Coping with the Changing Compounding Landscape

Compounding Constantly Changes!

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Remington-The Science and Practice of Pharmacy
Disclosures

Loyd V. Allen, Jr. declare(s) no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

The American College of Apothecaries is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

At the conclusion of this program, the participating pharmacist or technician will be able to discuss:

• Discuss the laws, regulations, standards and compliance policy guidelines (CPGs) affecting pharmaceutical compounding
• Describe how the impact on compounding pharmacies in today’s compounding environment
• Identify how changes are made and who can bring about changes in the laws, regulations, standards and CPGs
Coping with the Changing Compounding Landscape

Questions

• What agencies can enforce laws/regulations/guidances/standards on compounders?

• Which of the following basically does not all actually affect all compounders?

• What factors have resulted in attention being directed towards compounding?
Science-Based and Reasonable?

- Opinions
- Hidden motives
- Facts
- Science-based
- Limitations
- Unintended consequences
Coping with the Changing Compounding Landscape

• **INTRODUCTION AND HISTORY**
  • Basic introduction
  • Quality-based Compounding
  • Challenges
  • Factors causing change (Adverse events, Perceived needs, etc)

• **LAWS, REGULATIONS, STANDARDS AND COMPLIANCE POLICY GUIDELINES (CPGs)**
  • Laws
    • Federal
    • State
  • Regulations
  • Standards
  • Compliance Policy Guidelines

• **RESPONSES TO LAWS, REGULATIONS, STANDARDS AND CPGs**

• **CHANGING THE LAWS, REGULATIONS, STANDARDS AND CPGs**
Introduction and History

• We are in an era of increased emphasis and requirements on quality and documentation of compounded formulations.

• With every new law, regulation, standard and CPG that comes, changes must be made to remain compliant with authorities and balance that with financial considerations and patient care activities.
# Brief History of Compounding

<table>
<thead>
<tr>
<th>TIME</th>
<th>EVENTS</th>
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</thead>
<tbody>
<tr>
<td><strong>limited testing up to 2000</strong></td>
<td></td>
</tr>
<tr>
<td>1940s-1960s</td>
<td>Moderate compounding but declining</td>
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<tr>
<td></td>
<td>Growth of pharmaceutical industry</td>
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<tr>
<td></td>
<td>Taught in colleges of pharmacy</td>
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<tr>
<td>1970s-1980s</td>
<td>Late 70’s, compounding growing</td>
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<tr>
<td></td>
<td>Not taught as much-curriculum revision for PharmD program</td>
</tr>
<tr>
<td>1995 USP</td>
<td>USP Advisory Panel on Pharmacy Compounding</td>
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<tr>
<td>1990s-2000</td>
<td>USP Pharmacy Compounding Expert Committee</td>
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<td>USP 795 (Developed/2000-2005)</td>
</tr>
<tr>
<td>1997</td>
<td>FDAMA 97</td>
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</table>
# Brief History of Compounding

**BASIC TESTING STARTED 2000-2010**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>2002</td>
<td>USP &lt;795&gt; becomes official</td>
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<td></td>
<td>US Supreme Court decision supporting compounding</td>
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<tr>
<td>2000-2005</td>
<td>Expert Committee on Parenteral Products-Compounding and Preparation</td>
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<tr>
<td></td>
<td>Two USP committees (Nonsterile and Sterile)</td>
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<tr>
<td>2004</td>
<td>USP &lt;797&gt; (Official)</td>
</tr>
</tbody>
</table>
## Brief History of Compounding

### INCREASED TESTING 2010 - Current

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Description</th>
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<tbody>
<tr>
<td>2010 on</td>
<td>Both Expert Committees joined as one Expert Committee</td>
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<tr>
<td>2012</td>
<td>NECC</td>
</tr>
<tr>
<td>2013</td>
<td>DQSA</td>
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<tr>
<td>2015-2016</td>
<td>FDA Inspections</td>
</tr>
<tr>
<td>2017</td>
<td>Pharmakon Indicted &lt;br&gt;USP &lt;800&gt; Introduced to become effective July 1, 2018.</td>
</tr>
</tbody>
</table>

### ROUTINE AND MANDATED TESTING

- All will probably increase
INTRODUCTION AND HISTORY
 Basic introduction
 Quality-based Compounding
 Challenges
 Factors causing change (Adverse events, Perceived needs, etc)

LAWS, REGULATIONS, STANDARDS AND COMPLIANCE POLICY GUIDELINES (CPGs)

Laws
 Federal
 State
 Regulations
 Standards
 Compliance Policy Guidelines

RESPONSES TO LAWS, REGULATIONS, STANDARDS AND CPGs
CHANGING THE LAWS, REGULATIONS, STANDARDS AND CPGs
Federal Level

Federal Laws
- FDA Modernization Act of 1997
- Drug Quality and Security Act of 2013

Federal Regulations
- FDA Interpretations of DQSA

Compliance Policy Guidelines
- FDA Interpretations/Implementation of DQSA
State

Laws
Legislature, etc.

