USP 797 and the NIOSH Alert

A **Q&A** update for oncology pharmacy and cancer program administrators

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In Brief

In the United States, standards and guidelines for the sterile compounding and handling of hazardous medications continue to evolve and change. To protect patients and staff and to be in compliance with recognized standards, community cancer centers must continually monitor all changes and be prepared to make adjustments—including facility upgrades and remodels—when necessary.

Q. *What are the USP 797 and the NIOSH Alert?*

A. USP 797 are standards for compounded sterile products (CSPs) developed by the United States Pharmacopeia (USP).[1] Released in January 2004, these standards have since undergone several revisions. The National Institute of Occupational Safety and Health (NIOSH) also issued its *High Risk Drug Alert* in 2004.[2] Due to the cytotoxic nature of anticancer therapies both documents are important to oncology programs.

In the two years since the release of USP 797 and the NIOSH *Alert,* practitioners and cancer programs have made significant efforts, bringing sterile compounding operations into compliance and enhancing the safety of healthcare staff exposed to hazardous drugs.

Q. *How do the two documents compare?*

A. Initially, USP 797 and the NIOSH *Alert* were developed with very little communication between the groups. While USP 797 focused on product protection and safety, the NIOSH *Alert* focused on provider protection and safety. Discrepancies between the two documents created some early problems for programs attempting to implement both the USP standards and the NIOSH guidelines.

USP quickly recognized this challenge, and a first set of proposed revisions—which incorporated some of the divergent NIOSH issues—was published in 2005.[3] Since that time, USP has taken the extra step of expanding the Sterile Products Expert Committee, the group charged with revising 797, to include personnel involved in creating the NIOSH *Alert.* On May 2, 2006 the USP Sterile Products Expert Committee published its latest proposed revisions to USP 797 for public comment. These revisions incorporated additional elements of the NIOSH *Alert* to more clearly articulate and define the overall desired practice standards under the heading: *Hazardous Drugs as CSPs* (compounded sterile products).

It is important to note that all revisions at this point are merely proposed. No changes to the current published version of USP Chapter 797 become official until the release of the new chapter in January 2007

Still, a major point of divergence between USP 797 and the NIOSH *Alert* is the issue of where these standards and guidelines are to be applied. The NIOSH *Alert* is suggested for all areas that handle hazardous drugs. Conversely, USP 797 is intended only for those areas where drug products are prepared, stored, and dispensed. For more on the issue of applicability see below.

Q. *Is compliance mandatory? If so, how are these standards enforced?*

A. USP chapters numbered below 1,000 are enforceable by the U.S. Food and Drug Administration (FDA). Individual states can also use USP 797 to create regulatory standards, which are then enforceable by state

boards of pharmacy. To date, the following states have adopted USP 797 into practice acts or standards, thus mandating compliance: Arkansas, Indiana, Kansas, Louisiana, Maryland, Massachusetts, Nevada, North Carolina, Ohio, Oklahoma, South Carolina, South Dakota, Texas, Utah, Virginia, and West Virginia. In addition, organizations may be surveyed for USP 797 compliance by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). (See the next question for more information.)

While the NIOSH *Alert* suggests a new standard of practice for handling high-risk drugs and may serve as the basis for future regulatory action by OSHA, at present, it constitutes guidelines only and is *not* enforceable.

Q. *How does USP 797 affect JCAHO accreditation?*

A. While the majority of practitioners were under the impression that full compliance with USP 797 is required, JCAHO recently stated that it would *not* survey for "compliance with the details of USP 797." In its clarification JCAHO wrote:

> "An accredited organization can decide its compliance with USP 797 with advice from experts and stakeholders, such as the organization's director of pharmacy, risk manager, facility manager, microbiologist, infection control staff and legal counsel taking into account state laws and regulations."[5]

While it appears that JCAHO will survey against its published Medication Management Standard MM.8.10, it will not specifically survey against the detailed elements of USP 797.

Q. *How have the 2006 USP 797 revisions changed how these standards should be applied in community cancer centers?*

A. Initially, USP 797 did *not* apply to areas where products are prepared for immediate use. Immediate use is defined as administration beginning within one hour of preparation. Many oncology infusion areas and/or satellite centers prepare compounded sterile products for immediate patient use, so products prepared in these areas are not batched or stored. By definition, then, these areas would be exempt from USP 797 provisions.

However, the 2006 USP 797 revision created a radical departure. Now, compounded sterile products, such as cancer chemotherapy drugs, must be prepared using suitable ISO Class 5 environment containment equipment and/or devices in a manner fully compliant with the revised 2006 USP 797 standards.[4] If this proposed revision is adopted by USP, many community cancer centers will have to upgrade their facilities. This situation should be monitored closely, particularly in states where USP 797 has been adopted and carries force of law. A dialogue should be established with the Board of Pharmacy to clearly understand its interpretation of adherence to 797 standards and its plan for enforcement.

