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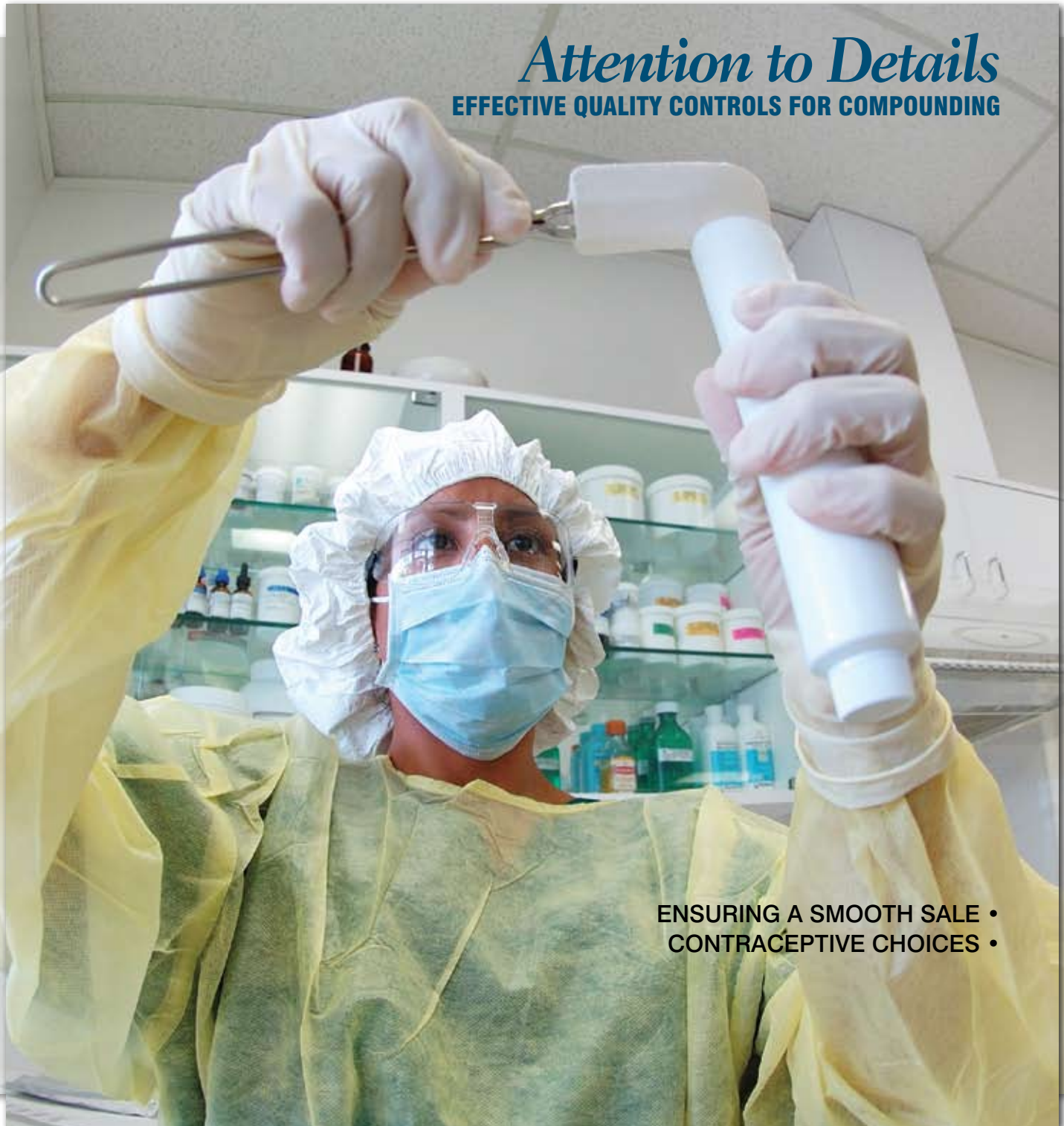
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# PHARMACIST

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*Attention to Details*  
**EFFECTIVE QUALITY CONTROLS FOR COMPOUNDING**



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# Higher Quality Compounding

Implementing quality assurance and quality control programs can improve compounding pharmacy procedures

By William J. Zolner, PhD

Photography by Bryan Sparks/PCCA

**Q**uality assurance (QA) and quality control (QC) are becoming ever more important in today's compounding pharmacy. Heightened public awareness, increased regulatory attention, and most importantly, the desire of pharmacists to provide the highest quality preparations for their patients, while improving their pharmacy operations, have all created increased interest in QA and QC.