Regulations
State Boards

Standards
State Boards
Either adopt or write their own
Control is a major issue
Regulations and Standards

- More applicable at local level
- Protect patient
- Protect patient access
- Responsible for enforcement
- Minimize unintended consequences
- More easily modify what is not working
- Recourse?
State Board Examples

+ Must use all ingredients from supplier of Master Formula (MF) in order to utilize supplier-provided BUD.

+ May not substitute a monographed API from a different supplier as this would “invalidate” the MF BUD.
State Board  Examples

Any mfg-supplied MF and BUD must account for ALL variables, not just container-closure.

Temperature and humidity at time of preparation.

Temperature and humidity of finished preparation storage.
State Board  Examples

ALL equipment used must be same or validated that it will not affect mfg BUD.

Supplier BUD must identify container used for dispensing and only those may be used in order to use the BUD provided by the supplier.
Discussion

- USP monograph requirements
- USP container-closure requirements
- Science-based and reasonable?
USP Legal Authority

USP develops and publishes standards for:

- drug substances,
- drug products,
- excipients, and
- dietary supplements

USP Monograph Requirements

Monographs set forth the article’s name, definition, specification, and other requirements related to packaging, storage and labeling.

The specification consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality and purity of the article.
USP Container-Closure Requirements

- USP <659> Packaging and Storage Requirements (Official May 1, 2016)
Comments on Container-Closures

• Packaging must not interact physically or chemically with official articles in any way that causes their safety, identity, strength, or purity to fail to conform to requirements.

• Packaging (container-closure system) must maintain the contents in conformance to requirements, i.e., the specifications in the official monographs.

• The container-closure is useful only during the time period during which the contents are enclosed.
Comments on Container-Closures

• Once removed, the contents are manufactured, compounded, repackaged, etc. and a new container-closure is involved with identical requirements of protecting its contents until use.

• The container-closure system is "neutral" in its relationship with its contents; it does not interact with the contents.

• Containers used in dispensing/compounding must meet the same requirements further detailed in USP <671> Containers-Performance Testing.

• Moving the drug product or ingredient from one appropriate container-closure system to another should have no effect on the requirement that the contents meet specifications.
Comments on Container-Closures

• Stability studies establishing beyond-use dates for compounded preparations must use **stability-indicating analytical methods** that will detect any change in intact drug that may occur regardless of cause, including any interaction with the container-closure system. The container-closure systems used in stability studies supporting beyond-use dating must be described in the studies. The container-closure systems used for the studies must meet USP <659> requirements.

• The **requirements/standards** for container-closure systems used in studies and for dispensing to the patient are the same, i.e., maintain the contents in conformance to the specifications in the monographs.

• In summary, the container-closure system is nonreactive and protective. A drug product is generally involved in two or more container-closure systems during its manufacturing, compounding, distribution and dispensing.
Issues

• Sterilizing Filters for Human Use Issue

• Compliance Policy Guidelines
Basis for Regulations

- Science
- Facts
- Opinions
- Private interest
Responses to Laws, Regulations, Standards and CPGs

INTRODUCTION AND HISTORY
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LAWS, REGULATIONS, STANDARDS AND COMPLIANCE POLICY GUIDELINES (CPGs)
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RESPONSES TO LAWS, REGULATIONS, STANDARDS AND CPGs
CHANGING THE LAWS, REGULATIONS, STANDARDS AND CPGs
Responses to Laws, Regulations, Standards and CPGs

• EVALUATE—ARE THEY
  – Reasonable?
  – Achievable?
  – Science-based?

• EVALUATE--DO THEY
  – Protect patient and personnel?
  – Maintain public access to their medications?
# Use of Testing Methods

<table>
<thead>
<tr>
<th>Bulk Substances and Dosage Forms</th>
<th>TESTING METHODS—Up to 2000</th>
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<td>----------------------------------</td>
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<td>Bulk substances</td>
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<td>Capsules</td>
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*Note: Wt, Vol, pH, Osm, RI, Sp Gr, MP, UV/Vis, HPLC, GC, IR, Sterile, Endotoxin, PM*
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CHANGING THE LAWS, REGULATIONS, STANDARDS AND CPGs
Responses to Laws, Regulations, Standards and CPGs

Work with elected federal congressional members
Work with state officials
Work with state boards of pharmacy
You can impact the landscape of pharmaceutical compounding!
Coping with the Changing Compounding Landscape

What agencies can enforce laws/regulations/guidances/standards on compounders?
I. State Boards of Pharmacy
II. FDA
III. USP

A. I only
B. III only
C. I and II only
D. II and III only
E. I, II and III
Coping with the Changing Compounding Landscape

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Which of the following basically does not actually affect all compounders?

A. USP <795>
B. USP <797>
C. USP <800>
D. DQSA
E. NIOSH
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B. **USP <797>**
C. USP <800>
D. DQSA
E. NIOSH
Coping with the Changing Compounding Landscape

What factors have resulted in attention being directed towards compounding?

A. NECC
B. Doc’s Pharmacy – Walnut Creek, CA
C. Franck’s Pharmacy – Ocala, FL
D. KCL Injection errors in hospitals
E. All the above
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Science-Based and Reasonable?

Fact vs Opinion
Documentation
Unintended Consequences
Need More Information?

Loyd V. Allen, Jr., Ph.D., R.Ph.
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www.CompoundingToday.com