

ASCO Safe Handling Toolkit

ASCO developed this toolkit as a resource to ASCO members as their states consider policies related to the safe handling of hazardous drugs.

Contents

- Policy Brief
- FAQ
- 2019 ASCO Standards

Current Legislation

To view current legislation related to safe handling and other important issues in your state, visit the [ASCO ACT Network](#) and click on your state in the map.

Other Resources

You can find helpful state advocacy resources on the [ASCO State Advocacy Site](#).

ASCO Staff Contacts

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Safe Handling of Chemotherapy

The American Society of Clinical Oncology (ASCO) is deeply committed to ensuring that patients receive safe and appropriate cancer treatment and to safeguarding all professionals who work with or near oncology drugs. This commitment applies to all settings where oncology treatments with hazardous drugs are prepared, delivered, and administered.

ASCO released Standards on the Safe Handling of Hazardous Drugs in January 2019. ASCO's standards largely endorse the standards and best practices issued by other stakeholder groups for safely handling hazardous drugs, but offer alternatives in key areas where more research is needed to identify evidence-based safety measures.

In the standards, ASCO recommends a comprehensive set of practices and procedures to help guide entities which handle hazardous drugs to incorporate a culture of safe handling and best practices into their occupational safety plan. According to the standards, an entity's health and safety management system, at a minimum, must include:

- A list of hazardous drugs
- Facility and engineering controls
- Competent personnel
- Safe work practices
- Proper use of appropriate Personal Protective Equipment
- Policies for hazardous drug waste segregation and disposal

ASCO's safe handling standards differ from existing standards in four areas: (1) the use of medical surveillance, (2) closed system transfer devices (CSTDs), (3) external ventilation of containment secondary engineering controls (C-SEC) or containment segregated compounding areas (C-SCA), and (4) alternative duties. In a systematic review of the available scientific literature, ASCO found that best practices in these areas are currently not supported by any high-quality, unbiased studies on health outcomes.

Independent oncology practices provide critically important community-based points of access to high-quality, high-value cancer care services for individuals with cancer. These practices are subject to a growing number of administrative burdens and financial pressures. The costs of adhering to additional expensive requirements, with uncertain and unfounded benefit for the handling of cancer drugs, could place physician practices at risk of limiting access to cancer patients or completely ceasing operations. Adding requirements for which there is limited or no evidence, and that do not translate into a demonstrated and meaningful improvement in safety, will divert attention and resources away from activities that are known to promote safe handling and worker welfare.

As policymakers consider the development of new requirements that apply to the handling of drugs in physician practices, we encourage them to actively involve ASCO and the local medical oncology community, who have significant practical experience in the day-to-day operations of modern oncology practices. ASCO offers its chemotherapy safe handling standards as a resource for entities to promote best practices and the development of policy to ensure the safe handling of hazardous drugs. It is critical that any new regulatory requirements serve the needs of individuals with cancer, protect the safety of

the health care workforce and avoid unnecessary burdens for the oncology practices that serve local communities.

Please contact the ASCO State Advocacy team with questions or for assistance on individual state safe handling issues by emailing Katherine.flannigan@asco.org or by phone at 571-483-1677.

Frequently Asked Questions: The Regulation of Safe Handling Practices for Hazardous Drugs Used in the Treatment of Individuals with Cancer

The American Society of Clinical Oncology (ASCO) is committed to promoting and supporting research, guidance, and educational materials to help ensure the safety of professionals in the oncology workforce who handle or otherwise potentially come into contact with hazardous drugs. This document addresses frequently asked questions regarding the safe handling of hazardous drugs.

What is the USP and how are the USP's standards enforceable?

The United States Pharmacopeia (USP) is a private, non-profit, scientific organization that sets standards for the safe and proper use of medications. USP is not an enforcement agency, so the USP does not enforce adherence to any of its standards at the national or state level. Historically, USP has focused on developing standards that define the content and purity of drugs and other substances. Some of these standards are incorporated by reference into the laws and regulations that the U.S. Food and Drug Administration (FDA) actively enforces.

