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USP Patient Safety
CAPSLink™

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USP Patient Safety CAPSLink™

This message has been sent to you as a service of the U.S. Pharmacopeia, Center for the Advancement of Patient Safety (CAPS). USP is a not-for-profit, non-governmental organization that promotes the public health by establishing state-of-the-art standards to ensure the quality of medicines and other health care technologies. CAPS is a component of USP's Patient Safety public health program. The USP Center for the Advancement of Patient Safety was created to encourage medication error reporting, conduct data analysis and research, develop educational programs, and propose standards, recommendations, and guidelines that ultimately improve the safety and quality of patient care.

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Requirements for Compounding Sterile Preparations: Evolution of USP's Chapter <797>

This month's CAPSLink is devoted to the patient safety issues related to the compounding of sterile pharmaceutical products for patient use. The requirements of USP's Chapter <797> became effective January 1, 2004 and are enforceable by the FDA, state boards of pharmacy, and accreditation

organizations, such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Accreditation Commission for Health Care, Inc. (ACHC), and Community Health Accreditation Program (CHAP). The following article describes the history of <797> followed by a section on frequently asked questions.

Evolution of <797> and Update on the USP Revision Process

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During the 1980s and early 1990s, the development of pharmacy compounding standards was prompted by the increasingly early hospital discharges of patients receiving intravenous therapy and a coincidence of nation wide injuries and deaths from pharmacy compounded injectable preparations.¹ In 1990, four patients died of enterobacter infection from a non-sterile cardioplegic solution compounded and sterilized by filtration in hospital. In this particular incident, five bottles of the solution tested were non-sterile, several subsequent bottles tested were sterile, and another 93 bottles were dispensed without being tested. Another incident occurred in the same year where two patients became blind, and several others were infected by pseudomonas after using indomethacin eye drops compounded and sterilized by autoclaving in a retail pharmacy.² As a result of these tragic events and enhanced public attention, some FDA officials began considering banning some types of pharmacy compounding by regulating compounded preparations as unapproved new drugs under the adulteration and misbranding provisions of the FDC Act.^{1,3,4} However, the existence of sterile compounding remains necessary in spite of the risks. Its importance can be illustrated by many sterile compounding preparations which were initially compounded as high-risk preparations under current American Society of Health-System Pharmacists (ASHP)⁵ and USP^{6,7} classifications and later became commercially manufactured drug products, such as phenytoin,⁸ nitroglycerin⁹ and concentrated morphine injections^{1,10}.

With the increasing need for sterile compounding and pressure from FDA to address microbial contamination of compounded products in U.S. hospitals, several pharmacy organizations, including ASHP, USP, and the National Association of Boards of Pharmacy, issued practice recommendations in an effort to provide professional practice assistance to pharmacists and technicians who compound sterile preparations.¹¹ Among them, the first detailed US information sources specifically for pharmaceutical sterile compounding preparations were the American Society of Hospital Pharmacists' 1992 Draft Technical Assistance Bulletin, entitled "Quality Assurance for Pharmacy-Prepared Sterile Products"¹² and Chapter <1206> "Sterile Products for Home Use" in the United States Pharmacopeia - National Formulary (USP-NF) in 1995.¹

The development of USP-NF Chapter <1206> was stimulated by Resolution No.5 of the 1985 USP Convention which urged USP to develop standards for compounded parenterals for home use and led to the appointment of the USP Home Health Care Subcommittee of the Committee of Revision.¹ The first official proposal of this committee was USP-NF Chapter <1074> "Dispensing Practices for Sterile Drug Product Intended for Home Use", published in the March-April, 1992 issue of USP's bi-monthly Journal, *Pharmaceutical Forum*.¹³

The transformation of USP-NF Chapter <1206> to <797>, from informational status (a chapter numbered above 1000) to required or mandatory standards (a chapter numbered less than 1000), began with the June 2000 establishment of USP Parenteral Preparations and Compounding Expert Committee, now called Sterile Compounding Expert Committee, followed by the July 13 and 14, 2000 meeting of the FDA Pharmacy Compounding Advisory Committee.¹

