Extended Beyond Use Dates for Compounding Preparations

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Disclosures

Thomas Kupiec 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.
Objectives

At the conclusion of the program, the participants should be able to:

1. Explain the differences between stability, instability and incompatibility

2. Define and explain beyond use date (BUD) and stability studies.

3. Compare and contrast stability criteria for sterile and non-sterile preparations.

4. Identify factors that affect stability of compounded products.
EXPLAIN THE DIFFERENCES BETWEEN STABILITY, INSTABILITY AND INCOMPATIBILITY
What is Stability?

Definition – USP <1191>

The extent to which a product 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.
What is Instability?

Definition

Chemical reactions that are “...incessant, irreversible, and result in distinctly different chemical entities (degradation products) that can be both therapeutically inactive and possible exhibit greater toxicity.”

What is Incompatibility?

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>The inability of a substance to maintain its identity or to exercise its inherent properties when brought into contact with or into the sphere of influence of another substance or a physical force.</td>
</tr>
<tr>
<td><strong>Physical, Chemical or Physiologic</strong></td>
</tr>
</tbody>
</table>

How is Incompatibility determined?

1. A physical or visual incompatibility was reported (visible or electronically detected *particulate formation, haze, precipitation, color change or gas evolution*).

2. Greater than 10% decomposition of one or more components in 24 hours or less under the specified conditions was reported. (Stability Indicating Assay)

Criteria should be tempered with professional judgment.

Incompatibilities

Gas Evolution

Particulate Matter

Turbidity
Compatibility and Stability of Palonosetron Hydrochloride and Propofol During Simulated Y-Site Administration

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ABSTRACT
Palonosetron hydrochloride is a longer-acting, selective 5-HT3 receptor antagonist that has been approved for prevention of chemotherapy-induced nausea and vomiting and is being evaluated for prevention of postoperative nausea and vomiting. The objective of this study was to evaluate the physical and chemical stability of palonosetron hydrochloride 50 mcg/mL when mixed with unlabeled propofol 1% during simulated Y-site administration. Duplicate samples of this mixture were tested. Samples were stored and evaluated for up to 4 hours at room temperature. Physical stability was assessed by visual inspection. Chemical stability was assessed by high-performance liquid chromatographic analysis. All of the admixtures were opaque white when viewed in normal fluorescent room light and when viewed with a Tyndall beam. After reconstitution, no evidence of precipitation was found. The drug concentrations were essentially unchanged in all of the samples throughout the study. Palonosetron hydrochloride is physically and chemically stable when mixed with propofol as unlabeled injections during simulated Y-site administration for 4 hours at ambient room temperature.

MATERIALS AND METHODS
Materials
Palonosetron HCl injection (Lot HP193, MCI PHARMA, Inc.) was supplied by the manufacturer. Propofol 1% (10 mg/mL) injection (Lot 99B71C, Seldane Laboratories, Bedford, Ohio) was obtained commercially. Palonosetron HCl reference standard (Lot E94991; Sterile Laboratories, Waukegan, Illinois) was supplied by MCI PHARMA, Inc., and was used without further purification. Because a reference standard for propofol was not available commercially, the commercial injection was used as a reference material. The acetic acid, methanol, and other middle phase components were suitable for high-performance liquid chromatographic (HPLC) analysis. The water was used HPLC-grade water (Harrington Narrows, Delafield, Iowa) and was prepared immediately before use.

All samples were stored in a refrigerator. The HCl Injection was studied using a Y-site technique. Sixty mg/mL samples were prepared by mixing 6 mL of unlabeled palonosetron HCl 50 mcg/mL with 6 mL of propofol 1% in a Tyndall beam.

Physical Stability
Propofol 1% Injection is an opaque white emulsion that requires that the product be used in the original package. The product should not be mixed with unlabeled palonosetron HCl 50 mcg/mL, and it should not be used in a Y-site injection device.

