

QUALITY ASSURANCE ISSUES IN COMPOUNDING PHARMACY

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To create compounded medicines, a pharmacist fills prescriptions by combining individual ingredients into specific dosage forms as determined by a medical practitioner. These forms include tablets, capsules, creams, gels, lozenges, and more.

Today, the majority of US pharmacies do little, if any, compounding, and only a small number of pharmacies specialize in compounding prescriptions. And yet the need for compounding pharmacies is clearly evident, as there will always be particular situations that require creating medicines for patients who have extraordinary needs.

Compounding is important and useful for patient care, but there are legitimate concerns about the quality and safety of compounded medicines as well as concerns about overseeing the pharmacies that compound them. This column will focus on quality assurance (QA) and quality control (QC) practices that should be routine in every compounding pharmacy. If faithfully followed, these practices will significantly increase the consistency and safety of compounded medicines.

CURRENT STATUS OF REGULATION, ENFORCEMENT, AND QUALITY ASSURANCE

The pharmacy profession is regulated solely by state pharmacy boards. The only official regulations are given by United States Pharmacopeia (USP, www.usp.org) in its compendium, *The United States Pharmacopeia and The National Formulary*. The 2 most pertinent chapters referring to compounding are: Chapter 797, "Pharmaceutical Compounding: Sterile Preparations;" and Chapter 795, "Pharmaceutical Compounding: Non-Sterile Preparations." (For more information on pertinent chapters, see Table 1.) The unfortunate truth, however, is that these USP guidelines are quite vague. In addition, it is completely up to individual state boards to both adopt the guidelines and enforce compliance within their jurisdictions. Herein lies one potential problem—individual state boards might choose to adopt quality guidelines differing from other states, thus creating a state-to-state disparity. Some states may even decide to adopt only portions of the guidelines; the decision is up to them. It is evident

what problems this creates in terms of consistency. Since 1990, the Food and Drug Administration (FDA) has become aware of more than 55 product quality problems associated with compounded products, many of which resulted in product recalls.¹

TABLE 1. USP CHAPTERS OF INTEREST TO PHARMACISTS

Chapter	Title
1	Injections
71	Sterility Tests
85	Bacterial Endotoxin Test
795	Pharmaceutical Compounding—Non-Sterile
797	Pharmaceutical Compounding—Sterile
1075	Good Compounding Practices
1160	Pharmaceutical Calculations
1191	Stability Considerations in Dispensing
1211	Sterilization and Sterility Assurance

Source: Trisse LA. An Update on USP Chapter <797> The New National Standard for Sterile Preparation. ASHP Advantage. Referenced Sep 1, 2006. www.ashp.org/SterileCPD/USP797_Update_Trissel.pdf.

The American Society of Health System Pharmacists (ASHP, www.ashp.org) also offers compounding guidelines, but these are voluntary and only serve as recommendations. ASHP itself finds fault with the USP guidelines. It states, "USP Chapter <797> sets forth standards, guidance, and examples for compounding sterile preparations, but it does not provide specific and comprehensive information describing how to meet those standards. Persons who compound sterile preparations should exercise their professional judgment to obtain the education and training necessary to prove their competence in managing sterile compounding facilities and in sterile compounding processes and quality assurance."²

This is one reason why opponents of compounding voice concerns regarding quality, purity, potency, sterility, and stability of the original bulk ingredients used in compounding. As I gathered information for this article, it became clear some of the same holes that exist in compounding also plague the nutritional supplements manufacturing industry. Specifically, lot-to-lot, independent,

comprehensive QA verification (identity, potency, microbiology, and contaminant testing) of raw materials seems to be lacking. The old refrains are common—"I buy my materials from a 'trusted source,' a 'pharmaceutical-grade source,' a 'pedigree, long-established source,'" and/or "I have a certificate of analysis." But these practices are inadequate for any type of manufacturer to rely upon, pharmacy or otherwise. In addition, compounding pharmacies equally lack adequate QA testing on finished products to ensure they meet label claims. Both are significant deficiencies that need to be addressed by the industry.

A STANDARDS REVIEW

A step in the right direction is independent accreditation of compounding pharmacies for compliance with a comprehensive quality standard. The Pharmacy Compounding Accreditation Board (PCAB, www.pcab.info) was recently formed to provide just such quality standards for compounding pharmacies through a voluntary accreditation program. PCAB assesses those pharmacies that apply and then awards the "PCAB Seal of Accreditation" to those that accept and meet the PCAB requirements and comply with the rules and terms of the PCAB program.

A read of PCAB standards reminds me of dietary supplement and pharmaceutical good manufacturing practice guidelines (GMPs). However, one of the gross deficiencies of GMPs is the lack of "specific" acceptable recommendations as to how intended QA parameters are accomplished. The PCAB standards have this same deficiency. I believe this to be a significant problem because it leaves the interpretation of how to comply with the standard up to the individual pharmacy attempting to conform. There is a further problem when different auditors come to audit compliance. On what basis do they decide? The lack of standards specificity certainly leads to divergences in QA and QC practices.

I have listed some of the more important PCAB standards and pointed out the problems. My objections appear after each standard.