In 2001, FDA conducted a survey to determine how pharmacies handled sterile product preparations. Investigators tested 29 samples of compounded medications from 12 Internet pharmacies consisting of 13 injections, 9 ophthalmics, 1 inhalation product, 2 implants and 4 oral dosage forms. The results showed that nine of the tested samples failed assays for potency; one of the tested samples failed limulus amoebocyte lysate testing for bacterial endotoxins, but none that labeled sterile tested nonsterile; five of the tested samples lacked expiration 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 1996.¹⁴ Under the climate of heightened awareness of patient safety and only marginal improvement of sterile compounding preparation, concerns grew over the quality of compounded preparations and were followed by a series of changes. In August 2001, FDA issued the Concept Paper pertaining to section 127 in the 1997 FDA Modernization Act (FDAMA), from which 503A was excerpted¹ and USP-NF Chapter <1206> was recognized as the chapter for use in Sterile Compounding. In May, 2002 the FDA reissued its March 16, 1992 Compliance Policy Guide on Pharmacy Compounding.¹²

During that period, after renumbering Chapter <1206> to <797> in July 2000, USP also renumbered Chapter <1161> to <795>, "Pharmaceutical Compounding Nonsterile Preparation", as another effort to reduce or prevent patient harm from compounded preparations via FDA enforcement.

The final converted version entitled "General Chapter <797>, Pharmaceutical Compounding-Sterile Preparations" was published and became official on January 1, 2004.⁶ This chapter is organized to facilitate practitioners' understanding of the fundamental accuracy and quality practices of Compounded Sterile Preparations (CSPs). They provide a foundation for the development and implementation of essential procedures for the safe preparation of CSPs in the three risk levels, which are classified according to the potential for microbial, chemical, and physical contamination. The chapter is divided into the following fourteen main sections¹⁵:

- Responsibilities of all compounding personnel
- The basis for the classification of a CSP into a low-, medium-, and high-risk level, with examples of CSPs and their quality assurance practices in each of these risk levels
- Verification of compounding accuracy and sterilization
- Personnel training and evaluation in aseptic manipulation skills, including representative sterile microbial culture medium transfer and fill challenges
- Environmental quality and control during the processing of CSPs
- Equipment used in the preparation of CSPs
- Verification of automated compounding devices for parenteral nutrition compounding
- Finished preparation release checks and tests
- Storage and beyond-use dating
- Maintaining product quality and control after CSPs leave the compounding facility, including education and training of personnel
- Packing, handling, storage, and transport of CSPs
- Patient or caregiver training
- Patient monitoring and adverse events reporting
- A quality assurance program for CSPs

It is the ultimate responsibility of all personnel who prepare CSPs to understand these fundamental practices and precautions, to develop and implement appropriate procedures, and to continually evaluate these procedures and the quality of the final CSPs to prevent harm and fatality to patients who are treated with CSPs.

Since the information in USP is subject to a continuous revision process, revisions to the official text of <797> are published in the *Pharmacopeial Forum* for public review and commentary. The proposed revision is published on the USP website (www.usp.org). Since the existence of <797>, a number of frequently asked questions have been noted. Some of them are addressed below.

Frequently Asked Questions on <797> Pharmaceutical Compounding-Sterile Preparations;

1. Can the pharmacy switch back and forth from one risk level to another depending on what is being compounded? If a pharmacy can switch back and forth, how will the pharmacy designate when a different risk level is used?

Yes. Most facilities prepare CSPs at low- and medium-risk levels, and fewer prepare CSPs at all three risk levels. USP is a standards-setting organization, not an enforcement agency. JCAHO and your State Board of Pharmacy determine when particular standards in <797> shall be required.

2. How were the sterility-based storage times in the <797> determined?

Based on the assumption of low concentration microbial contamination in every CSP, and the possibility under optimum conditions of exponential colonization,

<797> clearly allows longer storage times (for sterility assurance) and beyond-use dates (for chemical and physical stability) when evidence (from controlled direct or published studies) supports them.

3. Please clarify “Immediate Use Exemption from ISO Class 5”.

Immediate Use Exemption from ISO Class 5, defined as compounding with direct contact contamination in an air quality environment worse than ISO Class 5, is permitted when no more than three sterile ingredients are prepared or combined for administration that begins within one hour and is completed within twelve hours of completing the CSP, and the CSP has been continuously under the direct observation of the person who compounds it.

