

# Quality-Control Analytical Methods:

## Chemical Testing Aspects of *USP* Chapter <797> for Compounded Sterile Preparations

The regulations set forth by the *United States Pharmacopeia (USP)* Chapter <797>,<sup>1</sup> in effect since January 1 of 2004, have generated a great deal of interest because they have established the first practice standards of sterile pharmacy compounding in US history that are enforceable at both the federal and state levels.<sup>2</sup> *United States Pharmacopeia* Chapter <797> expands the scope of facilities governed by the regulations and defines the practices covered.<sup>3</sup> The purpose of this article is to help the reader understand the criteria set forth by *USP* Chapter <797> regarding chemical aspects of finished-product (or end-preparation) testing, including criteria for identity and strength (potency) and beyond-use date (BUD) testing.

### Identity and Strength (Potency) Testing

The purpose of identity testing is to correctly identify the drug. If monographs are not provided in the *USP*, it may be necessary to consult other sources. For example, some common drugs, such as ipratropium bromide, are not in the *USP*. Other compendial resources, such as the *British Pharmacopeia*, *Japanese Pharmacopeia* and *European Pharmacopeia*, contain monographs for some drugs that the *USP* might not list.

High-performance liquid chromatography (HPLC), infrared spectrophotometry, ultraviolet visible spectrophotometry and chemical testing can be used to test identity. The retention time of a chromatogram using HPLC analysis can be used.<sup>4</sup> Infrared spectrophotometry is used mostly for raw materials. Ultraviolet visible spectrophotometry produces a spectrum for comparison with a known reference standard. Chemical testing involves the addition of reagents to a substance that yields a predictable result if a compound is present.

The purpose of strength, or potency, testing is to establish or verify the concentration (potency) of the drug in the compounded preparation. The *USP* has established that the acceptable range of most compounded preparations is typically  $\pm 10\%$ ; however, it can be as great as  $\pm 20\%$  (as with some proteins) or as tight as  $\pm 5\%$  (as with potent analgesics). For some raw powders, potency is required to be within  $\pm 2\%$ . For determining potency, HPLC is the most commonly used methodology. It establishes concentration by comparison with a known reference standard at a known concentration.



Thomas C. Kupiec, PhD  
Analytical Research Laboratories, Inc.  
Oklahoma City, Oklahoma

Another methodology, titration, uses the principles of fundamental chemistry. This incorporates a titrant that has a known reaction rate with the chemical of interest. A microbial assay is commonly used for antibiotics. When testing antibiotics, it is possible to use a bacterial culture to assess potency of a compound. This would most likely be performed through zones of inhibition.

There are several common ways the concentration or potency of compounded preparations can be altered:

**Filtration** – If the active drug has not been totally dissolved or has an affinity for the filter membrane, then it will be retained on the membrane filter, decreasing the potency of the compounded preparation. Check with the manufacturer to determine compatibility of the filter with the drug and to avoid drug/membrane interactions or retention on the filter membrane. Many drug manufacturers conduct filter-drug-binding studies to minimize this variable.<sup>5</sup> For example, when compounding betamethasone, sodium phosphate and betamethasone acetate, it is imperative to

use a Teflon filter after solubilizing the acetate ester, whereas one would use a conventional 0.2- $\mu\text{m}$  aqueous filter for the sodium phosphate salt.

**Autoclave** – Temperature can enhance drug solubility; increased controlled heat can assist in solubilization of a drug. It is important not to overheat, as this can cause drug loss or degradation. Using a microwave oven to heat a preparation can result in a degraded product because of the uncontrolled heat source. This type of heating is not recommended. Instead, use a hot plate, which allows the temperature to be controlled, maintained and recorded for reproducibility.<sup>5</sup>

**Lyophilization** – Vacuum distillation can change the form of a drug, so it is necessary to ensure that the process is optimized. Heating or vacuum distilling too quickly causes degradation and, subsequently, low potency.

**Transfer technique** – The process of transferring drug from bottle to scales or beaker to mixing chamber can result in a loss of potency if there is incomplete transfer at any point.

**Degradation** – In general, heat, time and drug compatibility are the three variables to watch for when considering degradation.

**Table 1. Example of Protocol for Number of Samples to be Tested.**

Quantity of Sterile Units per Batch	Number of Samples	Tests
Up to 25 units	1	1 – potency 1 – sterility 1 – endotoxin
26 to 100 units	2	1 – potency 2 – sterility 2 – endotoxin
100 + units	3	1 – potency 3 – sterility 3 – endotoxin

**Accuracy and Common Errors**

A common error that may be encountered in compounding pharmacies is inaccurate, uncalibrated measuring devices, such as syringes, beakers, graduated cylinders, flasks, etc. These items are not usually calibrated to measure fluids for analytical purposes. Using labware such as the items mentioned above can cause dilutions to be outside specifications. By knowing relative tolerances and performing in-house calibrations of glassware used for dilutions, it is possible to make corrections to account for inaccuracies of the glassware. These can be performed by weighing water on a calibrated balance and marking the level of the volume of interest on the glassware. For example, beakers have scales on their sides. These scales usually have an accuracy of  $\pm 5\%$  for most brands. Using one of these beakers to make a 1-L dilution, it is possible to have 50 mL more or 50 mL less of the diluent. This could alter the final concentration of some end preparations.

