American Hospital Association

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United States Pharmacopeial Convention
12601 Twinbrook Parkway
Rockville, MD 20852-1790

Re: USP Proposed General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings; Pharmacopeial Forum 40(3) [13–Oct.–2014; updated 01–Dec.–2014].

To Whom It May Concern:

On behalf of our nearly 5,000 member hospitals, health systems and other health care organizations, and our 43,000 individual members, the American Hospital Association (AHA) appreciates the opportunity to comment on the United States Pharmacopeial (USP) Convention's revised proposed general chapter *<800> Hazardous Drugs – Handling in Healthcare Setting*. The AHA and its members value the collaborative nature of USP's standard development process. According to USP, this chapter was created to identify the requirements for receipt, storage, mixing, preparing, compounding, dispensing and administration of hazardous drugs (HDs) so as to protect patients, health care personnel and the environment. Our detailed comments on specific sections of the proposed chapter are attached.

Protecting patients and health care personnel from harm resulting from occupational exposures to environmental hazards, including HDs, is a priority for the AHA. Hospitals and health systems take many steps to ensure that health care personnel work in the safest possible environment and that patients are provided with safe and effective treatment. Our members rely on the USP to provide them with guidelines and other products that reflect evidence-based standards that help to ensure safe and effective pharmacy production and dispensing. **However, there is uncertainty regarding whether the proposed standards in this chapter fall within USP's routine scope. Further, many of the proposals are supported by limited evidence. Therefore, the AHA recommends that the USP renumber this chapter above 1000, which, as we understand it, would relegate it to a "best practice," rather than an enforceable standard.** This revision would allow USP and other health care organizations to continue to undertake reasonable and informed efforts to improve worker and patient safety until more robust employee-based practices are available.

We are concerned that the development of enforceable standards in the area of occupational exposure to HDs does not fall within USP's recognized scope. The mission of USP is to set standards for the identity, strength, quality and purity of medicines. The Food and Drug Administration (FDA) is responsible for enforcing USP's drug standards as part of its mission to assure the safety, efficacy and security of drugs. However, the standards contained in the proposed USP chapter <800> do not fall under the FDA's authority. Instead, they are directly within the scope of the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH) and the Environmental Protection Agency (EPA). Thus, USP is effectively creating enforceable standards on the subject of occupational exposure to HDs, thereby overstepping its boundaries and venturing into the realm of other regulatory agencies such as OSHA, NIOSH and EPA.

We also are concerned that many of the proposed requirements in USP chapter <800> lack an adequate basis in sound science. For example, one fundamental gap in chapter <800> is that quantified acceptable exposure rates for HDs do not exist, and therefore cannot be taken into account. Without the ability to consider acceptable exposure rates for HDs, it is difficult to balance appropriately the requirements and benefits to employee health and safety. Some sections of the proposed chapter that lack evidential support include those on the receipt and storage of HDs, environmental wipe sampling and medical surveillance, among others.

Further, as currently proposed, chapter <800> would apply to all HDs, including those drugs for which sufficient information on toxicity is unavailable. Specifically, while we agree that there is significant evidence supporting the dangers of exposure to antineoplastic HDs, we question whether there are adequate data indicating that worker exposure to non-antineoplastic HDs (e.g., diazepam and risperidone) is detrimental. **We encourage USP to refocus chapter <800> to address only antineoplastic drugs.** Antineoplastic drugs pose the greatest risk to patients and staff, and there is a significant body of evidence on how to appropriately manage or mitigate this risk.

In addition, there is no scientific evidence or other documentation cited to support USP's decision to exclude from proposed chapter <800> the low-volume exemption contained within the current USP chapter <797> *Pharmaceutical Compounding – Sterile Preparations*. This exemption permits facilities that prepare a low volume of HDs to place a biological safety cabinet or compounding aseptic containment isolator in a non-negative pressure room. By eliminating this allowance, draft chapter <800> would require all HD compounding to be done in a separate area, designated for HD compounding, under negative pressure. However, positive pressure rooms are the standard in small, rural facilities. We are concerned this requirement may force hospitals that prepare only a low volume of HDs, particularly small hospitals in rural areas, to limit the range of services they provide, reducing access to care in these communities. **The AHA urges USP to revise its proposals to provide alternative approaches that keep health care personnel and patients safe.**

If you have any questions concerning our attached detailed comments, please feel free to contact me or Roslyne Schulman, director of policy, at (202) 626-2273 or rschulman@aha.org.