Countless books and articles have been written about QA and QC, making the whole subject seem intimidating to many pharmacists trying to implement such a program. However, using the old adage that "every trip starts with one small step," this article may help in guiding compounders on the path to a process of improved quality.

Before beginning, it may be helpful to define the terms QA and QC. Quality assurance is a process and plan that specifies the steps and actions taken to ensure the creation and maintenance of proper standards for compounding. QA ensures that you are doing the right things, the right





way. QA activities guarantee that the process is defined, appropriate, and updated on a regular basis. For example, a QA review would focus on the way you make a preparation and to assure that the requirements are complete and being defined at the proper level of detail.

Quality control refers to the quality-related activities associated with the creation of a compounded preparation. These activities, which usually fall into the category of inspection and testing, are used to ensure that the preparation conforms to the appropriate and proper specifications. QC makes certain that the results of what you've done are what you expected.

Fortunately, there are several good resources to help determine what is expected in the area of QA/QC for pharmaceutical compounding. They include the following:

- United States Pharmacopeia (USP) <1075> Good Compounding Practices
- USP <795> Pharmaceutical Compounding—Nonsterile Preparations
- USP <797> Pharmaceutical Compounding—Sterile Preparations
- USP <1163> Quality Assurance in Pharmaceutical Compounding (to be published in 2007)
- Pharmaceutical Compounding Accreditation Board (PCAB)

Additionally, there are a number of pre-packaged QA/standard operating procedure (SOP) manuals available from professional organizations and suppliers to the compounding industry. These systems vary in complexity

from basic to complex and can be easily modified to suit the specific requirements of the individual pharmacy.

However, as already mentioned, it is not the lack of information, but the sheer amount and complexity of what is available that often makes getting started difficult. Some pharmacists also believe that they need a QA plan defined before they can begin a QC program. While this would be ideal, in actuality, either can be initiated independently because they involve different activities.

## QUALITY ASSURANCE

As defined previously, a QA program is intended to provide a clear description and plan for monitoring, evaluating, correcting, and improving all the activities and processes used by the pharmacy in providing compounded preparations. One of the main provisions of the QA program is improving the overall quality within the pharmacy and thus improving patient care.

To start in the development of a QA program, the pharmacist should create a written, formalized QA plan, which will define those areas to be addressed in the program. Some of these areas are general in scope and independent of the type of compounding performed at the pharmacy, while others depend specifically on the type and complexity of compounding performed. As could be expected, non-sterile, simple compounding, involving only the mixing of commercial products, will require a more basic QA plan compared to more complex, sterile, and high risk level compounding, or compounding with radiopharmaceuticals.

In developing the plan, particular care should be taken to establish objective, measurable indicators for all monitoring activities, and the development of action plans and follow up should these indicators move out of their acceptable range. As the overall quality of the pharmacy improves, these indicators and their target values will need to be evaluated and readjusted to ensure continued improvement in the pharmacy.

The QA plan should be a formalized, written document following the outline, and will provide the necessary framework for the pharmacy's overall QA/QC program. As a minimum, the QA plan should address the following areas:

### Quality Mission Statement

This is a short, simple statement that all members of the

pharmacy staff can understand. It clearly sets out the commitment of the pharmacy to a high quality standard and to the development, implementation, and continuous improvement of all aspects of the quality process.

### The Organization

Specific assignment of quality functional responsibilities is defined in this section of the QA plan.

### Documentation

This section of the QA plan explains the documentation process that will be used in the pharmacy. It should state that all significant procedures performed in the compounding area will be covered by Standard Operating Procedures (SOPs) and will be documented, how changes will be made to the QA plan, and who has responsibility for changing the document. In general, the QA plan and documentation should be reviewed at least on an annual basis, or when significant changes are made within the pharmacy.

