

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

Thomas C. Kupiec, Ph.D.
tkupiec@arlok.com

February 22, 2012

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

State Pharmacy Regs – QA

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

State Regs

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

Std 6.10 Beyond Use Date

- SOPs provide determination and assignment of BUD for all compounded preparations
- Demonstrates by inspection the use of BUD
- Documents **rationale used** to establish BUD which **exceeds USP standards** based upon pharmacist's professional **judgment**

Standard 6.2 Potency

- SOPs satisfy current USP standards for potency and microbiological integrity
- Provides documentation that it complies with state and federal Regulations regarding strength, quality, purity, potency and stability throughout intended period of use.

*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

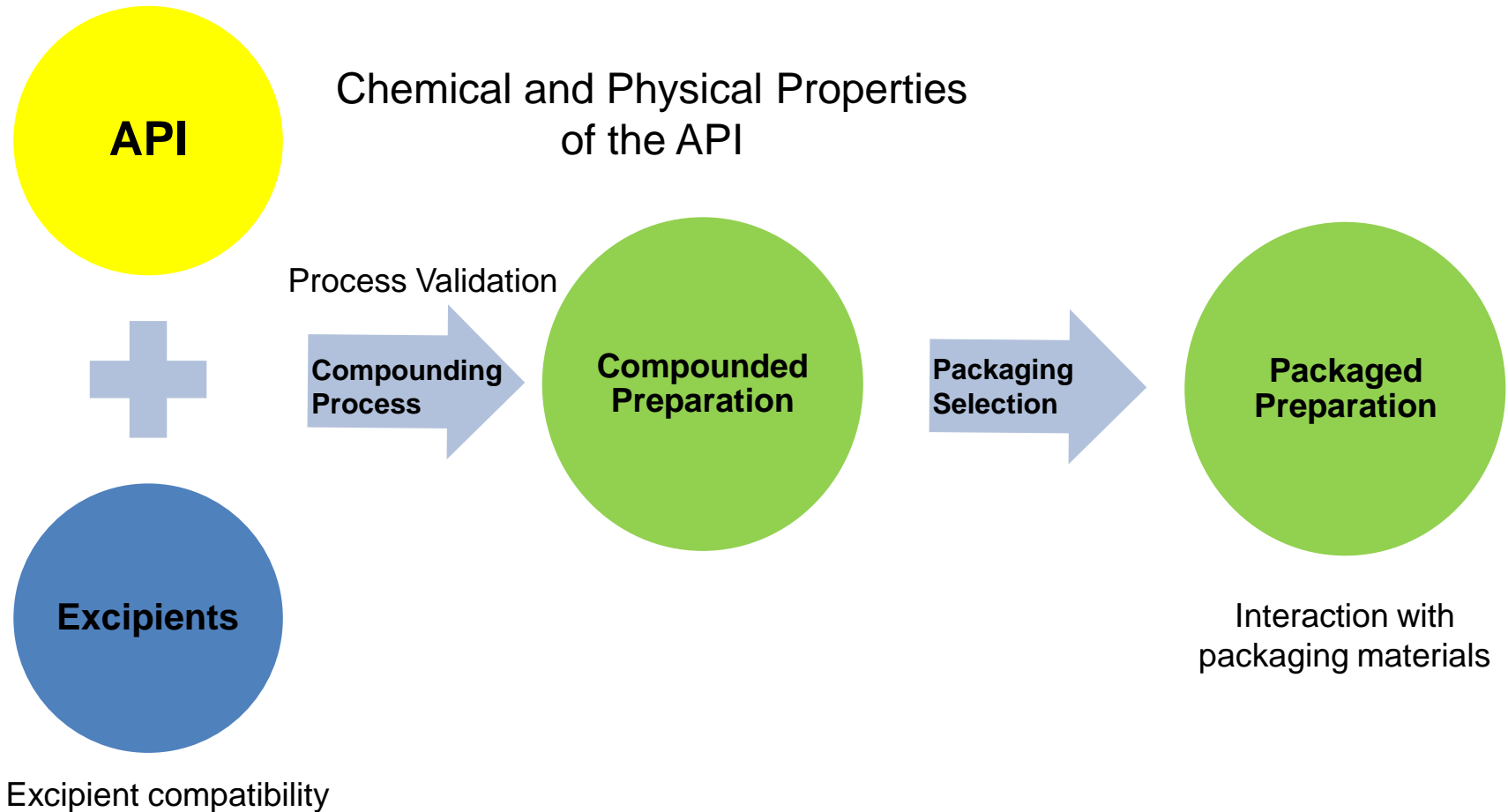
Type of Stability	Conditions Maintained Throughout the Shelf Life of the Drug Product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties, including appearance, palatability, uniformity, dissolution,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

