

A Primer on USP Chapter <797> “Pharmaceutical Compounding–Sterile Preparations,” and USP Process for Drug and Practice Standards

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Editor’s Note

In January 2004, Chapter <797> in the United States Pharmacopeia 27 became the first practice standards for sterile pharmacy compounding in US history that may be enforced by the US Food and Drug Administration. Dr. Newton is chairman and Mr. Trissel is a member of the 2000–2005 Sterile Compounding Committee^a of the Council of Experts of the United States Pharmacopeial Convention. Dr. Newton and Mr. Trissel are not available to interpret Chapter <797> to persons or organizations outside the United States Pharmacopeial Convention. An outlined summary of the features of Chapter <797>, whose author represents a vendor of isolation chambers, was recently published in the International Journal of Pharmaceutical Compounding.¹

Introduction and Purpose

For the past six years Dr. Newton has taught a required pharmaceutical calculations course for first-year PharmD students, to whom he cautions:

- “When one pharmacist’s mistake hurts or kills a person, it hurts all pharmacists.” A similar plea to avoid harm to patients with compounding sterile preparations was sounded in a recent editorial in the *American Journal of Health-System Pharmacy*.² Most important, such apparent compounding failures harm patients more than they hurt the profession of pharmacy.
- “A pharmacist is often a patient’s last chance for safe drug therapy.” In 2001 and 2002 patients died in North Carolina and California from meningitis resulting from pharmacy-compounded corticosteroid suspensions that were injected intraspinally.³ Because both of those injections were not being produced by their industrial manufacturers, pharmacy compounding became some patients’ last chance for both effective and safe therapy.

Chapter <795> “Pharmaceutical Compounding–Nonsterile Preparations” and Chapter <797> in the *United States Pharmacopeia (USP) 27* are not the first enforceable United States Pharmacopeial Convention (USP) standards for pharmaceutical practices, ie, as opposed to standards for articles (drugs and drug dosage forms), tests and assays. Many previous revisions of the *USP* included enforceable pharmaceutical practice standards in the “Prescribing and Dispensing,” “Preservation, Packaging, Storage” and “Labeling” sections of the *General Notices*. Furthermore,

Chapter <823> “Radiopharmaceuticals for Positron Emission Tomography–Compounding” has been official since *USP 19* in 1999, but it was introduced in 1996 as informational Chapter <1065>. ^b

The authority for the USP to set official standards was established with the passage of the 1906 Pure Food and Drugs Act by the US Congress and was explained in a recent article in the *International Journal of Pharmaceutical Compounding (IJPC)*.⁴ Chapter <797> in the 2004 *USP 27*⁵⁻⁶ has attracted both respect and criticism because (1) it may be partly or fully enforced at the discretion of the US Food and Drug Administration (FDA), (2) it has been cited as a practice expectation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO),⁷ and (3) state pharmacy boards may require compliance with its practices and conditions.

The purposes of this primer are:

- To describe the history, process, and rationale of *USP* Chapter <797>.
- To describe the general USP process and the USP-FDA relationship regarding official pharmaceutical standards.
- To reduce inaccurate and conflicting interpretations of Chapter <797> by persons and organizations interested in and affected by Chapter <797>.

Are Enforceable Sterile Compounding Standards Necessary?

Judged by the opinions of some non-USP pharmacists and other health-related individuals and organizations, the answer to this question is yes. The following are opinions from JCAHO:

“The provisions of the [Federal Food, Drug and Cosmetic] Act, and *USP-NF* standards are enforceable by the Food and Drug Administration. Thus, *USP-NF* standards must be considered applicable federal law and regulation, and as such, the Joint Commission [on Accreditation of Healthcare Organizations] will expect compliance with them.”⁷

“Based on a national survey last year, only 5.2% of hospitals were in compliance with similar guidelines. Evidence seems to indicate that the quality controls necessary to ensure patient safety with regard to compounding sterile drugs may be insufficiently practiced in many of the nation’s hospitals, and that major changes will be required to come into compliance with these new federal requirements [*USP* Chapter <797>].”^c

Note: The bracketed words shown in the above citation were added by the authors of this article.