### The Facility and Compounding Environment

What standards will be used to monitor and evaluate the physical environment where compounding will be performed? This section's complexity will largely depend on the type of compounding performed at the pharmacy, with high-risk sterile or radiopharmaceutical activities demanding attention to specific quality requirements. However, even simple compounding activities require environmental standards. Just because compounding is non-sterile, it does not mean that it can be done in a dirty environment. Some topics covered here would be:

- General cleaning
- Specific cleaning and sanitizing activities for critical areas
- Testing that will be done for particulates and micro-organisms
- Acceptable test limits
- What will be done should the tests exceed these limits

Instead of putting all the detail into the QA plan, this section may refer to specific SOPs that the pharmacy will use to accomplish these tasks. As a note, USP<1116> (Microbiological Evaluation of Clean Rooms and Other Controlled Environments) may help in setting acceptable quality goals for this area.



*The QA plan should be a formalized, written document, following an outline.*

### Compounding Equipment

Again, the topics in this section can range from the simple to the complex depending on the type of compounding performed. QA for most compounding equipment can follow a simple plan:

- **Installation**—Is the equipment installed correctly? For example, if we are considering a balance, is it installed on a level, vibration-free surface? Is the power source free from electrical noise? Are there interfering air currents present?
- **Performance**—Is the equipment designed for the purpose intended and does it meet the manufacturer's specifications? You will need to perform tests to check that the equipment is functioning as designed. Using the balance example again, if the balance specifications state that the linearity is within 1 percent from 10 mg to 99 grams, does the balance meet these specifications?
- **Operation**—Does the equipment function properly as you will use it in the pharmacy? The balance again provides a good example. If your requirements call for measuring ingredients to  $\pm 0.1$  mg and the balance display only indicates three digits to the right of the decimal in grams (0.000 grams), you have an operation quality problem. While the balance may be installed correctly, and function according to the manufacturer's specification, operation in your pharmacy, where an accuracy of 0.1 mg is required, will not lead to a quality measurement.

Each piece of critical compounding equipment should have a written installation, performance, and operation checklist as part of the documentation in the pharmacy. The equipment may also be subject to periodic maintenance, calibration, or testing requirements that will need to be documented. The QA plan should set out the schedule and procedure for these activities. The detailed instructions for these tasks are usually contained in the pharmacy SOP and can be referenced from the QA plan as needed.

### Personnel

This may be the most difficult area of the QA plan, as it is the most diverse from pharmacy to pharmacy and therefore does not lend itself to a standard outline. This section should clearly spell out the responsibilities of the person-

nel in the pharmacy and the necessary QA standards and measures that will assure that the personnel are selected, trained, and monitored to insure that they are qualified to conduct their assigned tasks.

This section is critical for the technicians and pharmacists who are actually compounding the preparations, but it also should cover the support personnel within the pharmacy. It may refer to the pharmacy policy and procedures manual for specific job descriptions, hiring qualifications, and training requirements; and to the pharmacy SOP for detailed testing procedures. For sterile compounding pharmacies it should also define a media fill testing procedure for all personnel working in the aseptic area.

### Compounding Materials

In a manufacturing environment this is sometimes referred to as incoming quality. Often overlooked in a QA plan for a pharmacy, this area is one of the most important in assuring a quality preparation. The old adage, "Garbage In, Garbage Out," says it all. The QA plan needs to address the actions that the pharmacy will take to ensure that all materials used in the compounding process are of the highest quality and suited to the compounding task intended. A clear delineation of the types of chemicals approved for use in the pharmacy should be part of this section, and USP <1075> offers some excellent guidance in this area. It may also be prudent to include in this section

the requirements for qualifying a material and/or chemical supplier, and the process needed to change suppliers.

### The Compounding Process

This section of the QA plan defines the process that the pharmacy will use to do the actual compounding of preparations. It can be somewhat general in nature and refer to specific SOPs for details. This section of the plan should contain specific assurances and cover topics such as:

- A statement that written procedures and formulations shall be available and shall be followed for all compounded preparations
- Defining the checking procedures that will be employed to assure correct implementation of the compounding process
- Specifying the labeling and labeling procedures that will be used
- Specifying what guidelines will be used to ensure the proper packaging and drug preparation containers
- Explaining how Beyond Use Dating will be determined
- Defining the specific tests and procedures that will be employed to check the accuracy, integrity, and suitability of the final compounded preparations. Examples include in-house tests, such as capsule weighing, pH, clarity; independent laboratory testing of sterility and endotoxin for sterile preparations; and potency testing procedures for sterile and/or non sterile preparations
- Post compounding storage

While many sections of the QA plan specify monitoring, measuring, and testing activities to verify that the preparation meets standards, it is this section of the QA plan that is most closely tied to quality control, and should provide a reviewer the general guidelines for the pharmacy's QC activities.