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 its packaged
 - Expected storage conditions
 - Intended duration of therapy

Role of Stability Testing

Verification of Formulation and Compounding process



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.

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

USP*	State Regs	PCAB^
<ul style="list-style-type: none">• Strength• Quality• Purity	<ul style="list-style-type: none">• Strength• Quality• Purity• Identity	<ul style="list-style-type: none">• Strength• Quality• Purity• Identity

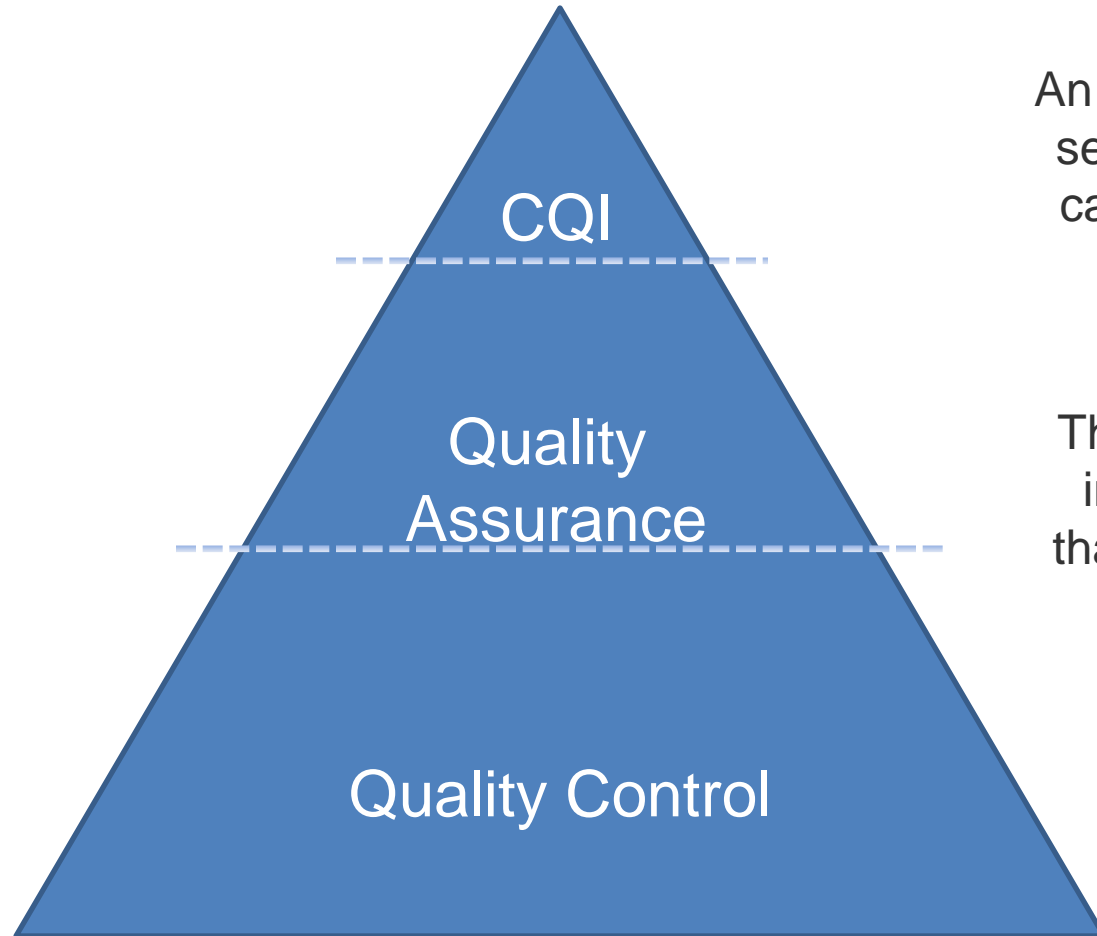
* As required USP <797>

^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