Compatibility of Caspofungin Acute Injection With Other Drugs During Simulated Y-Site Coadministration

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ABSTRACT
The physical compatibility of caspofungin acute injection with selected other drugs during simulated Y-site coadministration was evaluated using visual observation and turbidity measurement. Five-milliliter samples of caspofungin acute 37 mg/mL, 65% sodium chloride injection, and 0.9% sodium chloride injection were combined with 5 mL of 67 other drugs, including antineoplastics, analgesics, anti-infectives, and supportive care drugs, diluted or undiluted in 0.9% sodium chloride injection or 5% dextrose injection, and with a parenteral nutrition admixture. Visual examinations were performed with the unopened vial in normal laboratory fluorescent light and with a Tyndall beam (high-intensity monochromatic light beam) to enhance visualization of small particles and low-level turbidity. The turbidity of each sample was measured as well. The sample mixtures were evaluated immediately and at 1 and 4 hours after preparation. Nineteen of the drugs tested and the parenteral nutrition admixture were incompatible with caspofungin acute 0.07 mg/mL during the 4-hour observation period. The remaining drug samples were compatible for at least 4 hours. Gross precipitation or turbidity changes visible in normal diffuse light and with the unaided eye occurred with 17 drugs and with the parenteral nutrition admixture. Microscopic examination of particulate matter not visible with the unaided eye occurred with erythropoietin. The measured turbidity of the caspofungin acute control solutions and the compatible test samples remained essentially unchanged throughout the observation period. In combination with caspofungin acute, 48 drugs and the parenteral nutrition admixture were considered to be physically compatible. In all, 19 drugs with the parenteral nutrition admixture exhibited Fbung precipitation or incompatibility formation within 4 hours and should not be simultaneously administered via Y-site with caspofungin acute.
DEFINE AND EXPLAIN BEYOND USE DATE (BUD) AND STABILITY STUDIES
What is Beyond Use Date?

Definition - USP <795>

The date after which a compounded preparation shall not be used; determined from the date the preparation is compounded.
## BUD Terminology

### Beyond-Use Date
- Assigned by **compounding** personnel
- 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

### 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 Guide

**Sterile** preparations BUD is based on:
1. Chemical stability in conjunction with
2. Microbiological sterility, *whichever is shorter*

**Non-Sterile** preparations BUD is based on:
1. Chemical stability of the drug in the formulation and packaging at specific storage conditions.
2. Microbiological limits, *whichever is shorter*
USP <797>
Microbiological BUD Guidelines

In the absence of passing a sterility test - The storage period cannot exceed the following time periods before administration

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Ambient</th>
<th>Refrigerated</th>
<th>Freezer (&lt;-20ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Medium</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>
Methods to Extend BUD

• Stability studies published in Literature (peer-reviewed preferred)
• **Stability/Compatibility studies conducted on your preparations (scientifically valid & most stringent)**
• Manufacturer (if mfg’d product involved)
• Physicochemical properties of ingredients
• General Chapters and USP/NF Monographs
• Extrapolation of above based on professional judgment
What is Stability?

**Definition – USP <1191>**

The extent to which a product *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.
Types of Stability

- Chemical
- Physical
- Toxicological
- Therapeutic
- Microbiological

USP <1191> Stability considerations in dispensing practice
### 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>

USP <1191> Stability considerations in dispensing practice
COMPARE AND CONTRAST STABILITY CRITERIA FOR STERILE AND NON-STERILE PREPARATIONS
Tests Involved in a Stability Study

- Assay (Stability Indicating Method) – USP <621>
- Sterility – USP <71>
- Endotoxin – USP <85>
- pH – USP <791>
- Visual Inspection (Appearance)
Tests Involved in a Stability Study

• Particulate Matter – USP <788> / <789>
• Preservative Effectiveness – USP <51>
• Preservative Quantification – USP <341>
• Microbial Limits – USP <61>
• Absence of Specified Organisms – USP <62>
# Compare and Contrast Stability