The American Society of Hospital Pharmacists (ASHP) and USP produced voluntary sterile and nonsterile compounding standards in 1992 and 1995, respectively. Richard Talley, the editor of ASHP’s journal (*American Journal of Hospital Pharmacy*), recently stated the following:

“ . . . after decades of effort by many to ensure the safe compounding of sterile prescriptions. . . . Why are there substantial *gaps between expert advice* [emphasis added] on compounding sterile prescriptions *and what is seen in*

practice or admitted by practitioners [emphasis added]? When pharmacists first began compounding intravenous admixtures in hospitals, some nurses and physicians expressed concern that, since those pharmacists were far removed from patients' bedsides, they might become *indifferent, negligent* [emphasis added] or *careless* [emphasis added] in providing this service. It appears that *some have* [emphasis added], and this *must be corrected* [emphasis added].² Mr. Talley's editorial opinion refers to the results of a 2002 survey of 182 hospital pharmacies regarding their compliance with ASHP's 2000 Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products. The authors of that study drew the following conclusion: "Quality assurance practices for some quality domains showed low compliance with the 2000 ASHP guidelines. Rates of compliance with the 2000 ASHP guidelines leave much room for improvement."⁸

The summary opinion about USP Chapter <797> from Mr. Joseph Deffenbaugh, ASHP's Director of Public Health and Quality and liaison to USP for compounding activities, is "This is all about patient safety. Let's not forget what the purpose of all this is."⁷

In 2001, FDA investigators tested 29 samples of compounded medications from 12 Internet pharmacies.⁹ The following are the salient findings:

- Thirteen injections, 9 ophthalmics, 1 inhalation, 2 implants and 4 oral dosage forms were tested.
- Nine of the tested samples failed assay for potency [less than 90% of labeled strength].
- One of the tested samples failed limulus amoebocyte lysate (LAL) testing for bacterial endotoxins, but none that should have been sterile tested to be unsterile.
- Five of the tested samples lacked expiration [beyond-use] dates.
- The 34% failure rate [10/29] of compounded preparations is large compared to less than 2% for 3,000 manufactured products tested by the FDA since 1996.

Note: The bracketed words shown in the statistical information above were added by the authors of this article.

With the rapid growth of pharmacokinetics after the mid-1960s, it became clear that clinical response to drugs correlated better with drug in plasma concentrations than with the amount of the administered dose. Consequently, in 1975 USP adopted enforceable *in vitro* dissolution test standards for its solid oral capsule and tablet dosage forms, and extended those in the 1990s to capsules and tablets of minerals and water-soluble vitamins. The obvious premise for those article-specific standards was that if active ingredients cannot adequately dissolve *in vitro* they cannot be expected to be absorbed *in vivo*.

USP dissolution standards were initially met with protest from pharmaceutical manufacturers. Today some vendors of vitamin and mineral tablets use this USP requirement for apparent marketing promotion by adding label statements, such as "Meets USP dissolution time." USP introduced those dissolution standards to enhance

therapeutic effectiveness, but it transformed sterile compounding practices to enforceable status for therapeutic safety.

Prohibition gangster Al Capone was right when he said, “You get more cooperation with a kind word and a gun than with just a kind word.” When the word *gun* is used figuratively to mean FDA enforcement of sterile compounding standards instead of literally to mean criminal extortion of money, the outcome of safe treatment daily for thousands of US patients justifies the cooperation of compounders. This theme was asserted in the following 2002 excerpt by a private practice pharmacist who began compounding in 1988 but added sterile preparations later.

“For pharmacies like mine, this means that sterile products...must be prepared in compliance with the new *USP Chapter 797* [emphasis added], whether the pharmacy prepares one sterile product per month or 20 per day. The implementation of new procedures and documentation is not easy, but *it is necessary* [emphasis added].”¹⁰

Finally, the following admonition from a premier-in-1949 pharmacy book captures the quintessence of pharmaceutical compounding:

“Compounding is the pharmaceutical task in which all the scientific *knowledge* [emphasis added], professional *skill* [emphasis added] and sense of *responsibility* [emphasis added] . . . *must* [emphasis added] find their expression and justification.”¹¹

The above statement preceded by 20 years the national emergence of hospital intravenous admixture services using manufactured products, as well as these services increasing the compounding of sterile solutions from nonsterile ingredients for patient-specific treatment.

Where Is Chapter <797> Published and How Can It Be Obtained?

Chapter <797> is published in the combined *United States Pharmacopeia 27–National Formulary 22 (USP-NF)* of 2004⁵ as either a 2½-inch-thick dark red book or a compact disk. In *USP 27-NF 22*, Chapter <797> was printed in the same format as in-process revisions published in USP’s official bimonthly journal, *Pharmacopeial Forum (PF)*. That format includes text of both the new and former content. The “clean” version of <797>, which lacks the deleted former content, is printed in the First Supplement to *USP 27-NF 22*, which was released February 2, 2004.⁶ Chapter <797> may be purchased by contacting USP Customer Service at 1-800-227-8772 or custsvc@usp.org.

Who Serves on the 2000–2005 Sterile Compounding Committee and Who Is Its USP Staff Liaison?

All USP Council of Experts committee members are unpaid (by USP) volunteers. The seven Sterile Compounding Committee (SCC) members and one FDA ad hoc reviewer are pharmacists whose employers include pharmacies and healthcare facilities, pharmacy and medical schools and the FDA. Preceding 2000, USP oversight of sterile compounding matters was delegated to an ad hoc panel appointed by the USP Convention-elected Water and

Parenterals Subcommittee of the USP Committee of Revision. The USP salaried staff liaison for the SCC is pharmacist Claudia C. Okeke, PhD, Associate Director of the General Policies and Requirements Division.