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

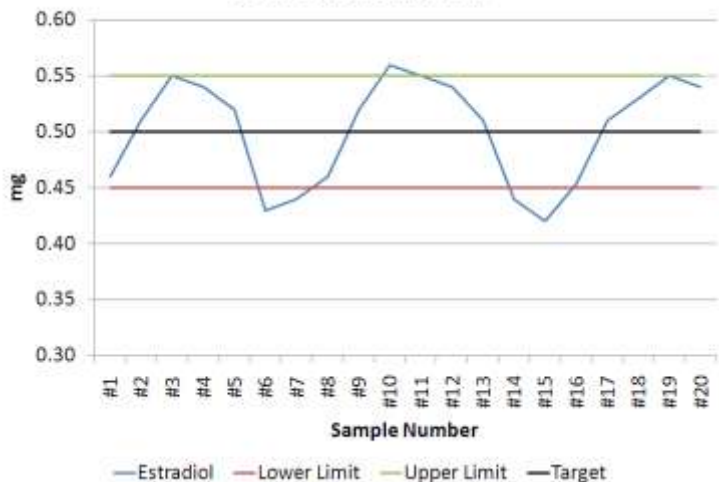
Quality Control Example:

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.

Measures	Estradiol	Estriol	Progesterone
No. of Failures	5	2	0
% Failure	25	10	0
Average	0.50	1.92	51.71
Standard Deviation	0.05	0.11	1.91
Std Dev %	9.3	5.6	3.7

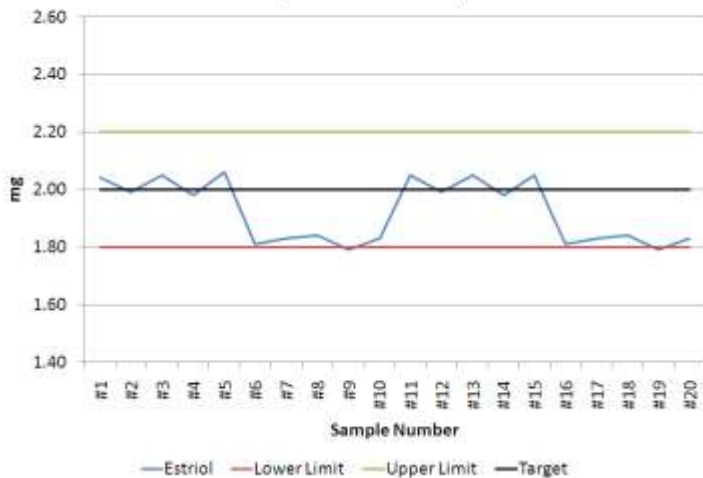
Quality Assurance Example:

Biest: Estradiol Analysis

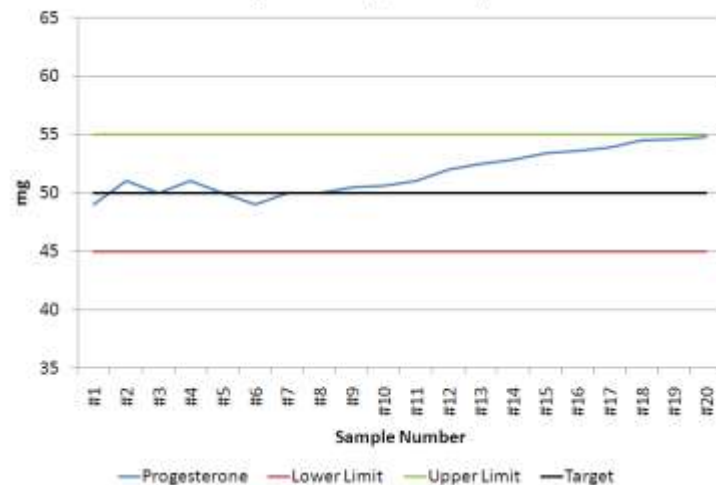


Measures	Estradiol	Estriol	Progesterone
Failures	5	2	0
% Failure	25	10	0
Average	0.50	1.92	51.71
Std Dev	0.05	0.11	1.91
Std Dev %	9.3	5.6	3.7