Sincerely,

/s/

Linda E. Fishman
Senior Vice President
Public Policy Analysis & Development

Attachment: Specific Comments of the American Hospital Association

Section 1: Introduction and Scope

- Overall: Many of the NIOSH-listed drugs are not considered hazardous in hospitals today (for example, diazepam and risperidone). We encourage USP to refocus the chapter to address only antineoplastic drugs, which pose the greatest risk to patients and staff, and there is a significant body of evidence on how to appropriately manage or mitigate this risk.
- Lines 5-17: The paragraph states that the proposed chapter applies to "all entities which…transport… HDs." It is unclear whether USP intends the proposed requirements to apply to both internal transportation of HD products within the health care system and external shipment from the wholesaler/distributor to the health care facility. The AHA notes that while hospitals and health care systems have control over transportation between facilities within the system, they have no control over wholesaler/distributor practices and how the products are shipped. Therefore, in order to properly implement the standards in the proposal, we urge USP to clarify its intent in this regard. If USP does intend the standard to apply to external transportation, it should explicitly direct manufacturers and wholesalers/distributors to package products properly to prevent unintended exposure upon delivery of products.
- Lines 18-22: This section lists the minimum requirements for an entity's health and safety management system. We recommend that the term "Competent personnel" be replaced with "Properly trained personnel."

Section 2: List of Hazardous Drugs

- Lines 48-58: USP indicates that the organizational list of HDs should include drugs beyond those on the NIOSH list. The AHA recommends that USP state the sources of information that health care facilities are expected to use in making informed decisions on whether to place a drug on the organizational HD list, especially for drugs that are new since the last release of the NIOSH list.
- Lines 52-53: It would be extremely burdensome to conduct a review of the HD list "whenever a new agent or dosage form is used" as the chapter would require. Non-formulary medication use occurs routinely in health care settings and should not precipitate a full-scale review of an entity's HD list each time. Instead, we recommend that a determination about whether a new agent or dosage form should be included on a facility's list be made in the context of a facility's formulary review process for new drugs.
- Lines 56-58: USP proposes that, by default, hospitals consider drugs approved after the most recent NIOSH list was issued as HDs if insufficient information is available to make an informed decision. This is an ill-advised and overly broad approach for handling the many drugs marketed without an adequate risk profile. It inappropriately makes health care providers accountable for information that should be provided by drug manufacturers. Health care providers should not be required to employ engineering controls or other protective measures in the absence of manufacturer guidance. Therefore, the AHA recommends that the default position instead be that new drugs are considered non-HD unless the manufacturer issues specific safe handling guidance. Regulators also should

require drug manufacturers to provide the appropriate information necessary to determine if a drug, in all its formulations, is hazardous.

- Lines 60-66: USP proposes to allow an assessment of risk (instead of automatically applying its strict containment strategies and/or work practices) for certain less risky dosage forms of HDs (e.g., tablets or capsules). We recommend that if a facility undertakes this type of a risk assessment and finds that a drug does not pose a significant risk, certain simple manipulations should be allowed in the process (e.g., halving or crushing tablets). Also, we urge USP to clarify that unit dose packaging is adequate containment.
- Line 68: The AHA requests that USP reference the studies or other evidence that support the inclusion of reproductive risk drugs as a category of HDs. In particular, we are unaware of data to support the assumption made here that being in the proximity of these drugs (e.g., administering infusions of oxytocin in a hospital labor and deliver unit), particularly those with no further manufacturer safe handling guidance, poses a risk to pregnant caregivers or fetuses.
- Lines 68-71: We recommend USP add "dosage form" after "manipulation."
- Line 72-75: We recommend USP provide examples of appropriate documentation for a risk assessment (e.g., sample risk assessment forms).