What Is the USP and What Is USP's Relationship with the FDA?

The USP was founded in 1820 by a few physicians.¹² The *USP* revision publication frequency has ranged from 10 years, to 5 years, to annually.^{12,d} The USP is a nonprofit and nongovernmental organization served by hundreds of volunteers as convention delegates and Council of Experts committee members. Volunteers include practitioners and scientists in medicine, pharmacy and other healthcare professions who represent academia, private practice, industrial manufacturing, national and state professional organizations, healthcare organizations and US government health agencies, as well as consumer organizations.^e

“The USP promotes the public health and benefits practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other healthcare technologies, and related practices used to maintain and improve health and promote optimal healthcare delivery.”^{13,f}

The FDA emerged in 1927 from the Bureau of Chemistry in the US Department of Agriculture, the latter having been created in 1862.¹⁴ The 1938 US Food, Drug, and Cosmetic Act assigned the FDA legal authority to enforce standards in the *USP* and *NF*. The *USP* “General Notices and Requirements,” drug monographs or articles, and chapters numbered <1> to <999> contain FDA-enforceable standards; whereas chapters numbered <1000> and higher contain information considered interpretive.¹⁵⁻¹⁶

Do the USP Chapter <797> Standards Provide All There Is to Know About Compounding Sterile Drugs?

In general, USP standards describe the necessary quality requirements for drugs, but they are not intended to be comprehensive sources for drug preparation information. Most USP standards are not accompanied by information describing explicitly how to meet them. Of many standards that could be described, the following are four such examples from *USP 27*:

1. The cefuroxime axetil tablets monograph gives no information on the names and amounts of excipients, and processing equipment and conditions to make tablets that meet the standard of not less than 60% of labeled cefuroxime axetil content dissolved in 15 minutes.
2. The fosphenytoin sodium injection monograph gives no information on the identity and amounts of added substances to achieve the pH range of 8.3 to 9.3.
3. Chapter <797> does not specify methods and conditions or frequency of verification of sterilization methods for particular preparations. Compounders are responsible for determining methods and verifying their efficacy to achieve sterility and maintain strength of ingredients in each compounded preparation.

4. The gentamicin injection monograph does not specify methods for sterilization, practices to satisfy the bacterial endotoxins limit, or amounts and names of substances used to buffer pH, preserve sterility, sequester divalent cations, and adjust tonicity.

Neither the practice standards in Chapter <797>^{5,6} nor the ASHP Guidelines¹⁷ will instruct explicitly how to compound particular preparations that will be sterile, pyrogen-free, physically stable and uniform, and chemically pure and stable. Both documents caution persons who compound sterile preparations to have acquired adequate education, training and experience before attempting to satisfy the practice standards therein. In addition to appropriate collegiate education and extracollegiate training, thorough study and proven competence regarding “hands-on” skills for aseptic manipulations and principles of sterile formulation, packaging and processing, such as those explained and illustrated in relevant ASHP publications and videos, are strongly recommended.

As a young PhD, Richard Feynman worked on the Manhattan Project. After World War II some of his colleagues suffered guilt over the destruction and death caused by the atomic bomb. In his 1955 address “The Value of Science” to the National Academy of Sciences, 10 years before his Nobel Prize in physics, Dr. Feynman reflected as follows:

“Scientific knowledge is an enabling power to do either good or bad—but it does not carry instructions on how to use it. Such power has evident value—even though the power may be negated by what one does with it.”¹⁸

Analogously, USP standards for drugs, dietary supplements and compounding practices are an enabling power, but *only to do good for public health*, and they do carry instructions for use, albeit not always complete or explicit ones. Before Chapter <797>, voluntary sterile compounding practice standards from ASHP and USP had evident or inherent healthcare value, but some compounders negated it by their ignorance and negligence that hurt and killed patients.

What Were the First US Sterile Compounding Practice Standards?

The first detailed US information sources specifically for compounding sterile pharmaceutical preparations were the American Society of Hospital Pharmacists’ 1992 Draft Technical Assistance Bulletin^{19,g} and Chapter <1206> “Sterile Products for Home Use” in *USP 23* in 1995.

The stimulus to create what became Chapter <1206> was resolution 5 to the 1985 USP Convention, urging USP to develop standards for compounded parenterals for home use. That resolution resulted initially in the appointment of the USP Home Health Care Subcommittee (of the Committee of Revision). The first official proposal was Chapter <1074> “Dispensing Practices for Sterile Drug Product Intended for Home Use,” published in the March-April, 1992 issue of USP’s journal, *PF*.²⁰

Those ASHP and USP documents were prompted by:

1. Increasing early hospital discharges during the 1980s of patients receiving intravenous therapy.^h
2. A coincidence of national injuries and deaths to patients during the late 1980s and early 1990s from pharmacy-compounded injections, ophthalmic solutions and organ transplant baths.