### QUALITY CONTROL

Just to refresh, QC is the inspection and testing activities that are used to ensure that the compounded medication conforms to the specifications that have been established for that preparation. Additionally, QC monitoring and testing is necessary to ensure that the facilities, equipment, personnel, and materials meet the specifications that have been established.

QA testing for the pharmacy facilities, equipment, personnel, and materials are basically straightforward, and

are discussed in some detail in several of the USP chapters referenced at the beginning of this article. Most of the testing is well defined (such as, balances must be calibrated on a six-month interval or when moved), and can be accomplished in house or with the help of a qualified testing service.

We have found, however, that it is the final QC testing of the compounded preparations that presents the most confusion and misunderstanding with pharmacists. This is understandable, as compounding by its very nature does not easily fall into any predefined type of activity. Adding to this difficulty is the traditional templates for pharmaceutical QC have been developed for large scale manufacturing operations, which clearly are not suitable for direct adoption into a pharmacy. The questions most pharmacists have are:

- What must I test and what should I test?
- How often should I test?
- How do I get started?

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Regulated testing requirements are addressed specifically by USP <797> and USP <795> and in some cases by the pharmacy board in the individual state where the pharmacy is licensed. USP <795> states that "the compounded preparations are to be prepared to ensure that each preparation shall contain not less than 90 percent and not more than 110 percent of the theoretically calculated and labeled quantity of active ingredient per unit weight or volume." However, it does not specifically state that you must test the preparation to show that it is within these limits.

In terms of USP <797>, it is more specific when it comes to testing requirements. There are two areas where testing is specified: to extend storage periods, and for finished preparation release checks and tests.

### Extended Storage Periods

Low, medium, and high risk level compounded sterile preparations (CSPs) all have very specific storage periods

that are listed in USP <797>. To extend the storage beyond these somewhat confining periods, these preparations must pass a sterility test (such as the USP <71> Test for Sterility). Even with a sterility test, however, you must also meet the beyond use date (BUD) requirements for the specific preparation. Finished preparation release checks and test are specified when:

- You have a high-risk level CSP.
- It is administered by injection into the vascular or central nervous system.
- It is prepared in groups of more than 25 identical individual single dose packages.
- It is prepared in multiple dose vials for administration to multiple patients.
- It is exposed longer than 12 hours between 2-8 degrees Celsius, and longer than six hours at warmer than 8 degrees (C) before it is sterilized.

If these conditions are met, then the CSP is tested for sterility (Sterility Tests USP <71>), and is tested for bacterial endotoxins (Bacterial Endotoxins Test USP <85>).

Finished preparation release checks and tests also specify when the strength (potency) of a finished CSP cannot be confirmed to be accurate based on the verification of the following factors:

- The label of the CSP has the correct names and amounts or concentrations of ingredients, the total volume, the BUD, the route of administration, the storage conditions, and other information for safe use.
- The correct identities, purities, and amounts of ingredients were obtained by comparing the original written order to the written compounding record for the CSP.
- The correct fill volumes in CSP and the correct quantities of filled units of the CSP were obtained.

If the strength (potency) of a finished CSP cannot be confirmed to be accurate based on the factors listed above, then the CSP must be assayed for potency by methods that are specific for the active ingredients.

The only other area where you need to look for testing requirements is your individual state board of pharmacy regulations. Many states are adopting language similar to the USP, but others have written into law specific requirements that may be more demanding of final preparation testing.

Now for the more interesting question—what should be tested? While there are many answers to this, they generally fall into four categories:

- To ensure that my patient is receiving a safe and effective preparation.
- To assist in improving the overall quality of the pharmacy by providing objective measures of compounded preparations.
- To prove to a potential regulatory authority that my preparation is correct.
- To help me sleep at night, knowing that I am doing things right.

