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Quality-Control Analytical Methods: A Discussion of *United States Pharmacopeia* Chapter <71> Sterility Tests

ABSTRACT

It is apparent that the quality assurance program of a compounding pharmacy cannot adhere to the strict requirements of some of the general chapters in the *United States Pharmacopeia*. Those chapters containing such strict requirements that may impact pharmacy compounding should be studied thoroughly by the appropriate United States Pharmacopeia expert committee. Afterward, a determination should be made of which standards are reasonable and which can be modified and implemented to ensure timely preparation of quality compounded medications.

The *United States Pharmacopeia (USP)* general chapter on sterility tests was introduced in *USP 20* in 1980. The first paragraph reads as follows:

“The sterility tests presented herein are suitable for revealing the presence of viable forms of bacteria, fungi, and yeasts in or on *Pharmacopeial* articles. Alternative procedures or procedural details may be employed to demonstrate that an article is sterile, provided the results obtained are at least of equivalent reliability (See Procedures under Tests and Assays in the General Notices.) Where a difference appears, or in the event of a dispute, when evidence of microbial contamination is obtained by the procedure given in this *Pharmacopeia*, the result so obtained is conclusive of failure of the article to meet the requirements of the test.¹”

This chapter, along with the *USP* chapter on sterilization (Chapter <1211>), was initially directed at the pharmaceutical industry. In fact, most of the general chapters in the *USP* were directed at the pharmaceutical industry; most were written in the latter third of the 20th century, at a time when mass-production by pharmaceutical companies came to dominate the manufacture of medications. At the same time, the usefulness of the *USP* to practicing pharmacists contracted. The United States Pharmacopeial Convention (*USP*) originated in 1820 when a group of physicians came together to establish standards for the medications they prescribed, which were all compounded by pharmacists. There had been "dumping" of inferior medicines into the U.S. from overseas, so it was important that standards be developed. Over the years, pharmacists became more involved in the activities of the *USP* and, in fact, the *USP* and *National Formulary (NF)* were used as textbooks in many colleges of pharmacy.

In the mid-1900s, however, as the pharmaceutical industry grew and the *USP* became more oriented toward setting standards for drugs manufactured commercially by the pharmaceutical industry, the utility of the *USP* for pharmacists became almost nonexistent. During this era, the primary work done on the *USP* was related to enhancing standards for the pharmaceutical industry. Consequently, many general chapters written for the pharmaceutical industry are currently being applied to pharmaceutical compounding.

Pharmaceutical compounding involves individualized medications, which are not mass-produced in large batches. Unlike commercial products, therefore, compounded preparations usually are not quarantined (i.e., held in batches until all sterility test results are in). Instead, the pharmacist stands across the counter from the patient who hands the pharmacist a prescription for a compounded medication,

and who expects to receive the compounded preparation within a matter of minutes or hours. This scenario is quite different than that in the pharmaceutical industry!

With the growth of pharmaceutical compounding in the past 20 years and the establishment of new *USP* general chapters related to compounding, the *USP* must now serve both the pharmaceutical industry and the pharmacy compounding profession. Many of the general chapters originally intended for industry cannot, however, be applied realistically to the compounding pharmacist. The *International Journal of Pharmaceutical Compounding* will feature in this quality assurance column over the next few issues a series of articles pointing out some of the difficulties involved in applying some of the *USP* general chapters to the compounding pharmacy profession. The *USP* expert committees are in the process of addressing many of these difficulties.



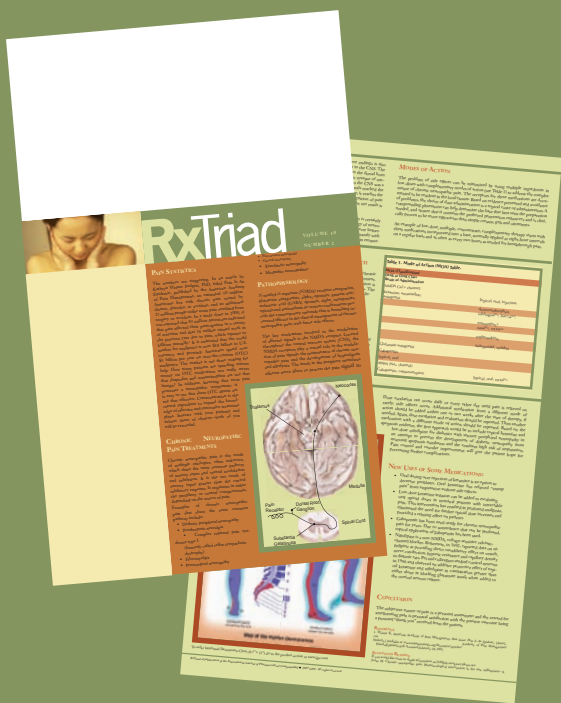
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USP CHAPTER <71> STERILITY TESTS