4. Where is the definition of compounding as defined by the USP found?

Compounding is defined at the beginning of USP-NF general chapter <1075>. Available in the Pharmacist’s Pharmacopeia (<http://www.usp.org/products/pharmacistsPharm.html>).

5. What is the definition of IV ADMIXTURE as defined by the USP?

IV ADMIXTURE is not defined. More general but descriptive terms such as “closed system” transfer are used and described in <797>.

6. Is it acceptable to locate a computer terminal keyboard, monitor, etc., and a label printer insider the ‘Anteroom’ or ‘Buffer Zone’ of the solutions compounding area in the pharmacy?

Placement of devices (e.g., computer and printers) and objects (e.g., carts and cabinets) that are not essential to compounding in buffer zones and clean rooms is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which must be verified by monitoring. It is the responsibility of each compounding facility to ensure that each source of ISO Class 5 environment for exposure of sterile critical sites and sterilization by filtration is properly located, operated, maintained, monitored and verified.

7. When compounding a solution for topical use, do the revisions of USP chapter <797> apply?

Nonsterile preparations are covered under general chapter <795> and not <797>. However, if the topical preparation is for a route specified in <797>, then it must be sterile before it is administered.

8. Please clarify a Class 8 room, such as when personnel need to gown up?

According to general chapter <797>, the anteroom provides a clean area for donning personal barriers, such as hair covers, gloves, gowns, or full clean-room attire. The anteroom also provides a physically isolated area for supplies, such as needles syringes, ampules, bags, vials of parenteral fluids are packages of transfer tubing sets for large-volume fluids are uncartoned and disinfected. <797> defines ISO Class 8 air quality as being an area where weighing, mixing, and other manipulations of nonsterile in-process CSPs take place. Further, it states that before processing CSPs, hands are resanitized after donning all appropriate garb, except for gloves. Most importantly, every decision should be made on the grounds of what is the best to protect patients from inadvertent contamination.

Moreover, policy decisions regarding personnel activities need to remain with the individual pharmacies and pharmacists. Per a comment by a member of the Expert Committee: "As an operational matter, one should reduce traffic in the ante-room to only those who must be there. That would include gowning for entry to the buffer room and those delivering materials into the ante-room to be transported into the clean room. All activities unrelated to work in the clean room should be prohibited from both the clean room and ante-room."

9. Does USP have a guideline for a "dust collecting surface"?

USP does not have any specifications for shelves and ledges. However, <797> does discuss dust collection on certain types of surfaces. Surfaces should be covered or caulked to avoid cracks and crevices where dirt collects. Dust-collecting over-hangs, such as window sills, should be avoided. USP states that any piece of equipment that can accumulate dust should not be kept in the clean room.

10. In regard to the definition of Controlled Room Temperature (20-25°C) and in particular "excursions between 15-30 °C," how long is the excursion defined as?

USP does not define the length of time for excursion. It could range from some minutes to hours or days so long as the time period is recorded and will not be detrimental to the product. The rationale for this is that the mean kinetic temperature (MKT) will be calculated and will be no more than 25°C. In most cases, if excursions occur where the temperature is 28 °C for example, then when the condition is restored, you may lower the temperature to 20 °C for the same period so as to equalize the condition. When controlled room temperature is employed, it is expected that the temperature condition is monitored so that MKT can be calculated.

11. What is the labeling and dating suggestion or requirement for opened multi-dose injection vials?

According to the USP-NF general chapter Pharmacy Compounding Sterile Preparations <797>, it is 30 days unless it meets other requirements.

As an on-going effort to maintain communication with pharmacists and other affected healthcare practitioners on the revisions to <797>, all information is presented on USP's website. It is prudent to continuously visit USP's website to get updated information on Expert Committee activities, and the availability of the USP Pharmacist's Pharmacopeia (<http://www.usp.org/products/pharmacistsPharm.html>) which contains information on <797> and much more.