The USP has developed standards in the areas of drug compounding and the safe handling of hazardous drugs. To date, we are not aware of any activity by the FDA to adopt or enforce these standards at the national level. In some instances, states have incorporated the USP's compounding standards in part or in whole within state requirements, most commonly within the regulation of pharmacies that are subject to the rules promulgated by state boards of pharmacy.

What is USP <800>?

USP released a final version of General Chapter <800> *Hazardous Drugs – Handling in Healthcare Settings* in February 2016. USP <800> lays out requirements for receiving, storing, compounding, dispensing, administering, and disposing of sterile and non-sterile hazardous drug products and preparations. The chapter aims to promote patient safety, worker safety, and environmental protection by reducing unintended exposure to hazardous drugs.

When will USP <800> be effective?

The USP states that USP <800> will become effective on December 1, 2019.

How can USP standards be adopted?

State and local governments, federal agencies, or private accreditation organizations could adopt USP standards in whole or in part at any time. At the state level, adoption could arise either by action through the state legislature or by action taken by a state agency, board of medicine, or board of pharmacy. Although the USP has set a specific implementation date, state or private entities could establish implementation dates that start before or after the USP's recommendation.

Are there any substantive concerns with USP <800> from the perspective of community-based oncology practices?

The development of USP <800> remains controversial. USP failed to adequately consult with physician specialty organizations while crafting the standards, even though USP takes the position that USP <800> has applicability to physician practices and other community-based settings of care. We understand that USP is working to revamp its process for developing new general chapters like USP <800>, but unfortunately, we believe that the flawed process contributed to some counterproductive requirements in the final policy.

ASCO is committed to promoting safety in the oncology workplace. Concerns arise when requirements of uncertain value are recommended or required that may divert attention or resources away from more effective interventions. There are some very good recommendations within USP <800>; however, there are some areas in which there is insufficient scientific evidence to conclude that some of the mandates under USP <800> would result in material benefits in safety for patients or the health care workforce. ASCO has specific concerns about requirements for external ventilation, closed system transfer devices, and other issues that are detailed in ASCO's comment letters on both drafts of USP <800> and can be found below:

[ASCO Comments July 2014](#)

[ASCO Comments May 2015](#)

How can I obtain a copy of USP <800>?

USP now allows free downloads of USP 800 available [here](#).

What work has ASCO done on standards for the oncology community for the safe handling of hazardous drugs?

ASCO took an evidence-based approach to developing a set of standards on the topic and released ASCO Standards on the Safe Handling of Hazardous Drugs in January 2019. In the development of the standards, the search for evidence found no studies that addressed health outcomes as they related to the identified interventions of interest. Thus, ASCO largely endorsed the best practices for safe handling of hazardous drugs as issued by USP <800> with the exception of the following: medical surveillance, closed system transfer devices (CSTD), external ventilation of containment secondary engineering controls or containment segregated compounding areas, and alternative duties.

The ASCO Standards can be found [here](#).

What is USP <797>?

The USP developed General Chapter <797> Pharmaceutical Compounding – Sterile Preparations to prevent patient harm from contaminated compounded sterile preparations. The USP released a significantly revised version of USP <797> in September 2015 and public comments were accepted until February 1, 2016. The USP released a revision to <797> in July 2018 and public comments were accepted until November 30, 2018. The current USP <797> is in effect until the revision is finalized.

Are there any substantive concerns with USP <797> from the perspective of community-based practices?

The current USP <797> is causing serious problems for physician practices in several states. The USP recently removed an exception within USP <797> for low volume compounding that could exacerbate the concerns already arising from USP <797> for physician practices in some states. Oncology drugs

should be prepared with aseptic technique, but the requirements in USP <797> seem more applicable to bulk compounding and are overly burdensome for oncology practices. The recently proposed revisions to USP <797> may exempt certain activities that commonly occur in physician oncology practices, such as mixing and diluting activities, from the requirements of the chapter. ASCO's comments on the revised USP <797> can be found below:

[ASCO Comments 2016](#)

[ASCO Comments 2018](#)

How can I obtain a copy of USP <797>?

