Analytical Testing of Extemporaneously Compounded Preparations

Thomas Kupiec, PhD; Pedro L. Huerta, Jr., PhD, RPh
Analytical Research Laboratories, 122 N. Bryant, Edmond, OK 73034

It protects you and your patients.

Quality assurance/quality control should be part of a good compounding program. Compounding pharmaceutical preparations is an art and science that is carefully developed through proper training and years of dispensing experience. The efficacy and safety of compounded preparations must be guaranteed by ensuring that they are correctly prepared. Many pharmacists have or should have considered the question, "How good is my technique and the preparations I make?" One important way to ensure efficacy and safety is to establish a quality control program that involves the submission of compounded preparations for analytical and microbiological testing.

Why does my pharmacy need a quality control program?

A well-established quality control program will provide the necessary documentation of the methods and procedures that your pharmacy uses in compounding extemporaneous preparations. The *USP/NF* sections <1161> (now <795>) and <1206> provide guidelines for the compounding pharmacist to consider regarding a quality assurance/quality control program.[1] A successful quality control program is a powerful marketing tool that will build excellent public relations with patients, physicians and the overall community. Your standard of practice will be openly validated to build better patient and physician confidence in you as a conscientious health provider.

What types of tests should compounding pharmacists have performed on their preparations?

Potency Tests

Potency tests supply qualitative (what is it) and quantitative (how much is there) determinations. These provide documentation that the correct drugs and quantities were used to compound the preparations. They are typically performed using a high-performance liquid chromatographic method. The method should be validated and, if appropriate, should be one that is published in the *USP/NF*.

Microbial Tests

Sterility, pyrogenicity (endotoxins) and other microbial tests demonstrate that preparations are free of bacterial and/or fungal contamination. The samples tested should be within the limits of the acceptable range of sterility according to USP/NF guidelines.

Preservative Effectiveness

This is another type of test to check for the effectiveness of the antimicrobial preservative added to the dosage form to protect it from microbial contamination.

Stability

Stability studies allow the assignment of reliable beyond-use dates or shelf-life to ensure that a preparation's efficacy will not be affected because of possible degradation during shipping and storage.[2] The dosage forms are subjected to different temperatures and relative-humidity environments over a period of time. Samples are tested initially and then at predetermined intervals to see if the product degrades and, if so, by how much. The addition of preservatives, antioxidants, etc., to the formulation is another factor to be considered to increase the shelf-life. It is important to ensure that the additives do not interfere with the analysis of the active ingredient.

What type of preparations should be tested?

The following types and examples of each preparation listed should be tested.

1. Dosage forms with low concentrations of highly potent drugs. To guarantee patient safety, the concentration should be tested when compounding preparations involving prostaglandins,

These volumetric flasks are used for preparing dilutions prior to analysis.

Photos: Lanny David © 2000

Here high-pressure liquid chromatography is being used for determining concentration.

A sample is obtained for pH adjustment for further analysis.

fentanyl, T_3 and T_4, sodium warfarin, and triple-estrogen preparations. A small error in weighing and improper mixing (nonhomogeneous mixture) could result in a problem related to the patient's safety and well-being.

2. Dosage forms of drugs with low stability profiles, e.g., secretin, acetylcysteine and heparin, to assign correct beyond-use dates.
3. Solutions, ointments or creams, e.g., estrogens, ketoprofen, morphine sulfate and anti-inflammatory steroids, that introduce potential degradation problems.
4. Parenteral dosage forms, e.g., fentanyl, bupivacaine, morphine (for intrathecal delivery) and progesterone in oil, to guarantee sterile and pyrogen-free preparations.
5. Extensively prepared products, e.g., inhalation solutions such as albuterol-ipratropium, progesterone in oil, hormone replacement therapies and erectile dysfunction mixtures.
6. Medications in a matrix that has the potential for growing microorganisms, e.g., syrups and Pluronic® lecithin organogel preparations.

When or how often should samples be tested?