With compounding pharmacy accreditation a reality, it may also be advantageous to consider preparation testing as part of the overall accreditation process, and make it a cornerstone in your marketing programs to health care providers and clients.

## QC TESTING GUIDELINES

Here are some general guidelines to consider when formulating your QC testing program. You should view testing on a continuum, from no testing on one end to testing everything at the other. In today's environment, the no-testing end is probably not a wise place to be, even for the most simple of compounds. Conversely, testing everything in a compounding environment is not necessary or economically prudent. Being somewhere in the middle of this continuum is necessary, and will depend on many factors.

The first factor is to be sure that you comply with all the “must test” regulations that USP and your state board of pharmacy have specified. It would then seem prudent to consider the level of risk associated with your preparation when deciding what additional, non-regulation based testing should be performed. Clearly, a narrow therapeutic range preparation has more risk if it is out of specification than does a preparation with a wide range.

If you are going to start making a preparation on a regular basis, you should initially test to make sure your formula and procedures are correct. Also, retest if you change how you make the preparation. You now are assured that the basic “process” that you use to make the preparation is correct.

Look at your pharmacy from a “process” perspective. In a pharmacy there will be many processes and associated sub-processes that define what is done on a daily basis. For

example, there may be a process for capsule making, which includes sub-processes for weighing powders, mixing powders, and filling capsules, to name a few.

This way of thinking is important when looking at QC activities that must be done in the pharmacy, especially when it comes to testing preparations. When you send a preparation for testing to a laboratory, you not only are testing the specific preparation, but you also are testing the “process” used to create that preparation.

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For example, if you send Biest capsules for potency testing, you will get the results for that specific batch of Biest. However, you also will get confirmation that your “process” for making the capsules is satisfactory. Over time, as you successfully pass tests on other lots of Biest capsules, you are accumulating a body of evidence that your overall capsule making “process” has a high level of quality, and is in control. Regularly testing various dosage forms (such as creams, suppositories, and capsules, to name several) will allow you to begin building up data on the quality of your various processes.

### SKIP LOT TESTING

A procedure known as Skip-Lot testing may provide the most optimum testing protocol. Skip-Lot testing is a statistically valid sampling plan where only a fraction of the lots of a compounded preparation are tested. This mode of sampling is economically efficient in expense, time, and effort and has been used extensively in areas where the quality of the tested products has been demonstrated to be very good. All of these attributes seem to make this an ideal sampling method for compounded preparations.

In summary, Skip-Lot testing consists of:

- Verifying that the compounded preparation is correct at the start of the program by appropriate potency testing in an independent laboratory.

- Choosing a sampling interval, which will define the maximum “out of specification” (OOS) limits that will be detected. Surprisingly, these intervals can be relatively long. For example if you test every 25th lot (or batch) of a preparation, which is a 4 percent sampling plan, you should be assured that your preparations will be within specification better than 95 percent of the time.
- Setting up a schedule (random or fixed) for the preparation to be sent out for repeated testing.
- Collecting and recording the data from the testing.
- Re-verification of the preparation if it fails a test, or if changes are made to the formula, procedures or people making the preparation.

The key to this procedure is the initial test, which demonstrates that the formula, procedures and the people doing the compounding can make a quality compounded preparation. The continued testing verifies that things are still “in control” and that the resultant quality continues to be maintained.

Finally, keep detailed records of the testing results, especially of the preparations that are OOS. Often we learn more about what we do from the OOS items and what we find out about our process and procedures when we take corrective actions. This will also demonstrate to any reasonable regulator that if a problem is encountered, you have worked diligently to correct and ensure that it does not reoccur.

As mentioned previously, the implementation of a QA/QC program in a pharmacy is becoming important. It will only happen if there is a commitment from the top of the organization through all of the pharmacy staff. In some situations, such as sterile compounding, a pharmacy should not even consider performing these tasks without the required QC testing that is mandated. In other cases, it may be best just to start by implementing a Skip-Lot QC testing program on several high volume preparations. By following the previously discussed steps, a pharmacist should be able to set out a roadmap to a viable QA/QC program that not only will improve the compounded preparations that the pharmacy provides, but also improve the overall operation of the business. **ap**

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