A subscription to the USP-NF or USP Compounding Compendium is required to view USP <797>. More information about those subscriptions can be found [here](#) and [here](#). Proposed revisions to USP <797> are publicly available and can be viewed [here](#).

What is NIOSH and how are its standards enforceable?

The National Institute for Occupational Safety and Health (NIOSH) is part of the Centers for Disease Control and Prevention (CDC) and is responsible for conducting research and making recommendations for the prevention of work-related injury and illness. NIOSH is not an enforcement agency. A few states have incorporated NIOSH standards within state laws, and in these instances, enforcement is the responsibility of the state governments.

What is the NIOSH Alert?

The NIOSH Alert is a document entitled "Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings" that NIOSH published in 2004. NIOSH officials are currently updating the Alert. NIOSH also maintains a list of hazardous drugs, and the most recent version of that document ("NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings") was released in 2014. This document contains updated recommendations on personal protective equipment (PPE) use.

How can I obtain a copy of the NIOSH Alert?

The NIOSH Alert can be accessed [here](#).

What other materials has NIOSH developed on safe handling?

NIOSH maintains a list of recent scientific articles about occupational exposure to hazardous drugs on their website and has developed supplementary materials. NIOSH released a draft protocol for testing the efficacy of Closed System Transfer Devices (CSTDs) that function by vapor containment ("A Vapor Containment Performance Protocol for Closed System Transfer Devices Used During Pharmacy Compounding and Administration of Hazardous Drugs") on September 8, 2015. On January 19, 2016, NIOSH issued a request for information for developing a similar protocol for CSTDs that use air filtering technology ("Request for Information on Development of a Performance Test Protocol for Closed System Transfer Devices That Incorporate Air-Cleaning Technology to Provide Worker Protection During Pharmacy Compounding and Administration of Hazardous Drugs"). In January 2015, NIOSH released a draft document "Current Intelligence Bulletin: Reproductive Risks Associated With Hazardous Drug Exposures in Healthcare Workers and Recommendations for Reducing Exposures."

What is OSHA and are its standards enforceable?

OSHA is a division of the United States Department of Labor and stands for the Occupational Safety and Health Administration. OSHA requires compliance with the latest U.S. Public Health Service guidelines for standards. NIOSH recommendations contain the latest U.S. Public Health Service guidelines.

An OSHA state by state organizational hazardous drug guideline map can be found [here](#).

Safe Handling of Hazardous Drugs: ASCO Standards

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abstract

PURPOSE To provide 2019 ASCO standards on the safe handling of hazardous drugs.

METHODS An Expert Panel was formed, and a systematic review of the literature on closed system transfer devices was performed to May 2017 using PubMed. The Cochrane Database of Systematic Reviews, PubMed, and Google Scholar were used to search for studies of medical surveillance and external ventilation/health effects of exposure to vapors to November 2017. Available standards were considered for endorsement. Public comments were solicited and considered in preparation of the final manuscript.

RESULTS The search for primary research found no studies that addressed health outcomes as they relate to the identified interventions of interest. The ASCO Expert Panel endorses the best practices for safe handling of hazardous drugs as issued by the Occupational Safety and Health Administration, US Pharmacopeia Chapter 800, and Oncology Nursing Society with clarifications in four key areas: medical surveillance, closed system transfer devices, external ventilation of containment secondary engineering controls or containment segregated compounding areas, and alternative duties.

CONCLUSION The ASCO standards address the need for clear standards concerning safe handling of hazardous oncology drugs. More research is needed in several key areas to quantify the level of risk associated with handling hazardous drugs in current workplace settings where the hierarchy of controls is consistently applied. Additional information is available at www.asco.org/safe-handling-standards.