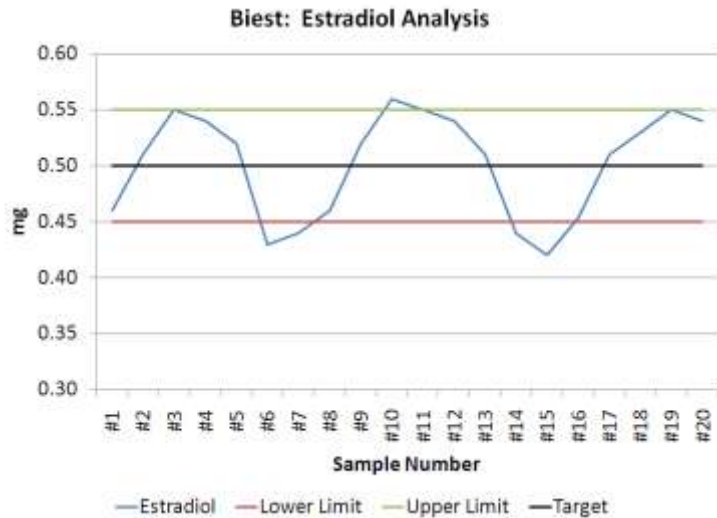
Biest Capsule: Estriol Analysis



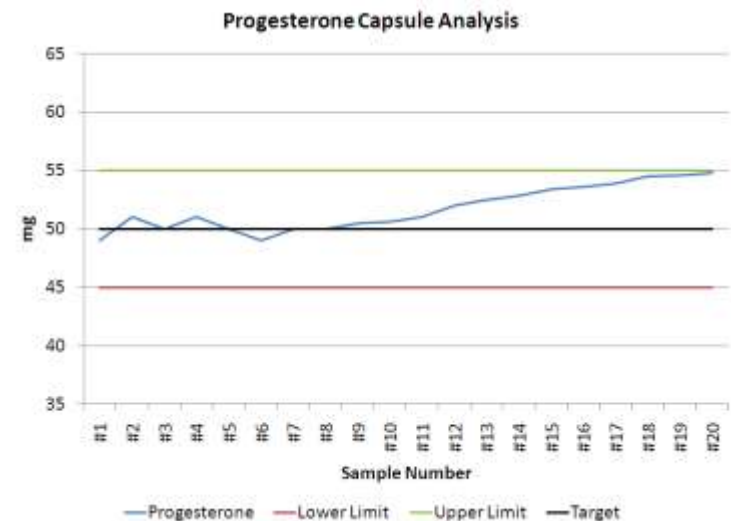
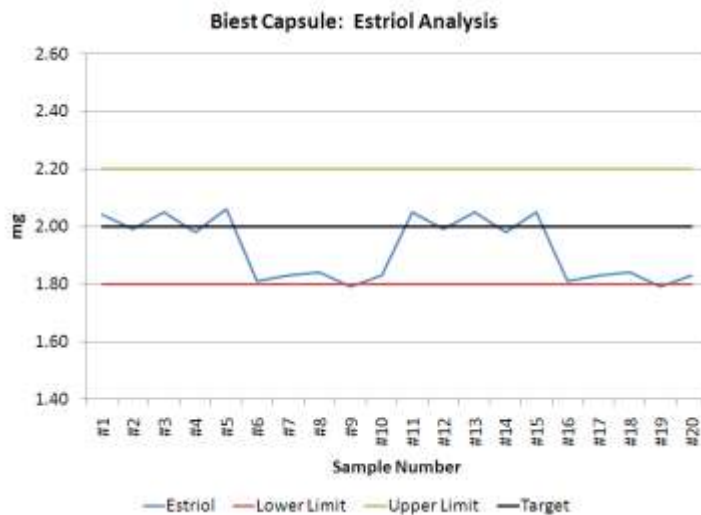
Progesterone Capsule Analysis