As a result of those tragic and publicized instances of alleged pharmacy compounding negligence, some FDA officials suggested banning some types of pharmacy compounding under FDA discretionary authority to regulate compounded preparations as unapproved new drugs under the adulteration and misbranding provisions of the FDC Act.^{7,21} The following summarizes the FDA perspective:

“Generally, FDA will defer to state authorities regarding less significant violations of the Act related to pharmacy compounding of human drugs. However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action.”²¹

For several decades before publication of those pioneer ASHP and USP sources for sterile compounding practice, patient-dedicated, risk-taking hospital pharmacists had compounded, especially sterile intravenous solutions, for their critical care patients. The importance of sterile compounding is illustrated by phenytoin,²² nitroglycerin²³ and concentrated morphine injections,^{24,i} which were initially compounded as high-risk preparations by current ASHP¹⁷ and USP^{5,6} designations and later became commercially manufactured drug products.

How and Why Was Chapter <1206> Transformed to Chapter <797>?

The impetus to transform *USP* <1206> to a chapter numbered less than 1000, ie, from informational status to required standards (enforceable status), began with the June 2000 establishment of the new USP Parenteral Products–Compounding and Preparation Committee, now the SCC, followed by the July 13 and 14, 2000 meeting of the FDA Pharmacy Compounding Advisory Committee.^j That meeting resulted in FDA’s August 2001 Concept Paper pertaining to section 127 in the 1997 FDA Modernization Act (FDAMA), from which the following is excerpted:

“FDAMA section 127 amended the {1938} Federal Food, Drug, and Cosmetic Act (the act) by adding section 503A (21 U.S.C. 353a), which governs the application of Federal law to pharmacy compounding. Under section 503A(a) of the act, a compounded drug product is a drug product made in response to, or in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient. Compounded drug products are exempt...from three key provisions of the act...

1. *Adulteration* provision of section 501(a)(2)(21 U.S.C. 351(a)(2)(B)) (current good manufacturing practice [CGMP] requirements);
2. *misbranding* provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (labeling of drugs with adequate directions for use); and
3. *new drug* provision of section 505 (21 U.S.C. 355) (...use of drugs under...INDs...NDAs...ANDAs).
...drug products that ‘present demonstrable difficulties for compounding that reasonably demonstrate adverse effect on the safety or effectiveness of that drug product’ (section 503A(b)(3) of the Act) {include} ...All sterile products that are compounded under procedures other than those described in Chapter 1206 [‘Sterile Drug Products for Home Use’] of the United States Pharmacopeia (USP).”²⁵

Note: The excerpt above is shown verbatim with the exception of those words shown in { }, which were added by the authors of this article. Also, for emphasis, italics were added to certain words of this excerpt by the authors of this article.

On April 29, 2002, the US Supreme Court declared section 503A of FDAMA invalid in its entirety because it “contained unconstitutional restrictions on commercial speech (ie, prohibitions on soliciting prescriptions for and advertising specific compounded drugs).”²¹

Consequently, in May 2002 the FDA reissued its March 16, 1992 Compliance Policy Guide on Pharmacy Compounding.¹⁹ The USP had originally planned to renumber Chapter <1206> to lower than <1000> after FDA proposed at its July 2000 Pharmacy Compounding Advisory Committee that <1206> shall be followed for sterile compounding. After section 503A was invalidated in April 2002, USP continued to assign numbers less than <999> to its nonsterile and sterile compounding chapters, hoping to reduce or preclude patient harm from compounded preparations via FDA enforcement.

The FDA proposal, stemming from now-defunct FDAMA section 503A, to require former USP informational Chapter <1206> for sterile compounding practice indicates FDA’s growing concern over the quality of compounded preparations. Some FDA officials have also suggested the possibility of requiring a label, such as the following, on all compounded preparations:^k “This preparation compounded by your pharmacy has not been evaluated for safety and effectiveness by the Food and Drug Administration.”²⁶ To reiterate Mr. Talley’s statement,² voluntary sterile compounding standards have not adequately prevented harm to patients from therapies that are supposed to save their lives and lessen their suffering. It should be noted that the quality requirements of Chapter <797> apply to all healthcare practitioners in all locations where sterile preparations are compounded because all patients deserve to be protected. There should be no exemptions from patient safety, according to practitioners or places of sterile compounding.

What Were the Main Events Leading to Chapter <797>?

