Quality in Compounding: QA/QC/CQI with USP and Practical Applications

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Agenda

• Standards and Regulations

• Quality Definitions/Examples
  – Quality Control (QC)
  – Quality Assurance (QA)
  – Continuous Quality Improvement (CQI)
    ▪ Written plan for Integrity, Potency, Quality, Strength
    ▪ Verify, Monitor, Review
    ▪ Process to deal with OOS

• Practical Applications

• Resources
California

Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the

- Integrity
- Potency
- Quality
- Labeled strength of compounded drug products
Standards and Regulations

Texas Regulations

**TITLE 22: PART 15: CHAPTER 291: SUBCHAPTER G:**

Rule §291.131: Pharmacies Compounding Non-Sterile Preparations

Rule §291.133: Pharmacies Compounding Sterile Preparations

North Carolina Regulations

State Specific Regs – Pharmacy Rules

21 NCAC 46 .1810 Compounding

21 NCAC 46 .2808 Quality Assurance
There shall be a documented, ongoing quality assurance program that monitors personnel performance, equipment and facilities. Appropriate samples of finished products shall be examined with such frequency as will assure the pharmacy is capable of consistently preparing sterile products meeting specifications.
Standards and Regulations

USP – general chapters, not regulations
  • Chapters <1000 may be enforced by State Boards or other Regulatory Body
  • Chapters >1000 are Informational

USP <795> Non-Sterile
USP <797> Sterile

PCAB Standards effective December 2010 - standards for PCAB accreditation
  • Standards 6 – Beyond Use Dating, Potency and Sterility
  • Standards 9 – Total Quality Management
## PCAB Compliance Indicators

<table>
<thead>
<tr>
<th>Std 6.10 Beyond Use Date</th>
<th>Standard 6.2 Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SOPs provide determination and assignment of BUD for all compounded preparations</td>
<td>• SOPs satisfy current USP standards for potency and microbiological integrity</td>
</tr>
<tr>
<td>• Demonstrates by inspection the use of BUD</td>
<td>• Provides documentation that it complies with state and federal Regulations regarding strength, quality, purity, potency and stability throughout intended period of use.</td>
</tr>
<tr>
<td>• Documents <em>rationale used</em> to establish BUD which <em>exceeds USP standards</em> based upon pharmacists professional judgment</td>
<td></td>
</tr>
</tbody>
</table>

*Reference: PCAB Standard 6 BUD, Potency and Sterility*
What is Stability?

Definition

The extent to which a preparation *retains*, within specified limits, and *throughout* its period of *storage* and use, the *same properties* and characteristics that it possessed at the time of compounding.
# BUD Terminology

## Expiration Date
- Applied to **manufactured products**
- Determined by multiple scientifically valid, product/package-specific research studies
- Very **strict, specific**, and proven to be valid
- Typically used terminology among manufacturers

## Beyond-Use Date
- Assigned by **compounding personnel**
- May deviate from the official labeling
- Should be **based** on drug-specific, **scientifically valid** research studies when possible
- May use general guidelines when specific information is unavailable
- Compounders typically use BUD terminology
## 5 Types of Stability

### Criteria for Acceptable Levels of Stability

<table>
<thead>
<tr>
<th>Type of Stability</th>
<th>Conditions Maintained Throughout the Shelf Life of the Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical</td>
<td>Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.</td>
</tr>
<tr>
<td>Physical</td>
<td>The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.</td>
</tr>
<tr>
<td>Microbiological</td>
<td>Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>The therapeutic effect remains unchanged.</td>
</tr>
<tr>
<td>Toxicological</td>
<td>No significant increase in toxicity occurs.</td>
</tr>
</tbody>
</table>
Factors to Consider in determining BUD’s

- Nature of Drug and its Degradation Mechanisms
- Dosage Form and its components
- Potential for microbial growth in preparation
- Container in which it’s packaged
- Expected storage conditions
- Intended duration of therapy
Role of Stability Testing
Verification of Formulation and Compounding process