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INTRODUCTION

In the United States each year, approximately 8 million health care workers have the potential for exposure to drugs that may be hazardous to health through the preparation and administration of anticancer regimens comprising one or more pharmaceutical agents.¹ A list of hazardous drugs is maintained by the National Institute for Occupational Safety and Health (NIOSH).² This list includes commonly used cytotoxic (antineoplastic) agents. Hazardous drugs are defined by their association with genotoxicity, carcinogenicity, teratogenicity, fertility impairment or reproductive toxicity, and/or serious organ toxicity at low doses. In recognition of this risk, ASCO professionals are committed to providing standards that promote the safety of pharmacists, physicians, nurses, and other professionals who collaborate in providing oncology care. Other safety standards have been developed both within the United States and internationally for health care providers who handle potentially hazardous drugs in oncology care settings.³⁻⁷ These ASCO standards consider recommendations contained in these previously

published products and incorporate the latest evidence regarding risks of harm associated with exposure to hazardous drugs and the benefits of control measures, as well as expert consensus. The overarching goal is to develop a set of evidence-based standards that are applicable to diverse workplaces where hazardous drugs are handled for oncology care.

Hierarchy of Controls

An established hierarchy of controls (NIOSH) is commonly used in industry or workplaces to guide efforts to minimize exposure to workplace hazards, such as cytotoxic drugs.⁸ This hierarchy is arranged from most effective at the top to least effective at the bottom. Examples of each type of control in the context of hazardous drugs include the following: accommodation in a different position within the organization that does not involve handling of hazardous drugs (elimination, substitution), biologic safety cabinets (engineering controls), educational programs (administrative controls), and gloves and gowns (personal protective equipment [PPE]).⁸

Author affiliations and support information (if applicable) appear at the end of this article.

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THE BOTTOM LINE

Safe Handling of Hazardous Drugs: ASCO Standards

Question

What are the standards for the safe handling of hazardous drugs?

Target Population

Pharmacists, physicians, nurses, and other professionals who handle hazardous drugs

Methods

An Expert Panel was convened to develop standards for the safe handling of hazardous oncology drugs based on a systematic review of the literature.

Standards

Standard 1

Endorsement of existing standards. The Expert Panel endorses a majority of the standards for safe handling of hazardous drugs as issued by the US Occupational Safety and Health Administration,²² the US Pharmacopeia (USP) Chapter 800,⁷ the National Institute for Occupational Safety and Health (NIOSH) 2004 Alert,¹⁹ and the Oncology Nursing Society.²⁵

Qualifying Statement. Although the Expert Panel endorses existing standards, the Expert Panel also identified areas for which an additional evidence review was required and provides consensus-based standards on these topics, including medical surveillance, closed-system transfer devices (CSTDs), external ventilation of containment secondary engineering controls (C-SECs) or containment segregated compounding areas (C-SCAs), and alternative duties. These topics are highlighted in this Bottom Line Box. Given the limitations of the evidence base, the standards presented within this box are consensus based and were developed by weighing the potential for benefit and risks of harm associated with each statement.

Standard 2

Medical surveillance. Workplace occupational health programs in settings where hazardous drugs are handled should include policies and procedures demonstrated to effectively monitor hazardous drug contamination in the health care setting and to monitor individuals who have been involved in an acute exposure (eg, a spill). The role of routine ongoing medical surveillance programs that include medical screening, laboratory testing, or other biologic monitoring is unclear, because there are no published data to reliably inform a standard or best practice.

Qualifying statements.

- There are currently no data from well-designed programs to inform whether screening and monitoring within medical surveillance programs increases or decreases benefits or harms related to health outcomes for workers who handle hazardous drugs. In addition, there is a lack of valid tests or techniques for detecting early signs of disease, no established levels of exposure that have been linked to adverse health effects, and other limitations that are outlined in the main text of this document.
- As an alternative to routine ongoing medical surveillance programs, this ASCO standard endorses larger-scale data collection in the context of a registry of health care workers. This standard also endorses the collection of data to test research hypotheses, provided that the necessary sample size to detect significant differences can reasonably be achieved, that peer-reviewed publication plans are determined a priori, and that approval has been given by a research ethics board. Gathering data with the purpose of examining it periodically for a small alteration²⁵ is not recommended.
- Workers should be encouraged to report occupational health issues to employee health services at the time that they are experienced.
- The Expert Panel will continue to monitor the literature for robust studies of the link between biologic markers and health outcomes and for studies that assess the outcomes of medical screening and biologic monitoring programs that may already be in place within specific institutions.
- Definitions of medical surveillance, medical screening, biologic monitoring, and laboratory testing are included within the full text of this standards document.