The formidable challenge to transform Chapter <1206> to current Chapter <797> began at the first meeting of the new SCC held in October 2000. The initial task was to review the most recent draft revision of Chapter <1206> published on pages 812–832 of the May–June 2000 issue of *PF*, which remained official until January 2004. The progress of the revision process of Chapter <1206> to Chapter <797> is represented by publications in the following three *PF* issues:

1. *PF* 2002; 28(2) [Mar.–Apr.]:498–534. In response to this version, many comments were received during May through July 2002,^{7,1} especially from the following contributors:

- Mr. Trissel submitted 40 detailed specific comments.
- The ASHP, via Mr. Joseph Deffenbaugh, submitted four pages of general comments and referred to the above 40 comments from Mr. Trissel.
- Baxter Healthcare Corporation (Deerfield, Illinois) submitted 16 relatively general comments.
- McGuff Compounding Pharmacy Services, Inc. (Santa Ana, California) submitted 48 detailed, specific comments.
- The International Academy of Compounding Pharmacists (IACP) (Sugar Land, Texas), via Mr. L.D. King, submitted 58 detailed specific comments.

Approximately 50 comments from Mr. Trissel, McGuff and IACP were substantively similar, and they served as the major basis of the revision. In addition the model of three microbial contamination risk levels and assignment of beyond-use dates based on nonsterility risk^m were adapted from the ASHP Guidelines.¹⁷

2. *PF* 2003; 29(3) [May–June]:750–809. This draft included content in the then official Chapter <1206> and that proposed to become Chapter <797>. This draft resulted from two separate two-day full SCC attendance meetings in Rockville, Maryland in the fall of 2002 (one during the local sniper shootings in October). It was the product of grueling analysis and discussion of the major comments USP received during May–July 2002 in response to the draft on pages 498–534 in the March–April 2002 *PF*.

3. *PF* 2003; 29(4) [July–Aug.]:940–965. This draft became official in January 2004.

Is Chapter <797> Too Lenient or Too Strict?

Depending on viewpoints, the requirements of Chapter <797> are neither too lenient nor are they too strict, but no answer will satisfy every person and organization affected by <797>. There are, and will continue to be, persons who categorically disagree with any compounding of sterile preparations at any time for any reason, and persons who object to legal standards of any kind for compounding anything from emollient ointments to critical care injections. In establishing the Chapter <797> standards, the SCC did not use the “lowest common denominator” but instead used high-quality compounding practices as models. All of the requirements of Chapter <797> are within the

current practices of these higher-quality compounding practices. In addition, everything cited in the chapter was believed by the SCC to be necessary adequately to protect patients from improperly compounded sterile preparations. The requirements in Chapter <797> are all within the realm of “best practices” for compounding sterile preparations.

A more interesting question to consider may be the following: “What if section 503A of FDAMA still existed or a similar relevant new federal law was passed, and the old Chapter <1206> from a previous *USP* had been renumbered <797> and made official in *USP 27* with the only modification being to change every ‘should’ in <1206> to ‘must’ or ‘shall’ in <797>?”

To explore that possibility, Table 1 compares selected conditions in the current Chapter <797> with those that would have occurred if Chapter <1206> in *USP 26* had simply been numbered <797> in *USP 27*. It should be apparent that the more rigorous standards in Chapter <1206> would be more difficult to satisfy, whether by a hospital pharmacy or specialty compounding pharmacy that has been compounding more than 100 preparations daily, or a community pharmacy that compounds only one preparation monthly.

Did the USP Consider Practitioners’ Cost and Convenience in Chapter <797>?

The paramount concern of the SCC was the protection of patients from inadequate and unsafe compounding practices. Patient safety was the primary consideration. However, the SCC did consider the practicality of the specific Chapter <797> requirements because this too serves patient safety. All of the requirements in Chapter <797> were considered by the SCC to be reasonable and achievable within current compounding practice settings to help ensure patient safety. The quality assurance requirements of Chapter <797> are already in place voluntarily in high-quality sterile compounding practices.

How Were Chapter <797> Storage and Stability Limits Decided?

The only specific storage limit in Chapter <1206> in the *USPs* from 1995 to 2003 was 7 days under refrigeration. The SCC decided to include more comprehensive storage limits in Chapter <797> in recognition of those in the ASHP Guidelines.¹⁷ In determining the length of storage limits in Chapter <797>, the SCC considered such things as the likelihood of occasional inadvertent contamination occurring even in the best sterile compounding settings, the exponential growth rate of bacteria with increasing temperature and the grave danger to patients from bacterial contamination of repackaged intravenous fat emulsion.^{27-28,n} Based thereon, the SCC assigned the respective storage limits conservatively for preparations compounded under low-risk, medium-risk and high-risk conditions for microbial contamination. With each Chapter <797> contamination risk level, the phrase “in the absence of passing a sterility test, the storage periods cannot exceed the following time periods” offers compounders the opportunity to store for longer durations based on appropriate testing results.