Chemical and Physical Properties of the API

Process Validation

Compounding Process

Compounded Preparation

Packaging Selection

Packaged Preparation

Interaction with packaging materials

API

Excipients

Excipient compatibility
# PCAB Compliance Indicators

## Standard 9.1: QA
- Written QA plan that **verifies, monitors and reviews** the compounding process
- How deviations were investigated, evaluated, corrected and documented
- QA plan provides that any product failing QC standards will be rejected

## Standard 9.2: QC
- SOPs and designated personnel for QC activities
- QC plan must demonstrate how compounded preps meet USP standards for strength, quality, purity, integrity and sterility and bacterial endotoxin when applicable.

*Reference: PCAB Standard 9*
PCAB QA Activities

- QA activities assure that compounded preparations meet criteria for –
  - Identity
  - Strength
  - Quality
  - Purity,

  and, where appropriate,

  - Sterility and bacterial endotoxin limit.
### Comparison

<table>
<thead>
<tr>
<th>USP*</th>
<th>State Regs</th>
<th>PCAB^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>Strength</td>
<td>Strength</td>
</tr>
<tr>
<td>Quality</td>
<td>Quality</td>
<td>Quality</td>
</tr>
<tr>
<td>Purity</td>
<td>Purity</td>
<td>Purity</td>
</tr>
<tr>
<td></td>
<td>Identity</td>
<td>Identity</td>
</tr>
</tbody>
</table>

* As required USP <797>

^Reference: PCAB Standard 9.1
Definition Regs – QA

1) Integrity - retention of potency until the expiration date noted on the label.

2) Potency – active ingredient strength within +/- 10% of the labeled amount.

3) Quality – absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, and absence of active ingredients other than those noted on the label.

4) Strength – amount of active ingredient per unit of a compounded drug product.
American Society for Quality

CQI

Quality Assurance

Quality Control

An ongoing effort to improve products, services or processes. These efforts can seek 'incremental' improvement over time or 'breakthrough' improvement all at once

The planned and systematic activities implemented in a quality system so that quality requirements for a product or service are fulfilled

The observation techniques and activities used to fulfill requirements for quality
Quality Control Example:

Pharmacy A documents the failure information, average and standard deviation results. The pharmacy destroys all samples that fail the potency testing and maintain documentation of the quality related incidents.

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<thead>
<tr>
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<th>Estriol</th>
<th>Progesterone</th>
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</thead>
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<tr>
<td>No. of Failures</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>% Failure</td>
<td>25</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Average</td>
<td>0.50</td>
<td>1.92</td>
<td>51.71</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.05</td>
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<tr>
<td>Std Dev %</td>
<td>9.3</td>
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Quality Assurance Example:

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CQI Example:

- Estradiol: Root cause analysis on estradiol resulted in a procedure change to use a more accurate measurement device.
- Estriol: Technician B consistently produced preparations near the lower limit.
- Progesterone: Identified a calibration issue causing a drift in the results upward, corrected the problem before failure.
Continuous Quality Improvement

Utilize the output of the Quality Assurance Plan to continuously improve:

• Compounded preparations
  – Process
  – Procedure
  – Personnel
• Customer Service
• Response Time
• Packaging
• Patient/Pharmacist Consultation
Quality Monitoring

- Routine testing to show the process is in control
  - Process
  - Procedures
  - Personnel
- Changes in any of the 3P’s
  - Re-verification process
- A testing program is just one part of a QA program. Verify licensure, documented training program, etc. are also part of a quality assurance program

*Reference: PCAB Standard 9.1*
## Process Verification

<table>
<thead>
<tr>
<th>Two Approaches</th>
<th>Verification Criteria</th>
<th>Verification Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Individual formulations</td>
<td>- Strength</td>
<td>- Quality Assessment Tools</td>
</tr>
<tr>
<td>- Dosage form processes</td>
<td>- Quality</td>
<td>- Outside Verification (Testing)</td>
</tr>
<tr>
<td></td>
<td>- Purity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Sterility*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Endotoxin*</td>
<td></td>
</tr>
</tbody>
</table>

*Note: * indicates critical parameters.
Individual Formulations
Testing Strategy

Each pharmacy needs a reasonable program that is appropriate for its own pharmacy and the justification is well-documented.