Section 3: Types of Exposure

- Line 83, Table 1: USP should state whether "transport: moving HDs within a healthcare setting" also includes transport to the facility. Similar to the concerns stated above in lines 5-17, while hospitals and health care systems have control over transportation among facilities within the system, they have no control over wholesaler/distributor practices and how the products are shipped. If USP intends the standard to apply to external transportation, it should explicitly direct manufacturers and wholesalers/distributors to package products properly to prevent unintended exposure upon delivery of products

Section 5: Facilities

- Lines 102-108: This section outlines restrictions applying to HD "handling areas." It is unclear whether USP intends these "handling areas" to include patient care areas in which HDs are administered, which would be impractical. For instance, this section states that "HD handling areas must be located away from break rooms and refreshment areas." However, oncology patients often eat and drink in the area where the HDs are being administered via infusion, as patients often spend extended periods of time in infusion centers. This section also states that access to areas where HDs are handled must be restricted to authorized personnel and that signs designating the hazard must be prominently displayed before the entrance to these handling areas. But if handling includes administration, then infusion centers could not include patients as they are not "authorized personnel." We urge USP to define "handling areas" in the context of Section 5 to exclude patient care areas where HDs are administered.
- Lines 114-118, Subsection 5.1 Receipt: We ask USP to clarify that receipt areas and storage areas may be co-located within the facility since both may require a negative pressure environment and 12 air exchanges per hour. Also, this section would prohibit HDs from being unpacked from their shipping containers in sterile compounding areas. We

request that USP clarify that HDs may be unpacked in an anteroom to a sterile compounding area under negative pressure.

- Line 120: USP proposes that HDs must be stored in a manner that prevents spillage or breakage if the container falls, including in areas prone to earthquakes. However, there is no practical way that hospitals can completely prevent spillage or breakage if something falls. Instead, the AHA recommends that this absolute prohibition be changed to indicate that hospitals should take appropriate precautions in storing HDs so as to "minimize the risk" of spillage or breakage if the container falls.
- Lines 124-129: This section would essentially require hospitals to use two storage rooms, one for storing chemotherapy drugs and one for storing other drugs. Currently, co-storage is common because many non-HDs are used adjunctively with HD (e.g., oncology clinics also routinely prepare steroids, anti-emetics and other supportive drugs as part of the regimen), and there is no evidence that co-storage poses a risk. Therefore, we are concerned that implementing this requirement would involve extensive changes to hospital storage and ventilation systems and additional and unnecessary traffic in the HD area. Further, due to space and resource limitations, smaller facilities would have great difficulty complying with the proposed requirements that certain antineoplastic HDs be stored in an area with 12 air changes per hour to the outside of building. We urge USP not to adopt this requirement, but instead to explore alternative options that would maintain access to these critical drugs in health care facilities.
- Line 130-133: This section addresses how sterile and nonsterile HDs may be stored, but it includes confusing and contradictory requirements. We urge USP to clarify its intent so that hospitals and health care systems can properly implement the proposed standards.
- Lines 134-138: This section would address the requirements for dedicated storage for refrigerated antineoplastic HDs. However, the language regarding refrigerators in the negative pressure buffer room areas seems to conflict with USP chapter <797> requirements. We urge USP to harmonize these requirements with those of chapter <797>.
- Lines 184-186: This section would allow "occasional" nonsterile HD compounding to take place in a containment primary engineering control (C-PEC) used for sterile compounding as long as the C-PEC is then decontaminated, cleaned and disinfected. We request that USP clarify what it means by "occasional" non-sterile compounding. We also urge USP to provide further detail about the recommended process for decontaminating the C-PEC in order for hospitals and health care systems to properly implement the proposed standards.