In addition to the microbiologic beyond-use limitations, the chemical and physical stability of sterile preparations must be considered. Beyond-use dates of compounded sterile preparations based on chemical and physical stability for Chapter <797> are the same as those for compounded nonsterile preparations in Chapter <795>.²⁹ During the 1993–1996 development of what was initially *USP* Chapter <1161> on pharmaceutical compounding practices³⁰ and is now Chapter <795> “Pharmaceutical Compounding—Nonsterile Preparations,”²⁹ the Advisory Panel on Pharmacy Compounding Practices received comments from interested parties protesting proposed beyond-use dates or durations as too short.^o A typical assertion was that pharmacists inherently command professional judgment adequate to assign beyond-use dates, a sentiment reiterated by one state board of pharmacy regarding Chapter <797> in a February 2004 communication to *USP*.

Pharmaceutical stability depends on the purity and concentration of specific ingredients, packaging and environmental exposure and storage (humidity, illumination and temperature), especially for solutions.³¹⁻³⁵ Small changes in any of those variables can cause rapid loss of drug strength or much shorter than expected shelf-life. Following are three illustrations of why even the most expert and caring pharmacist’s visual, olfactory or other professional judgment, in the absence of scientific testing results, about sterility and stability of compounded pharmaceuticals can be dangerously wrong:

- It takes approximately 1×10^7 bacteria per mL, a level which constitutes gross contamination, to see turbidity in originally clear fluids. However, invisible bacterial densities up to 1×10^6 per mL (a tenth of the amount that would be visible) can cause serious to fatal infections.³⁶
- Clinical concentrations of five adrenergic catecholamine injections were observed for up to 196 hours for the earliest visual evidence of their oxidation to inactive products, ie, change from colorless to pink- or amber-colored. When oxidation became visible, the drug strengths by stability-indicating high-performance liquid chromatography (HPLC) were 0% to 78% in four cases and 92% in one case, compared to their original or zero-time concentrations.³⁷
- A difference of one pH unit from the intended value in solutions of some drugs can decrease stability shelf-life to less than 50% of the beyond-use time assigned on labels of compounded preparations. There can be danger in either assuming correct compounding or expecting a seemingly small formulation change to produce an insignificantly small stability change.^{35,38}

How Do I Determine What the Appropriate Risk Level Is?

The decision as to which risk level (and the associated quality assurance needs) of specific preparations resides with the compounder. *USP* Chapter <797> gives general descriptions of the types of sterile compounded medication in each of the three categories, low-risk, medium-risk and high-risk, with examples, but a complete delineation of every possibility is impossible. Instead, compounding personnel are responsible for making the judgment on each specific preparation and also for being able to defend their decisions should the need arise. It is important to remember that the risk level refers to the risk to the patient’s health and even life from the compounded sterile

preparation should inadvertent contamination occur. Higher risk-level preparations require commensurately higher levels of quality assurance and more restricted beyond-use periods.

What Is the SCC's Perspective on Enforceable USP Compounding Practices?

Several SCC members who practice sterile compounding understood their new obligations when contributing to the development of Chapter <797>. All *USP* compounding chapters and monographs may forestall the need for adoption of more restrictive regulations by the FDA and states over this most historic and profession-symbolizing specialty practice of pharmacy. For example, the New Jersey pharmacy board introduced more stringent compounding practice requirements several years ago. Persons who compound drug and nutrient preparations that are intended and labeled to be sterile when administered clinically must be accountable to utilize appropriate conditions, ingredients and practices to achieve sterility and accuracy in such finished preparations.

The requirements for compounded sterile preparations should not be commensurate with those for manufactured sterile drugs and nutrients produced in large lots.^{39,p} Requiring manufacturing quality-assurance rigor for compounded sterile preparations could (1) deprive urgent, appropriate and humane care to patients whose therapists prescribe specific nonmanufactured drug and nutrition therapy and (2) create marketing advantage for large providers of compounded sterile preparations. To further illustrate this matter, Table 2 presents a simplistic comparison of pharmaceutical compounding and manufacturing according to selected attributes.^q

Compounded preparations administered by intravascular and intraspinal injection have the highest risk of causing infection when terminal sterility is not achieved before they are administered to patients.^{5,6} For example, several patients died in 2001 and 2002 from microbial contamination in intraspinally injected corticosteroid suspensions compounded by pharmacies in California and South Carolina.³ Furthermore, the risk of severe fever from bacterial endotoxins is greatest from the intrathecal injection route; thus, the *USP* endotoxins limit for intrathecal injections is 1/25th that for injections administered by other routes.⁴⁰

The *USP* should maintain an expert committee with specific responsibility to create and revise sterile compounding chapter(s) and monographs. The committee membership should be predominantly pharmacists who have both extensive practice experience with and strong advocacy for patient safety when compounded sterile preparations are therapeutically necessary.