To determine testing frequency consider:

• Volume of Rx’s,
• New Formula or dosage Form
• Risk (potent) and complexity of compounds
• Personnel Change – Pharmacist, Technician, Etc.
• Process Change
Recommend Approach by Dosage Form

- Capsules
- Ointments, Creams, Gels
- Oral and Topical Liquids
- Suppositories, Troches, Lollipops and Sticks
- Sterile Preparations
Quality Monitoring Program

Examples

What Type?

Sterile

High Risk

*Batch >25 units: Sterility/Endo
Recommended: Potency

Med/Low Risk

*Extend Beyond Use Dating: Sterility
Recommend: Potency Testing
  • Every 100th Rx
  • Every 10-25 Batches
  • >100 units/batch

Top Cmpds By Volume

Recommend: Potency of top 10 cmpds
  • 5 tested each even month
  • 5 tested each odd month

Track Rx Volume

Recommend: Potency every 100th Rx

Non-Sterile

*Required Testing by USP <797>
# Non-Sterile Dosage Forms

<table>
<thead>
<tr>
<th>Type</th>
<th>Quality Assessment Tools</th>
<th>Outside Verification</th>
</tr>
</thead>
</table>
| Capsules                                  | • Appearance  
• Weight Variation                                 | • Content Uniformity  
• Potency Testing on All Actives  
• Microbial Testing |
| Topical Preparations                      | • Globule Size Range  
• Appearance  
• Rheological Properties  
• Physical Stability | • Potency Testing  
• Microbial Testing |
| Suppositories, Troches, Lozenges, Lollipops| • Weight and Weight Variation  
• Specific Gravity  
• Color of preparation  
• Clarity (visual)  
• Texture-Surface  
• Appearance, Feel  
• Melting Test (oil-based preps) | • Content Uniformity  
• Potency Testing  
• Microbial Testing |
| Oral Solutions and Suspensions            | • Physical Observation  
• Weight / Volume  
• pH, Specific Gravity  
• Color of Solution | • Potency Testing  
• Microbial Testing |
Common Compounds Out of Specification

- T3/T4
- Fentanyl & Sufentanil
  - With other actives
- BiEst
- TriMix
- Budesonide
- Drugs with multiple salt forms
- Hydroscopic drugs, i.e. betamethasone
Case Study #1: Non-Sterile Preparations

**Type:**
- Capsules
- Creams, Gels, Ointments
- Oral & Topical Liquids
- Troches, Suppositories, Lollipops, & Sticks

**Volume : 50 Rx/day**
- 25 Rx for Capsules (mainly BHRT)
- 15 Rx for Creams, Gels, Ointments
- 5 Rx for Oral & Topical Liquids
- 5 Rx for Troches, Suppositories, Lollipops, & Sticks
Case Study #1: Non-Sterile (cont)

Initial Verification Procedures:
Developed SOP that details the process for verification of each formula/procedure with the following information:

- Purpose, scope, documentation of the specific formula and procedures to be verified, responsible person, tests to be performed on each dosage form, re-verification criteria, data storage, pass/fail limits, how/where to document the testing results.

Verification Testing:
- Each pharmacist and technician prepares each formula and competency is determined based on analysis of the formulation.
Case Study #1: Non-Sterile (cont)

To evaluate how many potency tests they will send over the course of a year based on testing every 50th batch of each dosage form, they took the following approach:

**Dosage Form:**

- **Capsules:** $10/day \times 5 \text{ day} \times 4 \text{ weeks} \times 12 \text{ months} = 2,400/\text{yr}$

- **Creams, Gels, Ointments:** $5/day \times 5 \times 4 \times 12 = 1,200/\text{yr}$

- **Oral & Topical Liquids:** $3/day \times 5 \times 4 \times 12 = 720/\text{yr}$