<table>
<thead>
<tr>
<th>Sterile Preparations</th>
<th>NonSterile Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP 51 – Preservative Effectiveness</td>
<td>USP 51 – Preservative Effectiveness</td>
</tr>
<tr>
<td>USP 71 – Sterility</td>
<td><strong>USP 61 – Microbial Limits</strong></td>
</tr>
<tr>
<td>USP 85 - Endotoxin</td>
<td><strong>USP 62 – Absence of Specified Organisms</strong></td>
</tr>
<tr>
<td>USP 341 - Preservative Quantification</td>
<td>USP 341 – Preservative Quantification</td>
</tr>
<tr>
<td>USP 621 - Assay</td>
<td><strong>USP 621 - Assay</strong></td>
</tr>
<tr>
<td><strong>USP 788/789 – Particulate Matter</strong></td>
<td><strong>USP 791 - pH</strong></td>
</tr>
<tr>
<td>USP 791 - pH</td>
<td><strong>USP 791 - pH</strong></td>
</tr>
</tbody>
</table>
USP <621> Chromatography
HPLC Stability Indicating Assay

What?
HPLC assay capable of separating out the degradants from the analyte

Why?
To ensure you are only reporting concentration of analyte
Must be formulation specific
1.2.2 “Specificity may be demonstrated . . . This should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis and oxidation.”
SPECIFICITY

“If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test products to a second well-characterized procedure (e.g., a Pharmacopeial or other validated procedure). These comparisons should include samples stored under relevant stress conditions (e.g., light, heat, humidity, acid/base hydrolysis, and oxidation).
Stress Studies

“Degradation information obtained from stress studies (e.g., products of acid and base hydrolysis, thermal degradation, photolysis, oxidation) for the drug substance and for the active ingredient in the drug product should be provided to demonstrate the specificity of the assay and analytical procedures for impurities… do not interfere with the quantitation of the active ingredient.”
“Stress testing helps to determine the intrinsic stability characteristics of a molecule by establishing degradation pathways to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used.

Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the drug substance. . . Studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and hence support the suitability of the proposed analytical procedures. . . Results from these studies will form an integral part of the information provided to regulatory authorities.”
B. Drug Substance Testing

“If not previously generated or available by reference, stress testing studies should be conducted to establish the inherent stability characteristics of the drug substance, and support the suitability of the proposed analytical procedures.

Submission of data from stress testing of the drug substance using acid and base hydrolysis, temperature, photolysis and oxidation according to the Guideline for Submitting Samples and Analytical Data for Methods.

I. Specificity/selectivity

The analyte should have no interference from other extraneous components and be well resolved from them. . . generated and submitted to show that the extraneous peaks either by addition of known compounds or samples from stress testing.
HPLC Stability Indicating Method Validation Parameters

• **Specificity** (Acid, Base, Heat, Peroxide, UV Light)

• System Suitability (Resolution, Tailing, RSD, Column Efficiency)

• Linearity

• Precision

• Accuracy
HPLC Stability Indicating Method Validation Parameters

- Ruggedness
- Robustness
- Sensitivity (LOD / LOQ)
- Freeze Thaw (when necessary)
Stability Indicating Method vs Potency Testing

Figure 1. Example chromatogram of a non-stability indicating HPLC method that evaluates potency of a single analyte.

Figure 2. Example chromatogram of a non-stability indicating HPLC method containing analyte and degradant sample peaks.

Figure 3. Example chromatogram of a non-stability indicating HPLC method where analyte and degradant peaks are not fully resolved from one another.

Figure 4. Example chromatogram of a stability indicating HPLC method containing analyte and degradant peaks that are fully resolved from one another.
USP <71> Sterility Tests

What?
A test to detect microbial contamination

Why?
To ensure that parenterals are free of microorganisms
USP <71>

United States Pharmacopeia Chapter <71> Sterility Tests are designed to detect a broad range of contaminating microorganisms:

- aerobic
- anaerobic
- spore forming bacteria
- fungal microorganisms such yeast and molds
USP <71> Sterility Tests

- The test preparations are observed for macroscopic evidence of microbial growth at the end of the incubation period (14 or 18 days)

- A “Sterile” (no growth) result is released which indicates that the product being examined meets the test requirements for sterility
USP <85> Endotoxin

What?
To detect endotoxins from Gram-negative bacteria

Why?
Endotoxin is not removed via sterilization processes. It can create a pyrogenic response in the patient.
Endotoxin Limit

- Conservatively represents the safe amount of endotoxin that is allowed in a **dose** of a **specific medication**

- USP monographs for drugs list the endotoxin limits for specific drugs in EU/mg or EU/ML

- Endotoxin limits can be calculated and **route specific** endotoxin limits are often used