(continued on following page)

THE BOTTOM LINE (CONTINUED)**Standard 3**

CSTDs. To inform a standard on this topic, a testing protocol for CSTDs is needed. In addition, there is a need for a process to identify and certify effective CSTDs.

Qualifying statements.

- Within a recent systematic review,³³ the quality of the published literature on CSTDs was rated as low quality and at high risk of bias using the GRADE methodology.³⁴ After implementation of CSTDs, some studies have noted a decrease in the percentage of surface sampling wipes that have detectable levels of antineoplastic drugs and/or a decrease in the percentage of workers who have detectable levels of antineoplastic drugs in their urine. There are no short- or long-term data to inform whether specific CSTDs have an impact on health outcomes.
- NIOSH recommends using CSTDs when transferring hazardous drugs from primary packaging to infusion bags, bottles, or pumps.¹⁹ USP 800 requires use of CSTDs for nursing administration of hazardous drugs and recommends use for sterile product compounding of hazardous drugs.⁷
- At this time, there is no standardized testing protocol to assess the performance of available CSTDs. NIOSH is in the process of developing an independent vapor containment performance protocol for CSTDs in health care settings.³⁵ These ASCO standards will be revised to incorporate the NIOSH CSTD testing protocol when it becomes available.
- We encourage NIOSH to develop a certification process so that practices can identify effective CSTDs.

Standard 4

External ventilation. External ventilation of C-SECs or C-SCAs may be viewed as part of a suite of protective measures that are designed to reduce the likelihood of exposure. Institutions should assess current engineering controls and may choose to incorporate external ventilation where it has not already been implemented.

Qualifying statements.

- Although there is no long-term clinical evidence to inform a standard, engineering controls such as barriers, enclosures, negative pressure, contaminant capture, and elimination (eg, use of external venting) are protective measures that may be used to potentially reduce health care workers' risk of exposure to hazardous drugs. None of these controls are expected to completely eliminate the risk of exposure to workers as standalone measures.
- External ventilation of C-SECs or C-SCAs is required by USP 800.⁷
- Preparing hazardous drugs off site and consolidating preparation activities in an externally ventilated location are alternative options that may be considered where external ventilation is not possible within existing facilities because of structural or other constraints.
- More research is needed on the optimal environment for workers who handle hazardous drugs.

Standard 5

Alternative duty. The health care setting has a policy that identifies potential alternative work options, where possible, for workers who are actively trying to conceive, are pregnant, or are breastfeeding. Health care workers are given information at the time of hire regarding the capacity of the organization to reassign to alternative duty. Reviewing the options for alternative work, where available, should be the shared responsibility of the employee and employer.

Important Note

Where USP 800⁷ has been officially adopted within certain states, users of these standards should refer to the requirements contained within USP 800 and outlined within the relevant qualifying statements in this Bottom Line Box.

Health Effects of Exposure to Hazardous Drugs

Therapeutic doses of cytotoxic drugs have known reproductive and other adverse effects among patients; therefore, there is concern regarding the effects of longer-term low-level exposure among healthy workers who handle these drugs in the occupational setting. Potential exposure may occur via inhalation or/and skin absorption

from handling, as well as ingestion by hand-to-mouth contact.⁹ To quantify risk, it is useful to know the baseline risk in the absence of controls and precautions, as well as the risk level when recommended precautions are in place.