The frequency of testing is dependent on several factors, including the size of the batch and the number of dosage units being compounded per patient. The larger the total volume of the compounding practice, the greater the need for quality control, i.e., a large-volume compounding shop performing no external quality control should be a concern for the pharmacist. As the incidence of pharmaceutical compounding increases, there will be greater impact on patients; therefore, the need for quality standards is going to increase. Determination of quality requires a tight, well-thought-out program and also involves using a contract analytical laboratory.

Where should I submit samples for testing?

The choice of a laboratory should be based on specific criteria that are advantageous for the compounding pharmacy. Historically, there are three main factors to consider: (1) turnaround time, (2) quality and (3) service.

Turnaround Time

The laboratory chosen should provide a rapid turnaround time to allow the timely dispensing of the pharmaceutical preparations and maintenance of a good client-service relationship. This ensures timeliness, especially if the compounding pharmacist has a product in quarantine pending results from the lab before sending it out. Generally, a larger quantity of the compounded preparation is prepared, the required quantity dispensed to the patient, and a portion sent for analysis. A reasonable turnaround time is one to two weeks, depending on the size of the project or study. If the volume of a compounded preparation is large, it may be advantageous to have a stability study performed to validate a longer beyond-use date on the preparation; otherwise, the conservative beyond-use date in the compounding chapter of the *USP/NF* must be used. A stability study could take several months to complete.

Quality

The client should be able to have confidence in the contract-laboratory results. The laboratory should be one with high integrity and a good reputation, to ensure that quality standardized results

are provided. The laboratory should use modern instrumentation as well as official USP standards and procedures outlined in the formulary. The laboratory should follow Good Laboratory Practices procedures and have a strong pharmaceutical background. It is important for the laboratory conducting your tests to have a quality assurance/quality control program itself. According to Meeks in a recent article on contract laboratories, "It all comes down to quality; quality work is what gives you a chance at getting business and then service is how you distinguish yourself and keep the business."[3]

Service

The contract laboratory should be willing to work with the compounding pharmacist regarding analysis of ingredients of specific formulations. The participating laboratory should always maintain confidentiality regarding analytical results and formulations. Select a lab that can provide needed services such as microbiological, as well as chemical, testing. Communication is important so that compounding pharmacists and the laboratory can determine what services need to be performed. It is essential that both the pharmacists and the laboratory are "playing from the same sheet of music." The laboratory can be a good resource for the compounding pharmacist.

Is it cost effective to submit compounded preparations for testing?

Yes, a testing program provides assurance of correct preparation of preparations, which increases patient safety. These two contributions minimize any potential medical-legal issues. The documentation validates the pharmacy's practice and procedures. Therefore, the cost consideration is nominal when compared to the benefits received.

Conclusion

In summary, "quality is meeting the requirements."[4] The requirements are to ensure that the compounding pharmacist's preparations are free of microbiological contamination and that the concentration is as stated on the label. The submission of samples for testing of compounded pharmaceutical preparations by a pharmacy is a positive, proactive approach. It minimizes or eliminates possible future negative effects concerning product efficacy and patient safety. Contemporary Food and Drug Administration regulations recommend a proactive approach and, if problems ever arise, regulatory agencies look favorably at pharmacies that have a quality control program in place.

References

1. *United States Pharmacopeia XXIV/National Formulary 19.* Rockville, MD, U.S. Pharmacopeial Convention, Inc., 1999.
2. Ansel HC, Popovich NG, Allen LV Jr. *Pharmaceutical Dosage Forms and Drug Delivery Systems.* Baltimore, MD, Williams & Wilkins, 1995.
3. Flickinger B. Integrated effort: The role of the contract lab in drug development and testing. *Pharmaceutical Formulation & Quality* 1999;3:26-30.
4. *The Pharmaceutical Quality Control Handbook.* Skokie, IL, G.D. Searle & Co., 1984, p 3. ■

An analytical chemist reviews data for quality control.