing Education Form.
   ✓ Keep the PINK copy for your records and place the YELLOW and WHITE copies in your CE Envelope.
   ✓ Make sure an Evaluation Form is in your CE Envelope for each session you attended (extra forms are available at the registration desk if you forgot to pick one up).
   ✓ Write your name and unique ID number (six digit number at the bottom of your name badge) in the designated area on the outside of the envelope, seal it, and place it in the drop box located near the registration area.

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• Lou Diorio, RPh, is Principal of LDT Health Solutions. The conflict of interest was resolved by peer review of slide content.

• Clinical trials and off-label/investigational uses will not be discussed during this presentation.
Objectives

- Summarize the USP General Chapter <797> requirements for the determination of compounding RISK Levels in CSP compounding.
- Outline products and services which can assist compounding operations in compliance with current chapter requirements and other applicable regulation.
- Describe the multi-factorial considerations when contemplating a contract with an Outsourcing Compounder for CSPs.
- Outline the development of a proper and complete request-for-proposal (RFP) document for Outsourcing Services.

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The Objective of USP <797>...

- “...is to describe conditions and practices to prevent harm, including death, to patients...”

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Enforceability

- “The standards in this chapter are intended to apply to all persons who prepare CSPs and all places where CSPs are prepared (e.g., hospitals and other healthcare institutions, patient treatment clinics, pharmacies, physician’s practice facilities, and other locations in which CSPs are prepared, stored, and transported).”
USP General Chapter <797>

• Is about three things...
  – CONTROL !
    – CONTROL !
    – CONTROL !

• Control of the compounding environment
• Control of the compounding personnel
• Control of the compounding processes

Quality Process

• Personnel
  – Capable and qualified to perform assigned duties

• Ingredients
  – Meet standards for identity, quality, and purity

• Critical processes
  – Validated, carried out as intended, under control

• Engineering controls and production environment
  – Suitable for intended purpose
  – Environmental cleanliness, control, monitoring, staff attire, and the setting of action limits, are appropriate

Quality Process

• Stability evaluation & testing procedures
  – Establishing reliable Beyond-use dating to ensure that finished CSPs have the expected potency, purity, quality, and characteristics at least until the labeled BUD

• Appropriate release checks
  – To assure that finished CSPs have their expected characteristics through their labeled BUD

• Preparation conditions and procedures
  – Adequate for preventing (and detecting potential) mix-ups

• Procedures and documentation for investigating and correcting failures or problems
  – In preparation, testing, or in the CSP itself
Quality Process

- **Process Control**
  - There is assurance that processes are always carried out as intended & under control.

- **In the final review, should always think in terms of...**
  - Trace-ability
  - Track-ability
  - Recall-ability

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Risk Levels of USP <797>

Are you sure how to properly categorize any CSP?
Can you verify the method(s) used to produce any outsourced or contract compounded CSPs?

- **Low Risk**
  - "Simple" single dose compounding
  - RTU, Pre-mixed, or UOU Commercial Doses

- **Medium Risk**
  - Using multiple sterile components (batch compounding)

- **High Risk**
  - Beginning from non-sterile components

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Why Three Risk Levels?

- Because different sterile preparations represent different degrees of risk (microbial contamination)
- Because pharmacists and others have not always recognized that there are differences in risk among compounded preparations
- Because patient safety requires a change in our compounding methods!
Self-Assessment Tools (SAT) or GAP Analysis

- Use a SAT or GAP Analysis to identify organizational points of compliance and operational gaps
  - High level situational analysis of current state of readiness
- SAT or GAP Analysis will serve as a placeholder for regulatory and accreditation agencies
  - It is only a starting point!
  - But the best place to start is at the beginning!

Reasons for Disruptions in Drug Product Production & Supply

<table>
<thead>
<tr>
<th>Problem</th>
<th>2010-2011</th>
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<tbody>
<tr>
<td>Problems at manufacturing facility</td>
<td>43%</td>
</tr>
<tr>
<td>API Shortage</td>
<td>8%</td>
</tr>
<tr>
<td>Product discontinuation</td>
<td>3%</td>
</tr>
<tr>
<td>Delays in manufacturing or shipping</td>
<td>10%</td>
</tr>
<tr>
<td>Demand Increase</td>
<td>8%</td>
</tr>
<tr>
<td>Improper labeling</td>
<td>2%</td>
</tr>
</tbody>
</table>

* A review of FDA's Approach to Medical Product Shortages (10.31.11)

Can Your Pharmacy Compound HIGH RISK CSPs?