In *USP 30*, the second paragraph of Chapter <71> states the following:

“ The following procedures are applicable for determining whether a Pharmacopeial article purporting to be sterile complies with the requirements set forth in the individual monograph with respect to the test for sterility.² ”

The current Chapter <71> explains that the procedures are applicable to a "Pharmacopeial article." However, the vast majority of sterile preparations are not "Pharmacopeial article[s]"; they are individual compounded prescriptions, and the vast majority of them have no monographs in the *USP*.

USP Chapter <797> Pharmaceutical Compounding—Sterile Preparations states that it "provides procedures and requirements for compounding sterile preparations." Under the section "Verification of Compounding Accuracy and Sterilization," reference is made to *USP* Chapter <71> Sterility Tests, whose section "Test for Sterility of the Product to be Examined" may be applied to specimens of low- and medium-risk compounded sterile preparations (CSPs) and describes how standard nonpathogenic bacterial cultures may be added to nondispensable specimens of high-risk CSPs before terminal sterilization for subsequent evaluation of sterility. That section of Chapter <71> discusses the minimum quantity to be used for each medium and the minimum number of articles to be tested in relation to the number of articles in the batch. Table 3 of that section relates to the number of articles to be tested.

For parenteral preparations, Table 3 states that, "for any batch of up to 100 containers, 10% or four containers, whichever is greater, must be tested." This would probably accommodate 99% of the compounders involved in compounding sterile preparations. If, however, a pharmacist receives a prescription for five containers, then according to this chapter, four of the containers must be used for the sterility test. This means that a total of nine containers must be compounded. If the active ingredient is inexpensive, this may not pose a problem. If the active ingredient is expensive, however, then the cost to the patient is going to include the additional drug used for preparing the additional containers for testing. This can drive up the cost of the preparation considerably. Moreover, if the preparation is quarantined and cannot be released until the sterility results are returned, the patient is forced to wait as long as 14 days for the medication, an untenable situation. Another problem with this standard is that very small-volume preparations, such as an ophthalmic injection with a total volume of 0.1 mL, do not lend themselves to proper sterility testing as dictated by Chapter <71>.

One way to ensure that the compounded preparation is sterile is to use the *man, method, and machine mentality*.

Man – The pharmacist and/or technician should be trained properly and thoroughly understand aseptic technique processes. This should include successful utilization of aseptic technique, personnel validation, or manipulation.

Method – The individual should use proper aseptic technique in compounding, utilizing proper gloves, gowning, and environment. A media-fill test mimicking the exact process may even be performed and monitored to ensure that no growth occurs in the media.

Machine – The compounding should be performed in a Class 100 cleanroom or barrier isolator. Any automated measuring device, such as scales or delivery systems, should be calibrated.

This man, method, and machine mentality should be thought of as a series of processes. By ensuring that these processes are performed using aseptic technique in a clean environment by trained individuals, a history of continuous quality improvement can be demonstrated and developed. Therefore, even when the pharmacist or technician compounds a single or very few preparations, aseptic technique is already in place through the process.

If the compounder looks at the beyond-use dates and tries to correlate them to the performance of sterility tests, the compounded preparation will be "out of date" and unusable before the results of the sterility test are finalized.

This situation calls for separate standards for compounding pharmacies and manufacturers. It is not practical for compounding pharmacists to test each and every sterile preparation that is compounded. Standards must be developed to account for the specific realities of pharmacy practice. The USP expert committee should focus more on process validation to complement preparation verification. Once the aseptic facilities of each pharmacy and skills of each staff member are validated, routine testing can be implemented to ensure that compliance is maintained. This type of standard would allow a pharmacist to dispense sterile preparations without waiting for a 14-day quarantine.

SUMMARY

It is apparent that the quality assurance program of a compounding pharmacy cannot adhere to the strict requirements of some of the general chapters in the USP. We recommend that the appropriate expert committees thoroughly study the chapters that may have an impact on pharmacy compounding and determine which standards are reasonable and which can be modified and implemented to ensure timely preparation of quality compounded medications.

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1. United States Pharmacopeial Convention, Inc. *United States Pharmacopeia 20–National Formulary 15*. Rockville, MD: US Pharmacopeial Convention, Inc.; 1979: 878–882.
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MD: US Pharmacopeial Convention, Inc.; 2006: 97–102, 334–351.

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