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

Process Verification

Two Approaches	Verification Criteria	Verification Tools
<ul style="list-style-type: none">• Individual formulations• Dosage form processes	<ul style="list-style-type: none">• Strength• Quality• Purity• Sterility*• Endotoxin* <p>Potency</p>	<ul style="list-style-type: none">• Quality Assessment Tools• Outside Verification (Testing)

Individual Formulations Testing Strategy

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

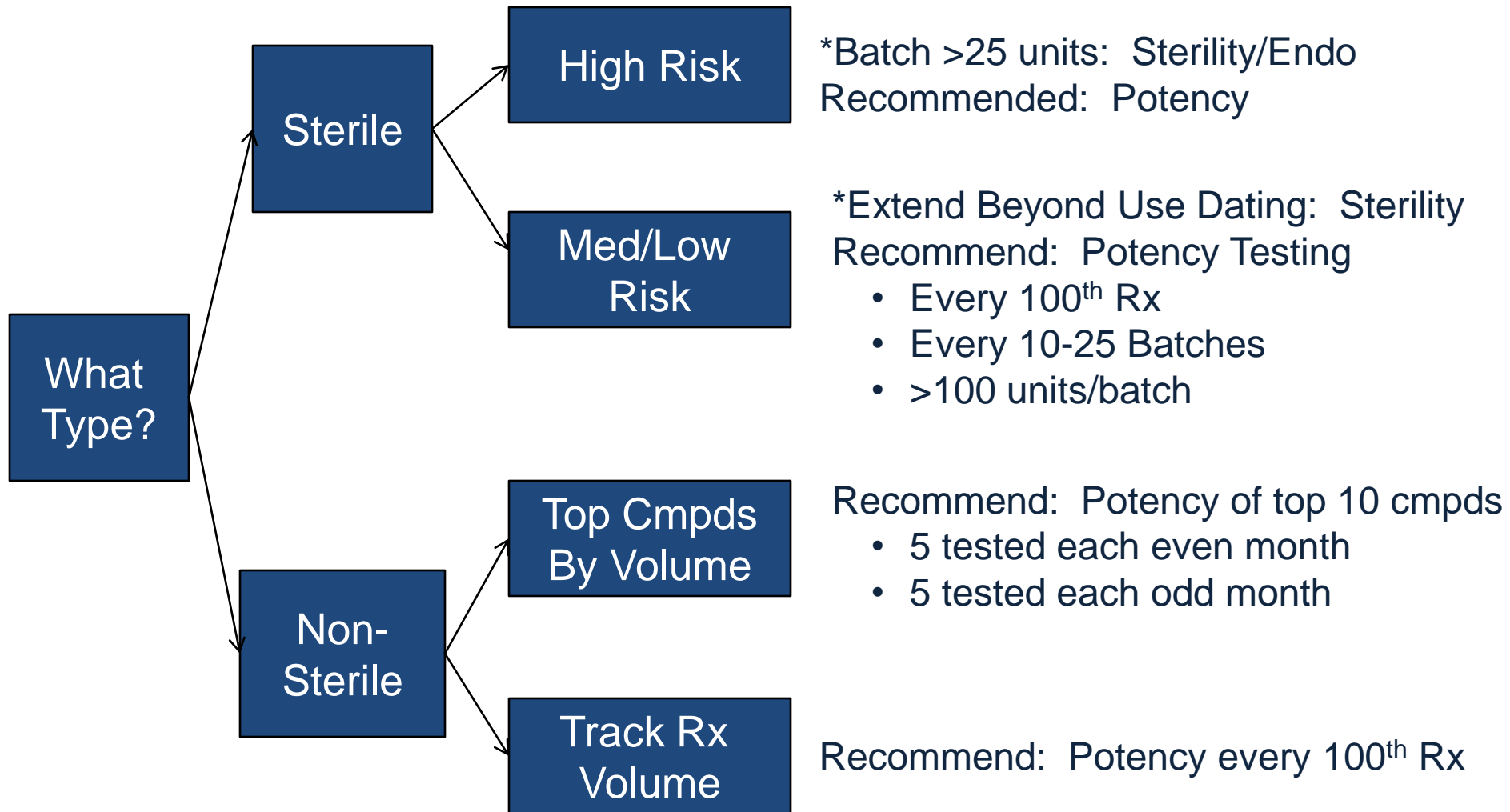
To determine testing frequency consider:

- 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



***Required Testing by USP <797>**

Non-Sterile Dosage Forms

Type	Quality Assessment Tools	Outside Verification
Capsules	<ul style="list-style-type: none"> •Appearance •Weight Variation 	<ul style="list-style-type: none"> •Content Uniformity •Potency Testing on All Actives •Microbial Testing
Topical Preparations	<ul style="list-style-type: none"> •Globule Size Range •Appearance •Rheological Properties •Physical Stability 	<ul style="list-style-type: none"> •Potency Testing •Microbial Testing
Suppositories, Troches, Lozenges, Lollipops	<ul style="list-style-type: none"> •Weight and Weight Variation •Specific Gravity •Color of preparation •Clarity (visual) •Texture-Surface •Appearance, Feel •Melting Test (oil-based preps) 	<ul style="list-style-type: none"> •Content Uniformity •Potency Testing •Microbial Testing
Oral Solutions and Suspensions	<ul style="list-style-type: none"> •Physical Observation •Weight / Volume •pH, Specific Gravity •Color of Solution 	<ul style="list-style-type: none"> •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 x 5 day x 4 weeks x 12 months = 2,400/yr

Creams, Gels, Ointments: 5/day x 5 x 4 x 12 = 1,200/yr

Oral & Topical Liquids: 3/day x 5 x 4 x 12 = 720/yr

Troches/Suppositories/ Lollipops/Sticks: 2/day x 5 x 4 x 12 = 480/yr

Total= 4,800/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)

Stages		Details
Process Validation	Every dosage form with each pharmacist/technician tested once/year	Potency determination
Process Monitoring	Every 50 th batch of each dosage form •Average 2 ingredients/formulation	96 batches/yr 192 potency tests/yr
	Every batch of T3 and T4 Triturates	12-15 potency tests/year

Sterile Dosage Forms

Dosage Form	Quality Assessment Tools	Outside Verification
Solutions and Suspensions for Injection	<ul style="list-style-type: none"> •Appearance •pH Testing 	<ul style="list-style-type: none"> •Potency Testing of All Actives •Sterility Testing •Endotoxin Testing •Particulate Matter Testing for Solutions
Solutions for Inhalation	<ul style="list-style-type: none"> •Appearance •pH Testing 	<ul style="list-style-type: none"> •Potency Testing of All Actives •Sterility Testing
Solutions for Ophthalmic Use	<ul style="list-style-type: none"> •Appearance •pH Testing •Osmolarity (Isotonicity) 	<ul style="list-style-type: none"> •Potency Testing of All Actives •Sterility Testing •Endotoxin Testing

Case Study #2: Sterile Preparations



Type:

- Intrathecal medications
- Sterile injectable hormones and erectile dysfunction preps.

Volume:

- 120 preparations/day

Case Study #2: Sterile (cont)

Stages		Details
Process Validation	All batched sterile preparations	Sterility, endotoxin, concentration
	All stock (bulk) sterile solutions	Sterility, endotoxin, and concentration
	Media fill testing	Every month on all staff
Process Monitoring	Random monthly samples by technician	Sterility, endotoxin, and concentration