Also, USP is conducting a workshop August 4-6 in San Francisco that will provide an in-depth analysis of current compounding issues and questions on <797>. See: <http://www.usp.org/eventsEducation/education/pe/pharmacy.html>

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1. JCAHO Updates

2006 JCAHO Patient Safety Goals Issued: The Joint Commission on Accreditation of Healthcare Organizations announced its 2006 national patient safety goals on May 31. Several new requirements have been added to the Goals including requirements to standardize handoffs of patients between caregivers and requirements related to labeling all medications and solutions used in perioperative settings.

[Click here to read more.](#) (hospitals)

[Click here to read more.](#) (home care agencies)

[Click here to read more.](#) (long-term-care facilities)

[Click here to read more.](#) (ambulatory care facilities)

Implementation Expectations for the 2006 National Patient Safety

Goals: Expectations for implementing the 2006 Goals is now available on the Joint Commission website. The website has additional resources for the NPSGs,

including the new Official “Do Not Use” Abbreviations list.

<http://www.jcaho.org/accredited+organizations/patient+safety/npsg.htm>

Transforming Medication Error Data into Meaningful Information: Advanced Workshop Series: Back by Popular Demand - Joint Commission Resources

and USP once again are offering day-long, interactive workshops that train patient safety practitioners to make sense of error data and assess the impact of risk-reduction strategies. This advanced workshop series will utilize demonstrations and case-study examples to provide attendees with specific “hands-on” experiences. This interactive program will be offered on the following dates in 2005:

- September 2 in Rosemont, IL (at JCAHO Headquarters) *
- September 16 in Dallas, TX (at Wyndham Arlington DFW Airport South) *
- November 2 in Rockville, MD (at USP Headquarters)
- December 3 in Las Vegas, NV (Preceding the ASHP meeting)

*JCR's *Hospital Executive Briefings* will be held in the same location one day following the workshop. A discount is available for joint registration.

Participants will:

- Identify various error data collection methods and learn what minimum elements are needed to capture meaningful information on medication error events within the healthcare facility
- Learn to prioritize error-reduction strategies
- Learn various methods to analyze data collected through medication error reports
- Translate findings of medication error reports into meaningful information through interpretation of data findings and in their presentation to committees and staff
- Apply JCAHO Medication Management Standards and 2006 National Patient Safety Goals as they relate to the promotion of Medication Safety
- Evaluate the potential impact of proposed actions taken in response to error

For more information and to register call- JCR Customer Service toll free at 877-223-6866 or go on-line at [Click here](#)

JCAHO To Modify Patient Safety Goal 2B: Speaking at the American Society of Health-System Pharmacists Meeting in June, Darryl Rich, Pharm.D., M.B.A., FASHP, announced that JCAHO will be adjusting National Patient Safety Goal requirement 2B (standardize a list of “do-not-use” abbreviations, acronyms, and symbols). JCAHO is heeding concerns raised by practitioners and pointing out that pharmacists should not be burdened with “policing” prescribers’ compliance with the standard. <http://www.ashp.org/news/ShowArticle.cfm?id=11255>

2. Needlestick Injuries a Frequent Occurrence with Nurses

According to a recent survey published in the journal *Current Medical Research and Opinion*, nearly four out of five nurses have been inadvertently stuck with a needle while treating patients. Disposable needles caused 80% of the injuries. The majority of cases occurred when the nurse was administering insulin. More than half (55%) of the injuries were the result of needles with improperly installed or used safety devices. [Click here to read more.](#)

3. Clinical Rules/Decision Support Is Vital to CPOE

A research study at a Veterans Administration hospital revealed that the computerized prescriber order entry system employed there failed to prevent many adverse drug events because the system lacked decision support for drug selection, dosage, and monitoring, researchers found.

<http://archinte.ama-assn.org/cgi/content/abstract/165/10/1111> (Abstract)

4. Further Research is Needed on Warfarin Interactions

A review of original literature reports of drug or food interactions with warfarin suggests that coadministration of certain drugs with warfarin should be avoided or closely monitored and that more systematic study of warfarin drug interactions is urgently needed.

<http://archinte.ama-assn.org/cgi/content/abstract/165/10/1095> (Abstract)

5. USP Practitioners' Reporting News

News items have been posted to USP's Patient Safety website

<http://www.usp.org/patientSafety/newsletters/practitionerReportingNews/>

A brief description of each posting is provided below for your convenience.