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USP <791> pH

What?
The amount of protons in a solution

Why?
General Chapters in USP <1> Injections and Implanted Drug Products (Parenterals) – Product Quality Tests

Can contribute to degradation of product thus changing the BUD
Visual Inspection (Appearance)

What?
Visual inspection of the final product should occur (e.g. color, homogeneity, presence of foreign material and observed particulate)

Why?
Sample can develop particle or color change over time thus changing the BUD (Example Morphine Sulfate)

USP <788> / <789> Particulate Matter

What?
Particulate matter consists of extraneous substances (e.g. dust, glass, drug precipitate, rubber, and other insoluble materials)

Why?
Particulate matter in parenterals can be life threatening when introduced into the bloodstream

USP <788> and <789> Particulate Matter Standards

- Particulate Matter in Injections USP <788> - solutions for injection administered by the intramuscular or subcutaneous route must meet the requirements.

- Particulate Matter in Ophthalmic Solutions USP <789> - every ophthalmic solution is subject to the particulate matter limits set forth for the test being applied, unless otherwise specified in the individual monograph.
USP <788> and <789> Particulate Matter Standards

• Used to determine the number of particles at 10 and 25 microns in injections and parenteral infusions

• Two methods of analysis

  • **Method 1: Light Obscuration** (Used for the majority of samples)

  • **Method 2: Microscopic Analysis** (Used for samples of reduced clarity, i.e., emulsions or viscous solutions,)
Quality-Control Analytical Methods: Particulate Matter in Injections. What Is It and What Are the Concerns?

Abstract

The presence of particulate matter in intravenous injections, especially in large numbers, represents a potentially life-threatening health hazard. The United States Pharmacopeia has established procedures and standards to ensure the quality of intravenous injections, including particulate counts. Compounding pharmacists can reduce the incidence of adverse events in patients by ensuring the quality of their preparations through filtration of intravenous preparations and analytical testing procedures.

Professionalism requires that pharmacists consider the issue of particulate matter when compounding injections, including admixtures and high-volume preparations. The objective of this article is to provide compounding pharmacists with information they need to reduce the risk to patients associated with exposure to particulates, as follows:

- Understand the importance of particulate matter and its potentially harmful effects
- Identify the sources of particulate matter and how it gets into a preparation
- Determine which preparations need particulate matter testing and the limits placed by the United States Pharmacopeia (USP) on those preparations

Definitions and Sources of Particulates

Particulate matter consists of randomly sourced, extraneous substances (other than gas bubbles) that cannot be quantitated by chemical analysis owing to the small amount of material that it represents and its heterogeneous composition. Particulate matter can consist of many different things (e.g., including dust, glass, precipitate from drug incompatibility, rubber, cotton fibers, latex, other insoluble materials).

Dr. Michael Aker has observed, "Anything that directly or indirectly comes in contact with a parenteral solution, including the solvent and solutes composing the solution itself, represents a potential source of particulate contamination." In a sterile product or compounded preparation, particulate contamination may originate from any of the following:

- The solution itself and its ingredients
- The production process and its variables (e.g., environment, equipment, personnel)
- The product’s packaging
- The preparation of the product for administration (e.g., manipulating the product, the environment in which it is prepared)

Reports have been published on the formation of precipitated particulates from physical and chemical incompatibilities, and on the generation of particulates from various containers, including plastic syringes.

Problems with Particulates

Particulate matter in injections can be harmful when introduced into the bloodstream. The contamination of parenteral fluids and drugs by particulate matter has been recognized as a potential health hazard. Adverse reactions may include vein irritation and phlebitis, clinically occult pulmonary granulomas observed at routine autopsy examination, local tissue inflammation, severe pulmonary dyspnea, occlusion of capillaries and arteries, anaphylactic shock, and death. Clearly, the presence of particulate matter in intravenous injections, especially in large amounts, represents a potentially life-threatening health hazard. In 1994, the US Food and Drug Administration received a report that described two deaths relating to calcium phosphate precipitation. The precipitation was in a three-in-one total parenteral nutrition admixture that was given to patients. Autopsies revealed that the patients had diffuse microvascular pulmonary emboli that contained calcium phosphate. This demonstrates the fatal effects that particulate matter can have on patients. Patients receiving parenteral nutrition require specific attention, because as a group they tend to receive more parenteral therapy and for longer periods than other patients. Compounding pharmacists are not the only
USP <51> Preservative Effectiveness

What?
To demonstrate the effectiveness of antimicrobial preservatives in preventing microbial proliferation in injections, topicals, oral products, single dose vials, and antacids packaged in multiple-dose containers.