Standard 4.10 General: "A pharmacy must provide documentation of the acquisition, storage, and proper destruction of drug substances and drug products used as components in the compounding of preparations. The drug substances and drug products used must be appropriate for the compounding that is performed. The pharmacy shall provide evidence that the drug substances and drug products used to compound meet or exceed any official compendium standards, if any, and, at minimum, are accompanied by a certificate of analysis that is retained by the pharmacy. The certificate of analysis must be reviewed prior to approval for use of the drug substance. A certificate of analysis shall be used to document the strength, quality, purity, and integrity of the chemical."

Objections: As I've mentioned in this column before, a certificate of analysis is never enough. The strength, quality, purity, and integrity of the individual ingredients must be verified independently by the purchasing pharmacy. Specific "how to test" guidelines must be given so each pharmacy has a uniform practice. For example, when stating "the drug substances and drug products used must be appropriate for the compounding" it should be clearly defined what, exactly, constitutes acceptable evidence of this. In addition, for a product to "meet or exceed any official compendium standards," there needs to be an enforceable standard of independent verification for each lot of raw materials. Without such standards, the pharmacist has to rely on, "I think and trust this is the right material, so I guess I'll use it." This policy is obviously unacceptable.

Standard 6.20 Stability and Sterility: "A pharmacy must provide documentation that demonstrates its compounded preparations adhere to compendia requirements of strength, quality, purity, stability, and, where required or appropriate, sterility and bacterial endotoxin content, throughout the period of intended use."

Objections: As there needs to be independent verification for each lot of raw materials, so is there a need for finished products verification. How can a pharmacy demonstrate compendium requirements without a program of independent testing for the finished compounded preparation? There is no way to do so without a program for testing the compounded batch, and there is no requirement for such testing.

Standard 9.10 Quality Assurance Plan: "A pharmacy must provide documentation of the development of and adherence to a quality assurance plan. The quality assurance plan must include verification, monitoring, and review of the adequacy of the compounding process. The quality assurance plan must include documentation of that review by the assigned personnel to demonstrate that the compounded preparation meets the specified criteria of strength, quality, purity, and, where appropriate, sterility, and bacterial endotoxin content."

Objections: Specific recommendations as to how to accomplish this must be given so it is not left to individual interpretation. For example, what verification must the QA plan provide, and how are specified criteria properly demonstrated?

DEVELOPING A QA GOLD STANDARD FOR COMPOUNDED MEDICINES

The following are suggestions and guidelines that compounding pharmacies should put in place and routinely

follow to produce standards of “consistent, safe, and quality products.”

1. The pharmacy should be independently audited for compliance to one of the following:

a) USP guidelines for the preparation of sterile and non-sterile products. (Keeping in mind the guidelines are so general they leave much open to interpretation.)

b) ASHP QA guidelines.

c) Some other set of QA guidelines generally deemed by the profession and regulating agencies to be “appropriate and adequate.”

2. The pharmacy must have written standard operating procedures (SOPs) that govern all of its manufacturing practices including procedures, training, and facilities management.

3. Each and every lot of raw material (*not* random lots) must be tested for identification or authenticity and given a microbiology profile and potency assay as well as, when appropriate, a test for individual heavy metals, chemical solvent residue(s), herbicides/pesticides, and aflatoxins.

4. The pharmacy must meet written raw-material and finished-product specifications before using a raw material or releasing a finished product for sale.

5. The pharmacy must make the time and monetary investment to perform full-profile, finished-product assays on a statistically significant number of product batches to validate manufacturing procedures and consistency. This testing also verifies label-claim potency and sterility (when appropriate). Once this group of test batches is completed, some form of skip-lot testing (a few batches per year) can be instituted to serve as an ongoing double check of consistency and potency. This type of QA program does represent a financial investment, but is feasible and not as onerous as testing each finished product lot.

6. The pharmacy must have potency test data for label-claim verification through the expiration dating period, ie, a stability-testing program. This can also be done using a statistical number of lots to prove stability, followed by a skip-lot program thereafter—eg, 1-2 lots per year.

7. The pharmacy must put suppliers and labs through an adequate certification process to evaluate *their* QA/QC practices.

Compounding medicines without these QA measures in place increases the risk of patients using products that may be inauthentic, adulterated, subpotent, or contaminated.

The general public places a huge amount of trust in pharmacists, far above many other professions. Compounding pharmacies provide a valuable service and are here to stay. They are part of the fabric of medical care and service. I believe the current QA and QC guidelines practiced by most compounding pharmacies are inadequate and the enforcement of any QA/QC guidelines is not rigorous enough.

It is important to note, however, that this review is of

regulatory standards, not individual pharmacies. Most likely, there are pharmacies with internal QA/QC standards in place. The onus is upon you, as the clinician, to find these pharmacies, query their practices, and buy only from those with adequate standards. As in all cases of consumerism, the power is in the pocket—if business drops off, compounders will respond. You have the power to create change.

Along with this, whether by state or by federal mandate, some comprehensive QA and QC guidelines must be put into place and each pharmacy must diligently comply. Our patients deserve consistent, authentic, potent, stable, and clean compounded medicines proven to be so according to an acceptable and sufficiently rigorous QA standard. I don't think anyone would suggest otherwise.

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REFERENCES

1. U.S. Food and Drug Administration Center for Drug Evaluation and Research. *Report: Limited FDA Survey of Compounded Drug Products*. January 28, 2003. www.fda.gov/cder/pharmcomp/survey.htm.
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