Analyses of data from the 1970s and early 1980s provide estimates of the potential risks of exposure to hazardous drugs during a time period when "a majority of staff used

inadequate protective garments or equipment,” and “most of those who did wear protective garments used only gloves, and their use was not consistent. Also in general, the flow hoods that were available prior to 1986 were horizontal flow hoods or biological safety cabinets, rather than vertical laminar flow hoods.”^{10(p9)} A case-control study published by Selevan et al¹¹ in 1985 investigated a population of unprotected nurses and found that after adjusting for previous fetal loss or induced abortion, alcohol consumption, and use of contraceptives at conception, the odds ratio (OR) for fetal loss (miscarriage) was 2.30 (95% CI, 1.20 to 4.39; $P = .01$) among nurses who were exposed to doxorubicin, cyclophosphamide, fluorouracil, and vincristine, alone or in combination. Other large studies that include mostly data from before 1986 have corroborated this finding.¹² A meta-analysis found a significant association between exposure of health care workers to cytotoxic drugs and spontaneous abortion (OR, 1.46; 95% CI, 1.11 to 1.92) and no significant association between exposure and congenital malformations (OR, 1.64; 95% CI, 0.91 to 2.94) or stillbirths (OR, 1.16; 95% CI, 0.73 to 1.82).¹³ Acute symptoms as a result of dermal exposure have been reported by nurses during unprotected handling,¹⁴ and high levels of unprotected exposure over a longer-term period have been associated with liver damage.¹⁵

In response to these findings and others, the Occupational Safety and Health Administration (OSHA) issued guidance for the safe handling of hazardous drugs in 1986,¹⁶ which included recommendations for biologic safety cabinets and PPE for drug compounding. It was recognized that vertical laminar flow hoods are more effective than horizontal laminar flow hoods. Presumably, where workplaces that have incorporated the controls listed in the OSHA 1986 guidance and more recent standards, the level of risk has been reduced; however, it is difficult to assess the effectiveness of these precautions, because few studies have been published using data obtained after the mid 1980s. The most recent study on reproductive outcomes, which used data from the Nurses Health Study II on pregnancies that occurred between 1993 and 2001, found significantly increased odds of early spontaneous abortion for the group that had an occupational exposure of ≥ 1 hour per day during the first trimester, compared with < 1 hour per day (OR, 2.13; 95% CI, 1.39 to 3.27).¹² No data on precautions or controls were available for this analysis; however, the similarity of the OR for spontaneous abortion to that of Selevan et al¹¹ suggests that recommended precautions were not consistently applied during the study period and that controls were not effective. Indeed, several studies that have assessed the use of PPE have found that there are barriers to its implementation in this context.^{17,18}

Another milestone in safe handling standards was the 2004 publication of the NIOSH Alert Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings.¹⁹ Data gathered after this date would

probably be the most relevant when estimating current prevalence of adverse outcomes related to hazardous drug exposure; however, to our knowledge, no individual studies or meta-analyses have been published that include data gathered after 2001.^{13,20,21} Because we are not aware of any studies of health effects of handling hazardous drugs in settings where the recommended hierarchy of controls has been consistently applied, it is difficult to estimate its effectiveness. In addition, there are no known data on the risk of harm associated with newer drugs that have been approved within the past 15 years. There may be potential for increased risk of adverse health effects in settings where controls are not in place or not consistently applied. More research is needed to quantify the level of risk associated with handling hazardous drugs in current workplace settings where the hierarchy of controls is consistently applied.

METHODS

Development of these 2019 Safe Handling Standards was led by an Expert Panel of oncologists, with representation from oncology pharmacy and health research methodology. Expert Panel members had substantial professional experience in the day-to-day operation of modern oncology centers in both freestanding and hospital-based settings in urban and rural areas throughout the United States. Considerable input from the oncology nursing community was gathered through participation of Oncology Nursing Society (ONS) representatives in Expert Panel meetings and the open comment process.