Why?
Preservative Effectiveness can change over time.
USP <51>  
Antimicrobial Effectiveness Testing

• Challenge organisms are generally based on likely contaminants to a drug product.

• The sample scheme and acceptance criteria are based on its physical attributes, formulation, and intended use.
The Essentials of United States Pharmacopeia Chapter <51>
Antimicrobial Effectiveness Testing
AND ITS APPLICATION IN PHARMACEUTICAL COMPOUNDING

Nicole Vu, PhD
Kevin Nguyen
Thomas G. Kaplec, PhD

INTRODUCTION
Antimicrobial preservatives are excipients added to multi-dose containers of both sterile and non-sterile drug products for inhibition of microbial growth. Microbial contamination may occur during manufacturing, processing, or during the period of use due to the repeated withdrawal of individual doses from multi-dose containers. Multi-dose pharmaceutical products containing preservatives offer several advantages over single-dose packages. Multi-dose drugs minimize product wastage and allow flexibility for dosage adjustments; repeated doses may be obtained from the same container without concerns for microbial growth during use; and their packaging is reduced because multiple doses are supplied in a single container. It is general knowledge that unit-dose packaging is the most optimal with respect to the maintenance of sterility, but it is not efficient and cost effective as preserved multi-dose preparations. Antimicrobial preservatives can be microbial, microstatic, and sporocidal.

ABSTRACT
Antimicrobial preservatives are excipients added to multi-dose containers of both sterile and non-sterile drug products. Antimicrobial preservatives are used primarily to inhibit growth of microbial contamination occurring during the period of use. Demonstration of antimicrobial preservative effectiveness is required for these functional excipients. This article reviews key factors for consideration in the selection of preservatives, principles of the preservative-effectiveness test, and the significance of requirements for preservative-effectiveness testing in the compounding practice.
**USP <341> Preservative Quantitation**

**What?**
To determine the potency of a preservative.

**Why?**
Prove the amount of labeled preservative is correct and quantitate the preservative throughout the stability study.
USP <61>
Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests

What?
To determine the total population of aerobic bacteria and yeast and molds in the product.

Why?
Used for bioburden determination in raw materials, during production, and in the finished product.
USP <61>
Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests

• The ability of the test to detect microorganisms in the presence of product to be tested must be established. (method suitability)

• The growth-promoting capabilities of media used in this procedure must be established. (growth promotion)
QUALITY CONTROL ANALYTICAL METHODS: Microbial Limit Tests for Nonsterile Pharmaceuticals, Part 1

ABSTRACT: Contamination of pharmaceuticals with microorganisms may lead to deleterious effects on the therapeutic properties of the drug, and may potentially cause injuries to intended recipients. Cases of contaminated nonsterile products have been reported in increasing numbers, and often associated with the presence of objectionable microorganisms. Methods for detection of these organisms are described in three major Pharmacopelias. Their functions and their limitations in the examination of microbiological quality for nonsterile products will be reviewed in this report.

Nicole Vu, PhD
Jessica R. Lohan, BS
Thomas C. Kugler, PhD

Nonsterile pharmaceuticals are not produced by aseptic processes, and therefore, are not expected to be totally free from microbial contaminants. The degree of contamination in nonsterile products is regulated, and is based on the acceptance criteria for microbiological quality established in Pharmacopoeial monographs. A review of the U.S. Food and Drug Administration’s (FDA) performance reports during 2004–2011 revealed that approximately 75% of nonsterile product recall requests were in fact due to contamination over the counter (OTC) or personal care products. The majority of these recalls were attributed to the following:

- Presence of "objectionable" organisms (75%)
- Contamination levels exceeding microbial limits (19%)
- Sensitivity or microbial diagnostic kit errors (7%)
- Failed microbiological tests (98%)
- Manufacturing deficiencies (39%)

The FDA has indicated that "toxicologic preparations contaminated with Gram-negative organisms are a probable moderator to serious health hazard," and that "Bordetella pertussis (Pertussis) organism is objectionable if found in topical products or materials intended for children." The FDA concerns were recently related to past incidents where various infections and deaths were linked to contaminated OTC anti-acne products, and Metronidazole Sulfini Sulfini Lotion. Since then, aqueous-based inhalants are required to be sterile.