Q. *How do these standards directly affect the environment, physical facilities, and equipment at community cancer centers?*

A. The NIOSH *Alert* provides detailed guidelines on selection of appropriate ventilated cabinets, use of closed-system devices, and removal of exhaust. It does not, however, address clean-room standards.

USP 797 does include clean room guidelines, specifying ISO-8 or better for the anteroom, ISO-7 or better for the buffer area, and ISO-5 or better for the ventilated cabinet, isolator, or laminar airflow workbench.

ISO standards specify a positive pressure environment with a pressure difference of 12 Pa (pascal), or 0.05 inch, of water column between the buffer/anteroom and external environment. However, guidelines for areas handling hazardous drugs, gene therapies, and radioactive agents indicate a negative pressure environment.

The proposed 2006 USP 797 revisions further clarify the question of positive vs. negative pressure. The revision requires a separate ISO Class 7, negative pressure environment for sterile compounding of hazardous medications. Negative pressure is defined as "A room that is at a lower pressure compared to adjacent spaces and, therefore, the net flow of air is into the room."[4] The revision further states that this area has no less than 0.01 inch water column negative pressure to an adjacent positive pressure ISO Class 7 or better anteroom.

Note that the general USP standard for anteroom air quality is ISO-8; however, if the hazardous CSP preparation area is mandated at ISO-7, the anteroom must also be ISO-7 to ensure that the air quality being drawn into the buffer area is the same. If USP were to adopt the proposed requirement for a separate ISO-7 environment for hazardous CSPs, many community cancer centers would need to remodel their existing sterile preparation facilities to come into compliance.

As noted earlier, all proposed revisions would only become official with the release of USP Chapter 797 in January 2007.

Q. *What do these standards say about isolator technology?*

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...closed systems can improve operator safety; however, *this safety comes at a price* **and many organizations are struggling to** justify the added expense of a closed system.

A. Barrier isolators are an option to biological safety cabinets. While many community cancer centers are using or considering them as a way to comply without incurring extensive remodeling or building expenses, neither USP 797 or the NIOSH *Alert* clearly state how and under what conditions this technology might be used.

USP 797 indicates that "a well-designed positive pressure barrier isolator, supported by adequate procedures for its maintenance, monitoring, and control, may offer an acceptable alternative to the use of conventional laminar airflow workbenches in clean rooms for aseptic processing."[3] Not all isolators are the same, however. There are aseptic, containment, aseptic/containment, positive pressure, negative pressure, turbulent flow, and unidirectional flow isolators. There are also many variations in transfer chambers and gloves/sleeves associated with these products. If your cancer center is considering using a barrier isolator for high-risk drugs, an aseptic/containment, negative pressure, unidirectional flow product with a suitable airlock would most likely be the best choice.

There is also concern about *where* to place an isolator: Should a barrier isolator be placed in an ISO-7 buffer environment or can it be placed in a less-controlled environment?

The proposed USP 797 revisions address these questions. The revisions specify a compounding aseptic isolator capable of maintaining an ISO Class 5 environment, which is then situated in a separate ISO Class 7 buffer room for hazardous CSP preparation and is 100 percent vented to the outside.[4]

The USP 797 revisions also allow for placement of compounding aseptic isolators in a separate room that is less than ISO-7 conditions if the compounding aseptic isolator provides isolation from the room and maintains an ISO Class 5 environment during dynamic operating conditions. In this instance the major concern is whether the compounding aseptic isolator can maintain ISO-5 conditions with negative pressure when loading and unloading in a "dirty air" environment.

Community cancer centers currently using or considering using isolators, should monitor these revisions closely.

Q. *Have the requirements for biological safety cabinets changed?*

A. As with isolator technology, the NIOSH *Alert* and USP 797 do not include formal specifications (other than the ISO-5 work area requirement) for biological safety cabinets used in hazardous medication preparation.

The 2006 proposed USP 797 revisions require that biological safety cabinets are Class II or III, capable of maintaining an ISO-5 environment, situated in a separate ISO Class 7 buffer area for hazardous CSPs, and be 100 percent vented to the outside.

Q. *What do these standards say about closed-system products?*

A. The use of closed-system products is another point of divergence between the NIOSH *Alert* and USP 797.

The NIOSH *Alert* recommends the use of closed-system products, such as PhaSeal, for preparation and administration of hazardous drugs. Numerous published studies document the effectiveness of this system in reducing both environmental and personal exposure/contamination from chemotherapeutic agents. NIOSH cites several case studies pointing toward the potential adverse effects of exposure to these agents, including a direct cause and effect relationship between exposure to chemotherapeutic agents and adverse reproductive/teratogenic effects.[2,7] The NIOSH *Alert* also includes data that suggest a link between exposure to these agents and cancer, although it would be impossible to design a study that would definitively establish this link.[2]

Based on current literature and the NIOSH recommendations, closed systems can improve operator safety; however, this safety comes at a price and many organizations are struggling to justify the added expense of a closed system.