Section 6: Environmental Quality and Control

- Lines 268-288: This section recommends routine environmental wipe sampling. However, this recommendation is premature given that there are no definitive data related to environmental exposure or quantified acceptable exposure rates to HDs. Indeed, USP itself discusses the absence of studies demonstrating wipe sample effectiveness, the lack of any known certifying agencies for wipe sample kits and the absence of any standard for acceptable limits for HD surface contamination. The AHA strongly recommends that this section be removed from the proposed chapter or, at the very least, relegated to a "best practice" chapter numbered above 1000.

Section 7: Personal Protective Equipment (PPE)

- Lines 304-305: This section would require the development of standard operating procedures for PPE based on the risk of exposure and activities performed. We request that USP provide further guidance regarding the types of risk of exposure and the related PPE requirements for the various HDs included in the NIOSH list. Without such clarification, hospitals and health care systems will be unable to properly implement the proposed standards.
- Line 320: We request USP clarify whether the requirement to change gloves every 30 minutes would apply when using containment boxes to prepare HDs and whether it would apply to the gloves attached to the box or only to the gloves worn directly by the employee. The AHA further requests that USP cite a reference for this requirement. Without such clarification, hospitals and health care systems will be unable to properly implement the proposed standards.
- Lines 336-337: This section would require gowns to be changed every two to three hours if manufacturers do not state the limits of permeation. However, rather than creating an arbitrary requirement, we urge USP to require that manufacturers certify their gowns as meeting clear manufacturing guidelines. Manufacturers should not be permitted to sell garments that cannot be guaranteed to provide operator safety for a longer period of time (e.g., eight hours, the average length of a work shift). Stating in a standard that gowns should be changed every two to three hours creates a disincentive for manufacturers to develop gowns that are certified for protection for longer periods of time. Also, requiring a shorter period of use is wasteful and would only serve to increase the manufacturers' sales volumes without their having to provide documentation of reduced permeability and impact on user safety.
- Lines 340-349, Section 7.3 Head, Hair, Shoe, and Sleeve Covers: We request that USP provide additional specificity regarding the circumstances in which these types of PPE should be worn. Without such clarification, hospitals and health care systems will be unable to properly implement the proposed standards.
- Lines 350-359, Section 7.4 Eye and Face Protection: We request USP clarify whether eye and face protection is required if a containment box is used to compound HDs. Without such clarification, hospitals and health care systems will be unable to properly implement the proposed standards.
- Lines 360-378, Section 7.5 Respiratory Protection: We request USP clarify which activities require respiratory protection equipment. Without such clarification, hospitals and health care systems will be unable to properly implement the proposed standards.
- Lines 370-372: This section would require that personnel who are unpacking HDs not contained in plastic wear an elastomeric half-mask with a multi-gas cartridge and P100-filter. However, many drugs are delivered to health care facilities in plain boxes via common courier. Donning the required mask to open each of these containers in anticipation that something might not be "contained in plastic" is unrealistic in the absence of obviously compromised package integrity. The AHA recommends that no specific respiratory protection be required in the absence of obvious damage to the shipping container or unless the shipping container includes a written warning.

Section 8: Hazard Communication Program

- Lines 389-405: We request USP clarify that labeling and Safety Data Sheets may be provided in an electronic format.

Section 9: Personnel Training

- Lines 407-421: USP should ensure that the proposed personnel training requirements align with other required training, for example from The Joint Commission and OSHA.
- Line 414: USP should clarify that the proposed assessment of personnel competency outside of the annual requirement only applies to a new HD if it involves a substantially different process than applies to the current HDs.