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

Measure

Analyze

Improve

Control

Quality Assurance

- Define preparations
- Measure results
- Track and trend data

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

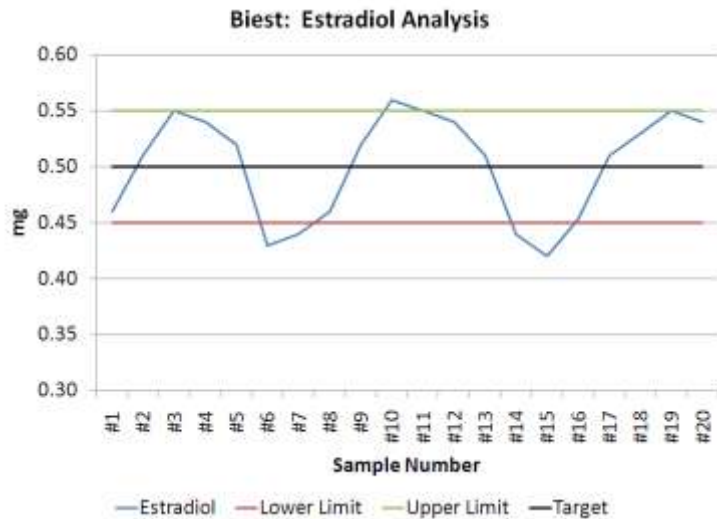
Analysis Tools

Identify Potential Variables

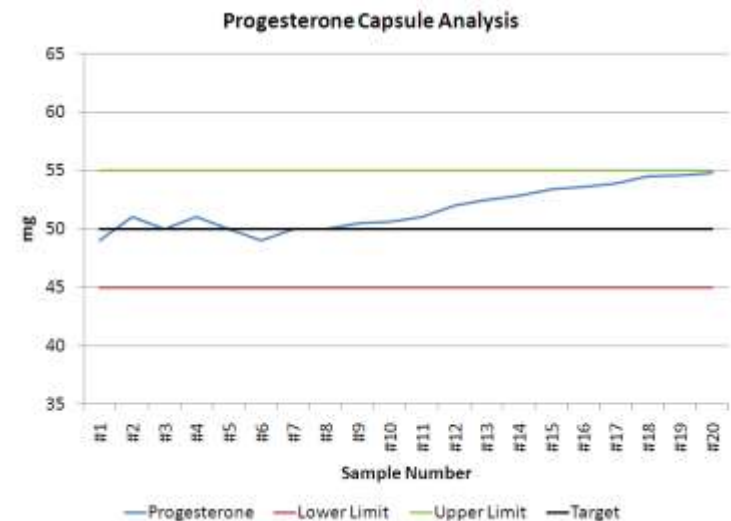
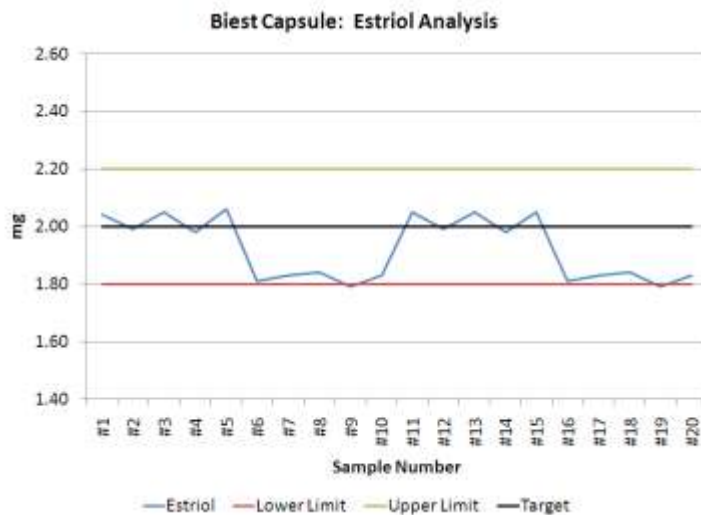
- Raw materials
- Container
- Concentration
- Mixing technique/equipment
- Measurement tools
- Temperature/humidity
- Technician