- **Troches/Suppositories/ Lollipops/Sticks:** $2/day \times 5 \times 4 \times 12 = 480/\text{yr}$

**Total:** $4,800/\text{yr}$

Testing every 50th batch = 96 batches per yr

Average 2 active ingredients/formula = 192 potency tests /yr

Each batch of T3 & T4 Triturates = 12 to 15 /yr
## Case Study #1: Non-Sterile (cont)

<table>
<thead>
<tr>
<th>Stages</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process Validation</strong></td>
<td>Every dosage form with each pharmacist/technician tested once/year</td>
</tr>
<tr>
<td></td>
<td>Potency determination</td>
</tr>
<tr>
<td><strong>Process Monitoring</strong></td>
<td>Every 50\textsuperscript{th} batch of each dosage form</td>
</tr>
<tr>
<td></td>
<td>• Average 2 ingredients/formulation</td>
</tr>
<tr>
<td></td>
<td>96 batches/yr</td>
</tr>
<tr>
<td></td>
<td>192 potency tests/yr</td>
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<tr>
<td></td>
<td>Every batch of T3 and T4 Triturates</td>
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<td></td>
<td>12-15 potency tests/year</td>
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</tbody>
</table>
## Sterile Dosage Forms

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Quality Assessment Tools</th>
<th>Outside Verification</th>
</tr>
</thead>
</table>
| Solutions and Suspensions for Injection | • Appearance  
• pH Testing                       | • Potency Testing of All Actives  
• Sterility Testing  
• Endotoxin Testing  
• Particulate Matter Testing for Solutions |
| Solutions for Inhalation             | • Appearance  
• pH Testing                       | • Potency Testing of All Actives  
• Sterility Testing                  |
| Solutions for Ophthalmic Use         | • Appearance  
• pH Testing  
• Osmolarity (Isotonicity)          | • Potency Testing of All Actives  
• Sterility Testing  
• Endotoxin Testing                  |

Reference: IJPC Vol 12 No. 3
Case Study #2: Sterile Preparations

**Type:**
- Intrathecal medications
- Sterile injectable hormones and erectile dysfunction preps.

**Volume:**
- 120 preparations/day
<table>
<thead>
<tr>
<th>Stages</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Validation</td>
<td>All batched sterile preparations</td>
</tr>
<tr>
<td></td>
<td>Sterility, endotoxin, concentration</td>
</tr>
<tr>
<td></td>
<td>All stock (bulk) sterile solutions</td>
</tr>
<tr>
<td></td>
<td>Sterility, endotoxin, and concentration</td>
</tr>
<tr>
<td></td>
<td>Media fill testing</td>
</tr>
<tr>
<td></td>
<td>Every month on all staff</td>
</tr>
<tr>
<td>Process Monitoring</td>
<td>Random monthly samples by technician</td>
</tr>
<tr>
<td></td>
<td>Sterility, endotoxin, and concentration</td>
</tr>
</tbody>
</table>
Case Study #2: Sterile (cont)

Continuous Quality Improvement

- All the data generated by the above testing is tracked and trended.
- This allows pharmacists to view all the information in a way that can determine if a change in process or increase training need to occur.

Quality Related Events

- Any failures are documented and the preparations in question are quarantined or destroyed.
- CAPA process is well documented and work to find the root cause so that it can be corrected if possible.
CQI Example

**Define**
- Define preparations
- Measure results
- Track and trend data

**Measure**

**Analyze**
- Trends
- Variability
- Not just OOS

**Improve**
- Identify root cause
- Implement solution
- Incorporate into policy and procedures

**Control**
- Verify solution
- Track results
- Control process
Analysis Tools

Identify Areas for Improvement

• OOS
• Variability: High
• Trend data: Increasing, decreasing, or changes
• Statistical analysis: T-test to compare variables
• Average and Standard Deviation by process
Analysis Tools

Identify Potential Variables

• Raw materials
• Container
• Concentration
• Mixing technique/equipment
• Measurement tools
• Temperature/humidity
• Technician
BiEst and Progesterone Data

<table>
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Results of Improvement Plan