How Does the Public Participate in Creation and Revision of *USP* Content?

Creation and revision of *USP* chapters and other content is assigned to appropriate specialty committees of the Council of Experts,^r which are called expert committees. Proposals for new and revised chapters are published in *USP's* journal, *PF*. The public may comment on *PF* proposals and *USP* content by corresponding with appropriate *USP* staff persons. The general process of introducing and revising *USP* content is also summarized in the beginning pages of each bimonthly issue of *PF*.

Whether it is a proposal in *PF* or official content in *USP*, the same public comment process applies. Upon accumulating and reviewing comments, usually for several months following a *PF* or *USP* publication, the appropriate expert committee meets to consider the comments. Subsequently, the expert committee further determines whether to revise or leave as is the content based on its decisions regarding the comments. For instance, revisions based on some apparent ambiguities and details in current Chapter <797>^{5,6} will likely result from the SCC's analysis of public comments that have been and will be received. Just as "the road to success is always under construction," so the *USP*, at age 184 years in 2004, undergoes continual revision.

What Is the "Bottom Line" of USP Chapter <797>?

Voluntary standards for compounding sterile preparations available from AHSP and USP for 12 and 9 years, respectively, have not prevented patients from dying from microbial contamination in drugs and nutrients that should have been sterile. Some compounding pharmacists are not and have not been aware of those pioneer ASHP and USP documents. The opinion quoted early in this primer by the ASHP's Mr. Joseph Deffenbaugh clearly argues the need for enforceable standards to achieve Al Capone's "cooperation" of pharmacists in properly compounding sterile preparations: "This is all about patient safety. Let's not forget what the purpose of all this is."⁷

Acknowledgment

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Explanatory Notes

^a At the start of the 2000–2005 USP quinquennium, the USP Council of Experts Committee responsible for monographs (articles) and chapter(s) on sterile pharmaceutical compounding was officially titled the Parenteral Products–Compounding and Preparation Committee. By unanimous vote of the USP General Policies and Requirements Division Executive Committee on November 17, 2003, that committee was renamed the Sterile Compounding Committee.

^b E-mail message from Mr. Frank Barletta, a USP staff pharmacist, to Dr. Newton on March 15, 2004. Mr. Barletta stated that Chapter <823> represents the USP contribution to resolving conflict between the FDA and compounders regarding whether Positron Emission Tomography (PET) is manufacturing or compounding.

^c E-mail message from Darryl S. Rich of the JACHO to USP marketing communications department on January 27, 2004. The message was forwarded from USP to Dr. Newton.

^d The *USP* was revised every 10 years after 1820 until *USP 11* in 1936. After the US Food, Drug and Cosmetic Act in 1938, *USP 12* (in 1942) began the 5-year cycle, followed by *USP 13* (in 1947) and then every half-decade quinquennia with *USP 14* (in 1950). In 2002 *USP 25* became the first annual revision.

^e As delegates to the convention and members of the Council of Experts committees, USP volunteers do not promote particular healthcare professions, professional organizations and businesses; do not pay membership dues; and do not derive member services and benefits.

^f USP standards are public as contrasted to those in FDA-approved new drug applications (NDAs), which are the private property of NDA sponsors.

^g Reference 18 by ASHP also includes recommendations for pharmacist-prepared nonsterile and ophthalmic products on pages 1452-1463. The three ASHP compounding documents in Reference 18 were followed by several updated versions. Dr. Newton was an invited prepublication reviewer for the ASHP Technical Assistance Bulletin on compounding nonsterile products in pharmacies. *Am J Hosp Pharm* 1994; 51: 1441-1448; and the ASHP Technical Assistance Bulletin on quality assurance for pharmacy-prepared sterile products. *Am J Hosp Pharm* 1993; 50: 2386-2398. Mr. Trissel of the 2000–2005 SCC was a contributor to all drafts of ASHP’s Technical Assistance Bulletin and eventual Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products (Reference 17).

^h In particular, the emergence of intravenous drug and nutrition therapy administered to patients in their homes resulted from the (then) new US governmental prospective payment limits for treating diseases and medical conditions, which were termed *diagnosis related groups (DRGs)*.

ⁱ Although reference 24 was published in 1995, its authors reported having compounded 50 mg/mL morphine sulfate injection “at this hospital for nearly 20 years...”

^j Dr. Loyd V. Allen, Jr., who chairs the 2000–2005 USP Compounding Pharmacy Committee (for nonsterile preparations), and Mr. Trissel are members of the FDA Pharmacy Compounding Advisory Committee.

^k Dr. Newton personally heard such comments in 2001 and 2002 in meetings of FDA and USP representatives who have responsibility for pharmaceutical compounding.