The 2006 proposed USP 797 revisions require that closed systems, if used, be used in conjunction with a biological safety cabinet or a compounding aseptic isolator and not as a "stand alone" alternative.[4] The USP revisions also allow the use of a closed-system device in conjunction with a biological safety cabinet or a compounding aseptic isolator as an alternative to a separate buffer room for hazardous medication preparation in organizations that prepare infrequent or low volumes of hazardous medications. USP 797 defines low-volume hazardous compounded sterile product preparation as less than five preparations per week.

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References

[1] Chapter 797 pharmaceutical compounding—sterile preparations. In: *United States Pharmacopeia*, 27th rev. *National Formulary*, 22nd ed. Rockville, MD: United States Pharmacopeial Convention; 2004.

[2] NIOSH alert: preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. DHHS

American vs. European Standards

Clean Room Guidelines

- The NIOSH *Alert* does not address clean-room standards.

- USP 797 specifies ISO-8 or better for the anteroom, ISO-7 or better for the buffer area, and ISO-5 or better for the ventilated cabinet, isolator, or laminar airflow workbench.

  The proposed 2006 USP 797 revisions require a separate ISO Class 7, negative pressure environment for sterile compounding of hazardous medications. If this hazardous CSP preparation area is mandated at ISO-7, then the anteroom must also be ISO-7 to ensure that the air quality being drawn into the buffer area is the same.

- European standard of Class A air is equivalent to the 2006 revisions of USP 797.

  European standards stipulate a partial vacuum for laboratories working with hazardous substances. In practice, Europeans address this issue by maintaining an airlock between the anteroom and the buffer room and keeping the anteroom at a higher positive pressure than the buffer room, thereby preventing any migration of air from the buffer room to the anteroom when the airlock is opened.

  Additionally, the European standards have added the requirement that all hazardous drugs be prepared in an area separate from other CSP preparation.

Preparation

- USP 797 requires that compounded sterile products be prepared using suitable ISO Class 5 environment containment equipment and/or devices in a manner fully compliant with revised 2006 standards.

- European Quality Standards require that compounded sterile products be prepared using suitable ISO Class 5 environment containment equipment and/or devices.[8]

Isolator Technology

- Neither the NIOSH *Alert* nor USP 797 clearly state how and under what conditions isolator technology may be used, although USP 797 indicates that positive pressure barrier isolators may offer an acceptable alternative to conventional laminar airflow workbenches.

  The 2006 revisions to USP 797 specify a compounding aseptic isolator capable of maintaining an ISO Class 5 environment, which is then situated in a separate ISO Class 7 buffer room for hazardous CSP preparation and is 100 percent vented to the outside.

- European standards do *not* recommend the use of isolators for hazardous CSP preparation; however, isolator technology has been employed in the United Kingdom since 1983. It was originally introduced for regulatory and economic reasons as an alternative to clean rooms. After extensive use, current UK standards now specify that isolators should be placed in a dedicated room. Construction and air quality standards for the UK isolator room are equivalent to American USP 797 buffer/anteroom standards.[6,8]

Biological Safety Cabinets

- As with isolator technology, the NIOSH *Alert* and USP 797 do not include formal specifications (other than the ISO-5 work area requirement) for biological safety cabinets used in hazardous medication preparation.

  The proposed USP 797 revisions require that biological safety cabinets are Class II or III, capable of maintaining an ISO-5 environment, situated in a separate ISO Class 7 buffer area for hazardous CSPs, and be 100 percent vented to the outside.

- European standards are equivalent to the proposed USP 797 revisions. The European standards indicate that cytostatic workbenches be Type H with a suggested exhaust air system.

Closed Systems

- The NIOSH *Alert* recommends the use of closed-system products for preparation and administration of hazardous drugs.

- USP 797 requires that closed systems must be used in conjunction with a biological safety cabinet or a compounding aseptic isolator and cannot be used as a "stand alone" alternative.

- The European standards describe closed systems but do not make any formal recommendations regarding their use.

(NIOSH) Publication No. 2004-165 (2004). Available online at: *www.cdc.gov/niosh/docs/2004-165*. Accessed July 25, 2006.

[3]Proposed revision to general chapter 797. Available online at: *www.usp.org/USPNF/pf/797comments.html*. Accessed July 25, 2006.

[4]USP 797 guidebook to proposed revisions pharmaceutical compounding-sterile preparations. Rockville, MD: United States Pharmacopeial Convention; 2006.

[5]Clarification: expectations related to USP-NF Chapter 797 on compounding sterile preparations. *Joint Commission Perspectives.* April 2006;26:5-5(1).

[6] Midcalf B et al. (eds.) Pharmaceutical isolators: a guide to their application, design and control. London: Pharmaceutical Press, 2004.

[7]Valanis B, Vollmer WM, Steele P. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med.* 1999;41:632-8.

[8] Institute for Applied Healthcare Sciences for the German Society of Oncology Pharmacy. Quality standard for the pharmacy oncology service. [as a result of the] 11th German Conference for Oncology Pharmacy Services, January 2003.