The major contaminants of nonsterile pharmaceutical products and ingredients are bacteria, yeast, and molds. Even drug formulations are susceptible to microbial contamination as the proliferation of microorganisms in solid dosage forms have been observed, especially in warm and humid climates. There are very few...
USP <62>
Microbiological Examination of Nonsterile Products: Tests for Specified Organisms

What?
To verify the absence of objectionable microorganisms in drug products and raw materials based on route of administration.

Why?
The route of administration provides avenues for the objectionable microorganisms to cause the patient harm.
USP <62>
Microbiological Examination of Nonsterile Products: Tests for Specified Organisms

• The ability of the test to detect microorganisms in the presence of product to be tested must be established. (method suitability)

• The growth-promoting capabilities as well as indicative and inhibitory properties of media used in this procedure must be established. (growth promotion)
Quality Control: Microbial Limit Tests for Nonsterile Pharmaceuticals, Part 2

ABSTRACT Cases of contaminated nonsterile products have been reported in increasing numbers. Often, these contaminated products are associated with the presence of objectionable microorganisms. The major contaminants of nonsterile pharmaceutical products and ingredients are bacteria, yeasts, and molds. The combination of parts 1 and 2 of this series of articles provides a thorough examination of microbiological quality testing for nonsterile products.

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# Stability Study Example

<table>
<thead>
<tr>
<th>Drug</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Names and Concentrations</td>
<td>Methylcobalamin 1000 mcg/mL</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Parenteral – Injectable – Multi-dose</td>
</tr>
<tr>
<td>Container Type(s)</td>
<td>5 mL amber vials with 5.5 mL</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>Refrigerated (2-8°C)</td>
</tr>
<tr>
<td>Replicates</td>
<td>Single Analysis</td>
</tr>
<tr>
<td>Lots</td>
<td>1</td>
</tr>
<tr>
<td>Time Points (Days)</td>
<td>0, 30, 60, 90, 120, 140</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Method Type</th>
<th>Time Points (Days)</th>
<th># of Time Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Visual</td>
<td>0, 30, 60, 90, 120, 140</td>
<td>6</td>
</tr>
<tr>
<td>pH</td>
<td>USP &lt;791&gt;</td>
<td>0, 30, 60, 90, 120, 140</td>
<td>6</td>
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<tr>
<td>Methylcobalamin Assay</td>
<td>HPLC</td>
<td>0, 30, 60, 90, 120, 140</td>
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<tr>
<td>Benzyl Alcohol Assay</td>
<td>USP &lt;341&gt;</td>
<td>0, 30, 60, 90, 120, 140</td>
<td>6</td>
</tr>
<tr>
<td>Particulate Matter</td>
<td>USP &lt;788&gt;</td>
<td>0, 30, 60, 90, 120, 140</td>
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</tr>
<tr>
<td>Sterility</td>
<td>USP &lt;71&gt;</td>
<td>0, 90, 140</td>
<td>3</td>
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<tr>
<td>Endotoxin</td>
<td>USP &lt;85&gt;</td>
<td>0, 140</td>
<td>2</td>
</tr>
<tr>
<td>Antimicrobial Effectiveness Test</td>
<td>USP &lt;51&gt;</td>
<td>0, 140</td>
<td>2</td>
</tr>
</tbody>
</table>
IDENTIFY FACTORS THAT AFFECT STABILITY OF COMPOUNDED PRODUCTS
Variables affecting Stability of Compounded Products

• Formulation and Dosage Form
  - Drug
  - Concentration(s)
  - Excipients and Vehicle

• Container Closure

• Storage Conditions
Dosage Form Factors Affecting Product Stability

- Particle size (emulsions and suspensions)
- pH
- Solvent system composition
- Compatibility of anions and cations
- Solution ionic strength
- Primary container
- Specific chemical additives
- Molecular binding
- Diffusion of drugs and excipients

Source: USP <1191> Stability Considerations In Dispensing Practice
Container Closure Factors Affecting Product Stability

- **Extractables** – Compounds that can be extracted from the container closure system when in the presence of a solvent.
- **Leachables** – Compounds that leach into the drug product formulation from the container closure as a result of direct contact with the formulation.
- **Absorption**
  - Drug absorbed by package.