Section 10: Receiving

- Line 424-426: This section indicates that HDs should be received from the supplier sealed in impervious plastic to segregate them from other drugs and to improve safety in the receiving and internal transfer process. We note that HD manufacturers and wholesalers are the entities responsible for packaging, and they are not obliged to abide by USP standards. While we encourage USP to engage manufacturers and wholesalers in discussions to encourage these safe practices, this language should be removed from the draft chapter.
- Line 427: Hospitals and health care systems cannot comply with the proposed requirement that HDs be delivered to the HD storage area *immediately* upon arrival. Some facilities have their HDs delivered to loading docks and thus they cannot practically be sent "immediately" to the pharmacy. Instead, the AHA recommends that "immediately" be revised to "as soon as possible."
- Line 436, Table 4. Summary of Requirements for Receiving and Handling Damaged HD Shipping Containers: The table notes that if a damaged shipping container must be opened, the receiving facility should "wipe the outside of the useable item with a disposable wipe." We request USP clarify whether wiping is sufficient or if it would be more appropriate to decontaminate the useable items. Without such clarification, hospitals and health care systems will be unable to properly implement the proposed standards.

Section 11: Labeling, Packaging, and Transport

- Line 468: This section would prohibit the use of pneumatic tubes for transporting any liquid or antineoplastic HD because of the potential for breakage and contamination. We recommend USP provide an exception to allow the use of pneumatic tubes to transport solid-oral formulations that are encased in unit dose packaging and, as appropriate, double-bagged.

Section 15: Deactivation/Decontamination, Cleaning, and Disinfection

- Line 577-578: This section recommends surface wipe sampling to document the effectiveness of HD decontamination. As we noted above in our comments to Section 6, there are no definitive data related to environmental exposure or quantified acceptable exposure rates. Therefore, this process would create sampling for which standards do not exist, and for which there is no known recourse if something is positive. In addition, end-user testing of the efficacy of a decontamination product constitutes an unnecessary

duplication of work. The manufacturer's documentation of effectiveness should be sufficient. Therefore, we urge USP to strike this provision.

- Lines 590-591: This section would require that all C-PECs used for either nonsterile or sterile compounding be decontaminated between compounding of different HDs. Doing so would entail decontaminating a single C-PEC dozens of times daily, an unnecessary and time-consuming process that we are concerned could significantly reduce the number of patients that a cancer center could serve. We recommend either removing this recommendation or adopting the cleaning language included in USP <797>.
- Line 594: We suggest USP also note that surface contamination would be reduced due to the recommendation to use a closed system drug-transfer device when compounding HDs when the dosage form allows.
- Line 596: In this section USP suggests using a wipe-down procedure that it notes has not been studied and "may" be effective. We urge USP to note that this procedure is not necessary when a closed system drug-transfer device is used for compounding.

Section 16: Spill Control

- Lines 619-623: This section would require that the circumstances and management of spills be documented. We request USP to clarify the intended purpose of the documentation, what details need to be maintained in the documentation, how long it must be kept and whether it is intended to be used for risk mitigation. Without such clarification, hospitals and health care systems will be unable to properly implement the proposed standard.

Section 18: Documentation and Standard Operating Procedures

- Line 662: This section includes a recommendation that a standard operating procedure for "environmental monitoring" be maintained. We urge USP to define environmental monitoring for the purposes of this section. Without further definition, hospitals and health care systems will be unable to properly implement the proposed standard.

Section 19: Medical Surveillance

- Lines 666-757: Section 19 proposes a routine medical surveillance program for health care workers who handle HDs as a regular part of their job. The AHA recommends that this section be removed entirely from the proposed chapter or relegated to a USP chapter numbered above 1000, making it a "best practice" rather than an enforceable standard.

  We are concerned that this proposal would require most hospitals to create a new type of medical surveillance program that is highly speculative and lacks evidence supporting its effectiveness for reducing HD exposures. We also are concerned that the routine prospective monitoring of workers' health through periodic medical surveillance would incorrectly lead to presumptions that any health or medical conditions (e.g., cancer) they have is a result of a system failure related to their occupational handling of HDs. Hospitals and health systems already have in place occupational health programs to which employees are referred for surveillance and follow-up if there is evidence of a problem related to a perceived exposure in the workplace, such as a known or suspected exposure to a spill.

We also have concerns about employee privacy that would emerge from such a routine medical surveillance program. The AHA urges USP to allow employees to opt out if a facility chooses to create such a surveillance program.