^l This explanatory note refers to a statement in reference 7 by Dr. Claudia Okeke of USP.

^m The beyond-use dates pertain to potential risks of clinically hazardous microbial contamination. Assignment of beyond-use dates in relation to physical and chemical stability of preparations requires additional relevant documentation or direct testing evidence.

ⁿ The authors of references 27 and 28 are 2000–2005 SCC members.

^o Dr. Newton and Dr. Loyd V. Allen, Jr., the founding editor of *IJPC* and chairman of the 2000–2005 USP Compounding Pharmacy Committee (for nonsterile preparations), served on the panel from its June 1993 inception until it became the Compounding Pharmacy Committee of the USP Council of Experts in June 2000.

^p “The agency [FDA] recognized in its brief...in 2002 Supreme Court case...that applying FDCA’s [Food, Drug and Cosmetic Act] new drug approval requirements to drugs compounded on a small scale is unrealistic – that is, not...feasible to require drug compounding pharmacies to undergo testing for new drug approval process for drugs compounded to meet the unique needs of individual patients.”³⁹

^q The *USP* refers to compounded drugs, nutrients and other therapies as *preparations* because the term *products* is generally construed to represent items resulting from industrial manufacturing.

^r Before the April 2000 USP Quinquennial Convention, the group of volunteers that created and revised *USP* and *NF* content was titled the Committee of Revision. During the 1995–2000 USP quinquennium, the USP ad hoc Committee on Structure and Processes of the USP Committee of Revision recommended that the Committee of Revision be renamed as the Council of Experts. In 2000 the Council of Experts and Board of Trustees were modified to adopt the new structure and process. Beginning with the 2000–2005 USP cycle, the chairpersons of the committees of the Council of Experts, or expert committees, were elected by majority vote of the several hundred delegates to the April 2000 USP Convention. Nonchairperson members of USP expert committees were recommended by chairpersons and approved by vote of all committee chairpersons in the particular USP division. For example, the SCC is assigned to the General Policies and Requirements Division, which consists of 12 expert committees, all of which are responsible for FDA-enforceable chapters and monographs.

^s The “few” designation assumes the traditional direct patient-prescriber-pharmacist triumvirate relationship for compounded therapies, as is described in *USP* Chapter <1075>.

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Table 1. Comparison of Selected Sterile Compounding Conditions in USP Chapters <797> and <1206>.

| | <i>USP 27, 2004</i> Chapter <797> | <i>USP 26, 2003</i> Chapter <1206> |
|--|--|--|
| <i>Example 1</i> | | |
| Numerous sterile ingredients are aseptically combined, eg, total parenteral nutrition. | Medium-risk level | High-risk level |
| <i>Example 2</i> | | |
| Ten 5-mL doses of initially unsterile compounded solution are sterilized by aseptic filtration or autoclaving. All ten single-dose containers will be administered within the next 72 hours to a single patient. | For less than 25 identical units, the sterilization procedure has been determined to achieve sterility. For example, filtration of a contaminated culture medium with filters of the same type did not result in bacterial colonization after proper incubation. | Sterility testing should be performed. |
| <i>Example 3</i> | | |
| Sterile disposable 0.2- μ m porosity membrane filters are used to sterilize solutions. | Compounding personnel must ascertain filters will achieve sterilization of preparations. To ascertain may include previous direct experience and manufacturers' or vendors' documentation. | A filter integrity test, such as bubble point testing, should be performed after the filter is used for sterilization. |
| <i>Example 4</i> | | |
| Media-fill procedure for personnel who compound low-risk level preparations. | Four 5-mL aliquots of sterile soybean-casein digest medium are aseptically transferred into each of three 30-mL | Twenty empty, sterile plastic bags are filled with 100 mL of sterile soybean-casein digest medium. The 20 bags are arranged in 10 pairs, |

Table 2. Comparison of Selected Attributes of Pharmaceutical Compounding and Manufacturing.^a

| Attribute | Compounding | Manufacturing |
|--|---|--|
| Direct distribution | To patients and prescribers | To pharmacies, wholesalers, and prescribers |
| Therapeutic paradigm | Match drug to patient | Match patient to drug |
| Public health risk from gross contamination or ingredient errors | Small: Few people exposed concurrently ^b | Large: Many people exposed concurrently |
| History | Thousands of years BC. It dominated first USP in 1820. USP renewed activity in 1993 by appointing an advisory panel ^c to create what initially became Chapter <1161> ³⁰ | Since the late 1700s industrial revolution, <i>USP</i> standards increased markedly during and after World War II, eg, 1942 Injections chapter, and 1974 solid oral-dosage forms dissolution test dissolution test |
| Main legal regulation | State pharmacy boards and practice acts | US Food and Drug Administration |

^aSee explanatory note “q.”

^bSee explanatory note “s.”

^cSee explanatory note “o.”