In terms of calibration, a key piece of equipment in a compounding pharmacy is the balance. If this piece of equipment is not weighing accurately, then dosage levels will be inaccurate. It is strongly recommended that balances be calibrated in-house using certified weights. In addition, the balance and weights need to be checked at least every 6 to 12 months (depending on use) by an outside certified lab, using National Institute of Standards Testing traceable equipment to ensure that they are working properly.

**Beyond-Use Dating**

As already indicated, *potency* refers to the determination of concentration. This is distinct and different from the BUD, which is based on stability-indicating methods.<sup>6</sup> The BUD establishes the shelf life of the preparation. It is based on the use of a validated HPLC stability-indicating method. It is able to separate degradation products from the analyte with accurate quantitation. Testing to establish the BUD should include testing at different storage conditions. For instance, results of testing at accelerated conditions (40°C at 75% relative humidity) are used to calculate the shelf life, using the  $Q_{10}$  rule.

Compounded preparations should also undergo real-time storage conditions (25°C at 60% relative humidity) to accurately reflect the life of the preparation when stored at commonly accepted room

temperature. Other conditions can also be tested, providing that they are properly documented. If a test is performed at refrigerated conditions, the labeling must say to refrigerate; labeling otherwise would invalidate the BUD. Many formulations do not have specific storage requirements. These are generally stored at room temperature, and they may be fine. However, improper storage of a preparation can cause problems. Storage at temperatures above recommended conditions can cause degradation of the active ingredient, which reduces the effective potency of the preparation and may create by-products that could be harmful to the patient.

The pH of a final solution can play a big role in its efficacy. Finding the correct pH enables a product to be safer to use and may extend the expiration of the preparation. A pH that is too low may give the patient a burning sensation. Also, adjusting the pH of a product can increase its stability and prevent corresponding degradation products.

**Number of Samples To Be Tested**

There is no generally agreed-upon protocol for determining the number of articles to be tested. Each practice should develop its own protocol to make such a determination. This should be based upon variables such as type of compounded preparation, volume, risk potential to the patient, procedures and personnel. The key to

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**Table 2. Number of Articles to be Tested, Based on Recommendations from the USP.**

Injections		Noninjections		Devices		Solid Bulk Preparations	
Batch Size	No. of Articles to be Tested	Batch Size	Number Tested	Batch Size	Number Tested	Batch Size	Number Tested
<100	10% or 4	<200	5% or 2 articles	<100	10% or 4 articles	<4	Each container
100 – 500	10	>200	10	100 – 500	10	4 – 50	20% or 4
>500	2% or 20	N/A	N/A	>500	2% or 20	>50	2% or 10
Large-volume	2% or 10	N/A	N/A	N/A	N/A	N/A	N/A
Antibiotic solids (<5 g)	20	N/A	N/A	N/A	N/A	N/A	N/A
Antibiotic solids (>5 g)	6	N/A	N/A	N/A	N/A	N/A	N/A
N/A = not applicable							

quality control is to develop a protocol that is appropriate, logical and well thought out for each compounding practice. An example of such a protocol is listed in Table 1. A suggested protocol based on recommendations from the USP is shown in Table 2.

**Summary**

In summary, it is important for the pharmacist who extemporaneously compounds to ensure the strength, quality, identity and

purity of compounded preparations. An outside analytical laboratory can assist by providing quality control and quality assurance. Determination of potency or concentration is invaluable in maintaining a good preparation that is accurate and precise. Remember, to determine the BUD, a stability-indicating HPLC method must be used. There have been reports of tragedies resulting from a lack of quality control in the compounding pharmacy. Some of these tragedies could probably have been avoided if the pharmacy had taken a more proactive role in quality control and assurance. Typically, one thinks mainly of sterility testing when one thinks of USP Chapter <797>; however, USP Chapter <797> also addresses potency, or concentration, so it is necessary to think about this issue, too, to ensure compliance.

**References**

- 1 US Pharmacopeial Convention, Inc. *United States Pharmacopeia 27-National Formulary 22*. Rockville, MD: US Pharmacopeial Convention, Inc.; 2004: 2350–2370.
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*Address correspondence to: Tom Kupiec, PhD, Analytical Research Laboratories, 840 Research Parkway, Suite 546, Oklahoma City, OK 73104. E-mail: tkupiec@arlok.com* ■



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