- Key differences between Medium and High Risk:
  - Physical plant
  - Personnel training
  - Personnel media qualification
  - Strict storage periods for High Risk CSPs in the absence of a sterility test [24 hrs RT / 3 d Cold]
  - Specific preparation guidance for all measuring, mixing, and purifying equipment
  - Specific guidance for filtration of these CSPs [0.45 um then 0.22 um porosity]
**HIGH Risk CSPs**

- The sterilization method SHALL be verified to achieve sterility for the quantity and type of containers
- SHALL meet allowable limits for bacterial endotoxins
- SHALL maintain acceptable strength and purity of ingredients and integrity of containers after sterilization
- Compounding personnel SHALL successfully pass media-fill tests at least semi-annually

*Appendix I – USP <797> Pharmaceutical Compounding - Sterile Preparations © USP
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**At the Cross-roads?**

- Can I safely compound from...
  - Non-sterile powders?
  - Bulk ingredients?
  - Active Pharmaceutical Ingredients (API)?
- What impact will that have on my service model?
- What does a fully compliant HIGH RISK compounding program look like?
- Do I have other options to service my patients?

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**Key Attributes of an Outsourcing Partner**

- **Solid “Controlled Processes”:**
  - Clear verification of the components and APIs
  - USP <71> compliant sterility testing on every batch!
  - Potency testing
  - Endotoxin testing
  - A clear policy around the determinations of BUDs
  - A clear Quarantine and Release P&P
  - Shipping and storage controls
  - Clear package labeling

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USP <71> - Sterility Tests

- Compliant sterility testing must:
  - Be a significant sample size
  - Be done by membrane filtration
  - Conducted at two temperatures (7 days at each)
  - Be testing for aerobic, anaerobic bacteria, and fungi
  - “Rapid testing” is allowable but not yet widely available

Other Testing & Documents

- USP <61> Microbial Limits Tests
- USP <85> Bacterial Endotoxins Test
- USP <788> Particulate Matter in Injections
- USP <791> pH
- Filter Integrity Tests (“bubble point testing”)
- Certificate of Analysis (“C-of-A”) for any API

Are All Outsourcing Compounders Created Equal?

- The short answer is NO!
- Because of the complexity involved in selecting a suitable outsourcing provider or providers, careful consideration in the following areas must be weighed:
  - A clear description of the provider’s exact license status
  - Cleaning and sanitation processes
  - Environmental monitoring program
  - Sterility testing program
  - Labeling standards
  - Recall processes
  - Quality Assurance program
  - Documentation standards
- Develop a formal RFP document to keep you focused
- Conduct announced and unannounced site visits
- Perform a comprehensive contract review
- Remember all providers are not created equal!
Assessing Outsourcing Compounders

• Resources
  – Screening tools are available, but will require some editing
  – Be sure the RFP developed is specific to your practice model
  – Assistance of a Qualified Consultant may help
  – Independent reviews and compounding verification reports may be available for the larger national or regional compounders

Can you start with an “Off-the-Rack” Screening Tool?

• Do you know the “origin” of the tool?
  • Beware of “weighted” scores!
  • Does it make sense for your service model?
Key Questions to Help Build Your RFP

• Does the provider clearly document their source component pedigrees?
• Can you review their BUD & Stability data?
• Can the provider show a certificate of analysis for all USP grade bulk ingredients in use?
• Has the provider disclosed any regulatory, disciplinary or punitive action by any agency in the past 36 months?
• What documentation & reports are available to confirm the provider’s procedures and CSPs

Key Questions to Help Build Your RFP

• What information is contained within the provider’s CSP bar-coding?
• What routine testing is in place to verify...
  – Personnel Media Qualifications?
  – Compounding Processes Validation?
• Are you notified regarding process or product changes BEFORE they occur?
• How are we notified in case of a problem or recall?

Common Pitfalls to Avoid

• Do not assume an “FDA registered” Compounder is a “Manufacturer”
• Use of a contract compounder or outsourcing provider does not release you of your responsibilities under USP <797> or BOP regulation
• Verify your local BOP regulations regarding contract compounders
• Verify the stability, BUD, and other quality data provided yourself
In closing...

“Trust, but verify”
— Ronald Reagan, (Our 40th President)

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Learning Assessment Questions & Answers
Please refer to the NHIA Annual Conference & Exposition 2012 On-Site Program for a brief post-test.

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