Leachables are a subset of Extractables.
Storage Conditions Affecting Product Stability

- Temperature
- Temperature excursions
- Light
- Humidity
- Oxygen
- Carbon Dioxide
- Package Components

Source: USP <1191>  Stability Considerations In Dispensing Practice

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Summary

• Defined Beyond Use Date (BUD)

• Tests involved BUD / Stability Study
  – Assay (Stability Indicating)
  – Sterility
  – Endotoxin
  – pH
  – Visual Inspection (Appearance)
  – Particulate Matter
  – Antimicrobial Effectiveness
  – Microbial Enumeration
  – Absence of Specified Organisms
Summary

• Factors affecting Stability
  – Formulation and Dosage Form
  – Container Closure
  – Storage Conditions
References and Resources

- United States Pharmacopeia (USP) General Chapters and Monographs
- International Journal of Pharmaceutical Compounding (IJPC)
- Remington’s Pharmaceutical Sciences
- State Board of Pharmacy Regulations
- 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
- Repackagers
- Laura Gillikin, cGMP Validation
- Scott Sutton, Microbiology Network
- Andy Gunn, Kymanox
- CompoundingToday.com
# U.S. Pharmacopeia Chapters referring to Stability or BUD

<table>
<thead>
<tr>
<th>General Testing</th>
<th>Chapter</th>
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<tbody>
<tr>
<td>Pharmaceutical Compounding - Nonsterile Preparations</td>
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<tr>
<td>Pharmaceutical Compounding - Sterile Preparations</td>
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<tr>
<td>Stability Considerations in Dispensing Practice</td>
<td>&lt;1191&gt;</td>
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<tr>
<td>Quality Assurance in Pharmaceutical Compounding</td>
<td>&lt;1163&gt;</td>
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<tr>
<td>Bulk Substances and Dosage Forms</td>
<td>Testing Methods</td>
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<tr>
<td></td>
<td>Wt</td>
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<tr>
<td>Bulk Substances</td>
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<td>Capsules</td>
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<td>Emulsions</td>
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<td>Gels</td>
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<td>Irrigations</td>
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Table 2 – Selected Compendial Testing Methods for Bulk Substances and Various Dosage Forms (continued)

<table>
<thead>
<tr>
<th>Bulk Substances and Dosage Forms</th>
<th>Testing Methods</th>
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<tr>
<td></td>
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<tr>
<td>Lozenges</td>
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<td>Otics</td>
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<td>Powders</td>
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<td>Semisolids</td>
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<tr>
<td>Solutions, nonsterile</td>
<td>+</td>
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<tr>
<td>Sterile implant gels</td>
<td>+</td>
</tr>
<tr>
<td>Bulk Substances and Dosage Forms</td>
<td>Testing Methods</td>
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<tr>
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<td>Sterile Implant Solids</td>
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<tr>
<td>Sticks</td>
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<tr>
<td>Suppository</td>
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<td>Suspension, nonsterile</td>
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<tr>
<td>Tablets</td>
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</tbody>
</table>

*a* Wt, weight; Vol, volume; Osm, osmolality/osmolarity; RI, refractive index; Sp Gr, specific gravity; MP, melting point; UV/Vis, ultraviolet/visible spectroscopy; HPLC, high-performance liquid chromatography; GC, gas chromatography; IR, infrared spectroscopy; PM, particulate matter; +, test applicable; -, test not applicable.

*b* Endotoxin testing may be needed for bulk substances used in compounding some sterile preparations.

*c* *, microbial limits (see *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use 1111* and *Pharmaceutical Compounding—Sterile Preparations 797*).

*d* Solutions only, not suspensions or ointments.
Thank You!

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