[Zyrtec® and Zyprexa® Confusion](#)

Lilly issues a "Dear Healthcare Professional" letter to alert practitioners about medication dispensing and prescribing errors with Zyrtec and Zyprexa. These errors could result in unnecessary adverse events or potential relapse in patients suffering from schizophrenia or bipolar disorder.

[Plastic Ampul Mix-up](#)

USP has received numerous reports on the problems with the current labeling of plastic ampuls. Practitioners should be alerted to this potential mix-up. USP CAPS department offers additional information on the topic.

[Reminyl® Renamed to Razadyne™](#)

Due to confusion between Reminyl and Amaryl®, Ortho-McNeil will now market Reminyl under the new trade name Razadyne. Prescriptions for Reminyl have been incorrectly written, interpreted, labeled or filled, leading to confusion between Reminyl and Amaryl. Consequently, the administration of Amaryl to Alzheimer's patients, who did not have diabetes resulted in serious events, including severe hypoglycemia and—in two cases—death.

[Total Bag/Vial Content Confusion](#)

View summaries of 3 cases reported to USP regarding total bag/vial content confusion.

If you have similar cases to share, report them to the MER Program via a [secure online form](#) or by calling 1-800-23-ERROR (1-800-233-7767) to obtain a reporting form.

6. Adverse Drug Event Symposium

The American Society for Clinical Pharmacology and Therapeutics will hold its 2005 Educational Symposium on "Adverse Drug Events and Medication Errors: Impact on Medical Care in the 21st Century" from September 29-30 at Loews Philadelphia Hotel, Philadelphia, PA. If you are interested in learning about the science behind, implications of, and potential solutions to adverse drug events and medication errors this is a conference you do not want to miss. Content information and registration forms are available at www.ascpt.org or contact Bethany Oxeer at 703-836-6981, or email: info@ascpt.org

7. HealthGrades Quality Study

HealthGrades recently released their second annual report on patient safety and found that hospitalized Medicare patients experienced 11.3% more adverse patient-safety incidents from 2001 to 2003 than from 2000 to 2002. At the same time, the variation among hospitals widened as the best-performing hospitals reduced their numbers of patient-safety incidents while the worst performers saw their incidents rise. On a positive note, there was a decline in two death indicators tracked -- failure to rescue and death in low-mortality DRGs. [Click here to read more.](#)

8. Summer Vacation for CAPSLink

CAPSLink will not be published in its traditional format for the months of July and August but will offer an abbreviated version (e.g., breaking news announcements) for its readers.

USP Medication Error Reporting Programs:



MEDMARX[®]—USP's comprehensive, Internet-accessible, anonymous medication errors reporting program, and quality improvement tool. The program facilitates productive and efficient documentation, tracking, trending, and prevention of medication errors.



Medication Errors Reporting (MER) Program—presented in cooperation with the Institute for Safe Medication Practices, this nationwide program makes it possible for health professionals to report medication errors confidentially and anonymously to USP.

Other USP patient safety resources:

- [MEDMARX Annual Data Summary reports](#)—provides readers with a wealth of information on reported error events including patterns in the types, causes, and level of harm associated with medication errors.
- [Understanding and Preventing Medication Errors: A Resource for Healthcare Practitioners](#)—a CD toolkit with practical guidelines, forms, and templates to help healthcare facilities improve error-reduction initiatives.
- [Advancing Patient Safety in U.S. Hospitals: Basic Strategies for Success](#)—a book in which hospitals share stories about how they reduced medication errors and promoted safer patient care.
- Medication Safety Pocket Reference—a pocket-sized reference booklet containing listings of similar drug names and dangerous abbreviations that could cause medication errors. Contact custsvc@usp.org and ask for item #3227702.
- Similar Drug Names Poster—a wall poster for easy reference listing look-alike and sound-alike drug names known to cause confusion and potential medication errors when handwritten or communicated verbally. Posters are packaged in quantities of 1 (item # 3728251) 10 (item # 3728252) and 50 (item # 3728253). Contact custsvc@usp.org and ask for the appropriate item number.

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