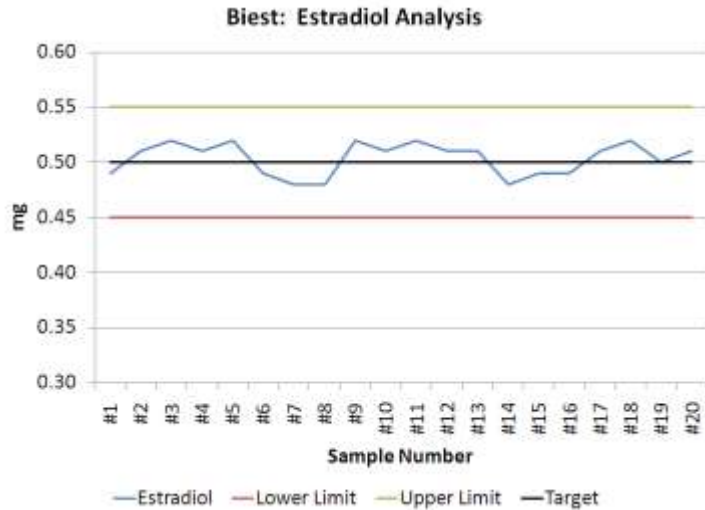
BiEst and Progesterone Data



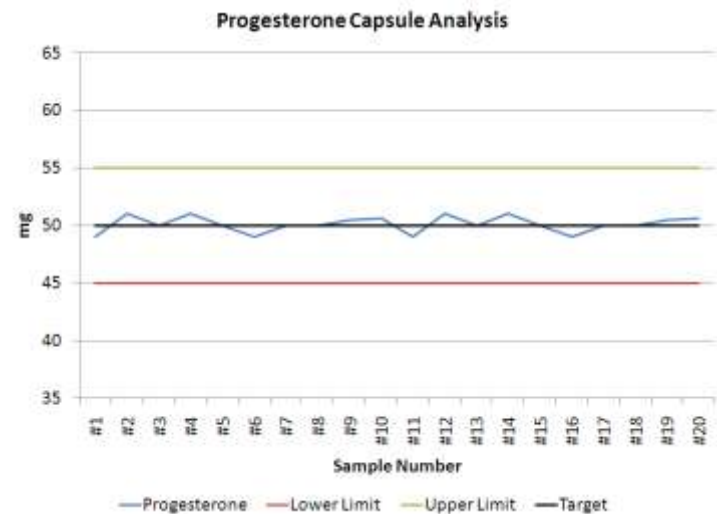
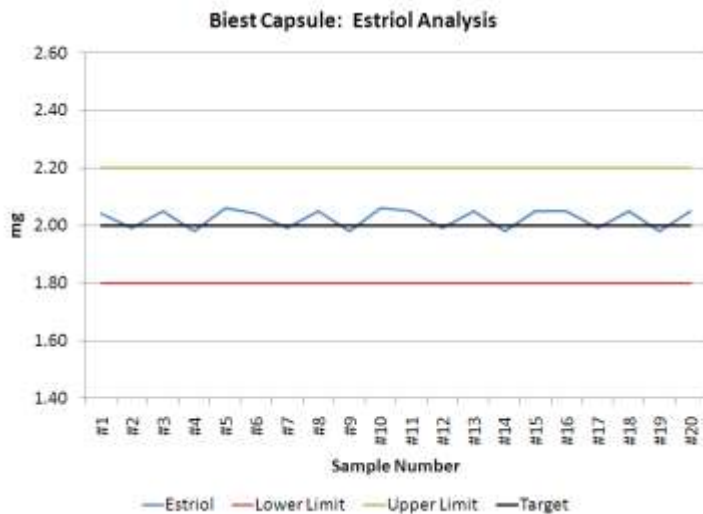
Measures	Estradiol	Estriol	Progest.
Failures	5	2	0
% Failure	25	10	0
Average	0.50	1.92	51.71
Std Dev	0.05	0.11	1.91
Std Dev %	9.3	5.6	3.7



Results of Improvement Plan



Measures	Estradiol	Estriol	Progest.
Failures	0	0	0
% Failure	0	0	0
Average	0.50	2.02	50.1
Std Dev	0.01	0.03	0.69
Std Dev %	2.9	1.6	1.4



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

Monitor

- 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>

Testing

- 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.)

Practical Applications

QA Program – USP <1163>

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

- Trissel, L.A. “Handbook on Injectable Drugs”. American Society of Health-System Pharmacists. 15th ed.
- 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