<table>
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<td>Failures</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>% Failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Average</td>
<td>0.50</td>
<td>2.02</td>
<td>50.1</td>
</tr>
<tr>
<td>Std Dev</td>
<td>0.01</td>
<td>0.03</td>
<td>0.69</td>
</tr>
<tr>
<td>Std Dev %</td>
<td>2.9</td>
<td>1.6</td>
<td>1.4</td>
</tr>
</tbody>
</table>
## Analyze and Improve

### Root Cause
- Estradiol: Measurement device not precise for low concentrations
- Estriol: Technician B consistently inaccurate
- Progesterone: Instrument calibration problem

### Improvement Plan
- Estradiol: Changed to a more accurate measurement device
- Estriol: Technician B was retrained
- Progesterone: Instrument was recalibrated and routine calibration check added to procedures
A QA program for compounded preparations should include testing during the process and of the finished preparation, when appropriate, as described in <795> and <797>.

Some testing methods can easily be performed at the compounding site, but some may need to be outsourced to a contract laboratory.

Some testing methods can be conducted in-house by an individual who possesses a good understanding of pharmaceutical analysis and proper training. See *USP* chapters for reference.  * USP <1163>
The goal in testing is to determine accurately the adequacy of the compounding process and the quality of the preparation.

Any testing procedure used should have accuracy, reproducibility, and specificity.

No single testing procedure is suitable for all drugs or preparations because a number of factors determine the validity and reliability of results.
Testing

• Acceptance criteria shall be determined prior to testing.

• Testing every compounded preparation is neither practical nor officially required, but compounders should conduct visual inspections and know
  – The importance in the overall quality program
  – When and What to test and how to interpret the results
  – Appropriate method(s) and equipment to use
  – Specific actions required when a preparation does not meet specifications (OOS)

• Investigative and corrective action should extend to other preparations that may have been associated with the specific failure or discrepancy.
Verification

- Verification involves authoritatively signed assurance and documentation that a process, procedure, or piece of equipment is functioning properly and producing the expected results.

- Verification involves checking to ensure the calculations, weighing and measuring, order of mixing, and compounding techniques and equipment were appropriate and accurately performed.

- The quality of ingredients should be verified upon receipt (e.g., Certificate of Analysis, manufacturer's label on commercial products, etc.)
Written procedures that clearly define and implement the following nine separate but integrated components:

• Training
• SOP’s
• Documentation
• Verification
• Testing
• Cleaning, disinfecting and safety
• Containers, packaging, repackaging, labeling & Storage
• Outsourcing
• Personnel
Practical Applications
SOP’s – USP <1163>

- Beyond-Use dating
- Chemical and physical stability
- Cleaning and disinfecting
- Component quality evaluation
- Compounding methods
- Dispensing
- Documentation
- Environmental quality and maintenance
- Equipment Maintenance, calibration and operation
- Formulation development
Practical Applications
SOP’s – USP <1163>

- Labeling
- Materials and final compounded preparation handling and storage
- Measuring and weighing
- Packaging and repackaging
- Patient monitoring, complaints and adverse event reporting
- Patient or caregiver education and training
- Personnel cleanliness and garb
- Purchasing
- Quality Assurance and Continuous Quality Monitoring
- Safety
- Shipping
- Testing
- Training and retraining
Resources

- United States Pharmacopeia (USP)
  - General Chapters and Monographs
- International Journal of Pharmaceutical Compounding (IJPC)
- Remington’s Pharmaceutical Sciences
- American Journal of Health-System Pharmacy
- PCAB Standards and Compliance Indicators
- Ansel’s Pharmaceutical Dosage Forms and Drug Delivery Systems The Art, Science and Technology of Pharmaceutical Compounding
- Your Testing Laboratory (ARL, Eagle, Dynalabs and others)
- Repackagers (PCCA, MEDISCA, LETCO and others)
- CompoundingToday.com
- USPNF.org
- Science and Technology for the Hospital Pharmacists Newsletter
  *International Journal of Pharmaceutical Compounding*