



Quality Release Checks for Compounded Sterile Preparations

Facilities that prepare, store, and dispense compounded sterile preparations (CSPs) are responsible for ensuring continued compliance with USP Chapter <797> through a series of in-process and finished-process quality checks. Appropriate quality checks will ensure preparations are consistently compounded correctly. In addition, risk assessments should be performed prior to the release of a medication. Risk assessments will ensure that all of the variables (materials, people, environment, methods, intended use, etc.) surrounding the preparation, in addition to performed and recorded quality checks, are taken into consideration prior to the finished preparation's release.

The intent of <797> is clear: "to prevent harm or fatality to patients that could result from microbial contamination (non-sterility), excessive bacterial endotoxins, large content errors in the strength of correct ingredients, and incorrect ingredients in CSPs." USP <797> defines the three microbial contamination risk levels as low, medium, and high, and follows up with an important set of statements regarding the responsibility of compounding supervisors to perform the appropriate risk assessments that will be used to further determine the level of rigor and vigilance with which CSPs should be assessed for quality prior to release.

The Importance of Quality Control Checks

Quality checks should be documented on the compounding log and include, but are not limited to, checks of materials, such as verification of raw material identity and expiration (including lot number checks and Certificates of Analysis for each), and weights and volumes of each component prior to com-



Photo courtesy of Millipore

The sterility test is perhaps the **most important** quality control test to be performed prior to the release of a finished preparation.

pounding. Checks against the theoretical yield versus the actual yield of a finished CSP should be made, and discrepancies should be handled appropriately. Through a review of test results, pharmacists should verify that preparations are sterile and pyrogen-free, and that the strengths of ingredients and the pH of the preparation are within acceptable limits. Pharmacists should also review the container/closure system to verify that it is appropriate for the preparation and its intended use, storage, and route of administration.

Equipment should be suitable and function as intended during the compounding process to ensure preparation quality. Supplies used should also be checked for suitability, and should be confirmed to be free from defects that could adversely affect the finished preparation. A visual inspection for particulates or container/closure breaches or defects should be performed, in addition to checks against the compounding log to ensure the CSP is labeled correctly.

► Ingredient and Component Selection

Components and ingredients used to prepare a CSP should be verified for accuracy and documented on the compounding log. USP recommends using official USP-NF grade materials for compounding. Certificates of Analysis (C of A) should be kept for all

materials used in compounding. The C of A should be reviewed during the selection of the ingredients, and the supplier, lot number, and expiration date of the material on the C of A should be confirmed against the raw materials container and, again, on the compounding log when the weights and volumes are checked by the pharmacist prior to compounding.

For preparations requiring the use of an appropriate sterile 0.2µm filter, an integrity test should be performed to ensure the filter performed as expected



and is without defect. As a matter of good documentation, recording this testing, as well as the manufacturer and lot number of the filter, can provide traceability for preparations sterilized with this lot of filters in the event the filter manufacturer issues a recall. Having this important information on hand can directly affect your pharmacy's decision, depending on the nature of the manufacturer's recall, to conduct an internal recall.

► Weight and Volume Measurements

Ingredient weight and volume measurements should be documented, with a secondary review and verification by a pharmacist. Equipment should follow a daily calibration schedule, and there should be documented evidence that the equipment and instruments used to weigh and measure ingredients are calibrated each day.

Pharmacists should review and document in the compounding log the finished preparation yield to ensure there is little to no variance in the theoretical yield versus the actual yield. A preparation with a variance greater than 10% should be failed and labeled "out of specification" (OOS), and an investigation to uncover the cause of the variance should be performed.

► Physical Inspection of Finished CSPs

CSPs should be inspected prior to labeling and, again, at the time of dispensing to ensure the accuracy of the final fill amounts and to ensure the containers remain free from defects. As part of a physical inspection, check for particulate matter in the preparation and for leaks in the bag, vial, etc. Visual inspection is most efficiently conducted using a light box with a white and black background. During inspection, close attention should be paid when looking for particulates and also when assessing the physical integrity of the containers. For example, the necks of vials and ampoules should be inspected for cracks or chips. It is important that the personnel performing visual inspections have the proper training on what to look for and the steps to perform when an inspection turns up a CSP that is not essentially free from particulate matter.

► Sterility and Endotoxins

The sterility test is perhaps the most important quality control test to be performed prior to the release of a finished preparation. <797> has specific testing standards for low-, medium-, and high-risk compounding. Those CSPs that fall into the low- to medium-risk category must be tested according to USP Chapter <71> if the beyond-use date (BUD) assigned by the pharmacist exceeds those listed in <797>. For batches larger than 25 preparations, all high-risk CSPs must be tested according to <71> for sterility and USP Chapter <85> for bacterial endotoxins, in addition to the low- and medium-risk testing standards. USP Chapter <85> has defined sets of limits for endotoxins, and these test results, in addition to the intended use and route of administration, must be reviewed and documented by the pharmacist as part of the release check.

A sterility test with negative results for contamination does not prove, in

and of itself, that a preparation is sterile. "Sterile" is an absolute term meaning "free from living microorganisms." In reality, it is impossible - short of performing sterility testing on and destroying each and every unit in a batch - to show a preparation is sterile. Sterility has been defined, then, as a measure of the probability that a microorganism will survive sterilization. The probability of sterility may come close to, but will never reach, zero.

► Environmental Considerations

Even with documented processes and personnel verification in place to ensure CSPs are consistently made with the desired quality attributes, each compounding log still contains its own set of unique variables. The probability of contamination is increased when the contributing variables are not monitored properly and fall out of a state of control. It is important for the pharmacist performing the quality checks to be aware of the equipment, materials, and personnel involved in the preparation of a CSP, as well as the state of control in which the CSP was made. The supervising pharmacist should know the compounding process and environment intimately. Environmental monitoring results, in addition to sterility testing and other quality control checks, should be used when assessing the quality of the finished product prior to release.

► Compounding Verification and Personnel Assessments

Procedures and sterilization methods for CSPs should be written and challenged to ensure that, when performed, they consistently produce a CSP with the desired quality attributes. A single, gowned operator can shed up to 10,000 colony forming units (CFUs) per hour, resulting in a significant source of airborne contamination.¹ Therefore, operators must be adequately trained on these procedures and methods, and perform them consistently and with little or no variability. Additionally, aseptic operators are required to demonstrate proficiency in proper gowning and hand-washing procedures, as well as in aseptic manipulations through media-fill challenge testing (annually for low- to medium-risk CSPs and semi-annually for high-risk CSPs). Operators present the greatest opportunity for variability in a process and subsequently the greatest opportunity for microbial contamination, especially when a problem is encountered during aseptic processing.

► Labeling

Pharmacists should ensure the CSP label accurately reflects the correct drug name, size, route of administration, ingredients, and ingredient concentrations. Any storage and handling requirements should appear on the label, as well. The lot number on the CSP label should also correlate with the lot number on the compounding log. In addition, the beyond-use date of the preparation should be verified against the compounding log.

Conclusion

It is vital for pharmacists to perform and document the many quality control





Environmental monitoring results, in addition to sterility testing and other quality control checks, should be used when **assessing the quality** of the finished product prior to release.

checks for CSPs. This set of checks, when viewed cumulatively with additional variables, such as the compounding personnel and environment, provides the data necessary for the pharmacist performing the finished preparation release checks to properly assess the quality of the finished preparation. The standards set forth in USP <797> provide pharmacists the means and direction to ensure “that quality is built into the preparation” of the CSPs dispensed by their pharmacies. ■

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