An initial search was conducted for existing publicly accessible guidelines or standards on safe handling of hazardous drugs. Many existing guidelines and standards were identified, and the Expert Panel determined that it would be most efficient to adapt or endorse an existing guideline/standard to avoid a duplication of effort. It was determined through discussion among the Expert Panel that the OSHA standards (Controlling Occupational Exposure to Hazardous Drugs)²² would be most suitable, given that they cover all topics of interest, are publicly available, are suitable for the US health care context, and include a discussion of the evidence of potential harms associated with health care workers' exposure to hazardous drugs.

The Expert Panel reviewed the OSHA standards²² and came to consensus on the endorsement of these recommendations for most areas. However, for some topics, there was a lack of consensus for endorsement of OSHA standards, including the areas of medical surveillance programs, closed-system transfer devices (CSTDs), external ventilation (*v* high-efficiency particulate air [HEPA] filters), and alternative duty. For the first three of these specific topics, the Expert Panel chose to conduct a systematic search of the peer-reviewed literature in order that the standards be evidence based, to the extent possible. The systematic search focused on articles that would be relevant to the following clinical questions, which are structured

according to the PICO (population, intervention, comparison, outcome) framework that is commonly used to organize clinical questions when conducting systematic reviews of the medical literature.²³

1. Do workers who handle hazardous drugs experience fewer adverse health outcomes when enrolled in workplace medical surveillance programs, compared with not being enrolled in a medical surveillance program or enrollment in an alternative type of health monitoring program?
2. Do workers who use CSTDs while compounding or administering hazardous drugs experience fewer adverse health effects, compared with workers who do not use CSTDs while performing these activities?
3. Do workers who practice drug compounding in an environment that is externally ventilated have fewer adverse health effects resulting from vapors from hazardous drugs, compared with workers who practice drug compounding in an environment that does not have external ventilation and where air is recirculated using an HEPA filtration system?

Outcomes of interest were any adverse health outcomes associated with exposure to hazardous drugs, including acute or chronic reproductive or other health outcomes. Eligible study designs included randomized or nonrandomized studies of any sample size, published in English. There was no limit placed on earliest publication date. Studies that were published as abstracts only were not eligible for inclusion. An individual study would not be considered for inclusion if the data within the study were captured in an included systematic review or a meta-analysis. Because there are no known levels that have been defined as unsafe, studies of biomarkers were not considered for inclusion in the evidence base.

A systematic review of the literature was performed using PubMed to May 2017 for CSTDs, and the Cochrane Database of Systematic Reviews, PubMed and Google Scholar to November 2017 for medical surveillance and external ventilation.

Drafting of the standards was informed by the principles of the GRADE system for grading of evidence and development of evidence-based recommendations for clinical practice guidelines.²⁴

An open comment period was conducted using the Survey Monkey Web-based survey tool from April 6 to 20, 2018. There were 10 responses to the request for public comments, and all public comments were reviewed by the Expert Panel and used to edit, revise, and clarify the standards. Final standards were approved by the executive members of the ASCO Board of Directors on July 26, 2018.

RESULTS

Standard 1: Endorsement of Standards

The Expert Panel endorses a majority of the standards for safe handling of hazardous drugs as issued by OSHA,²² the

US Pharmacopeia (USP) Chapter 800,⁷ the NIOSH 2004 Alert,¹⁹ and the ONS.²⁵

Although the Expert Panel endorses existing standards, the Expert Panel also identified areas for which an additional evidence review was required and provides consensus-based standards on these topics, including medical surveillance, CSTD, external ventilation of containment secondary engineering controls (C-SECs) or containment segregated compounding areas (C-SCAs), and alternative duties. These topics are highlighted in the Bottom Line Box. Given the limitations of the evidence base, the standards presented here are consensus based and were developed by weighing the potential for benefit and risks of harm associated with each statement. In addition, the key issues, challenges, and actions or potential solutions are summarized in Table 1.

Standard 2: Medical Surveillance

Question 1. Do medical surveillance programs result in improved health outcomes in workplaces where individuals may be exposed to hazardous drugs, compared with workplaces where no medical surveillance programs or other types of programs are in place? Is there a preferred time interval for medical surveillance questionnaires/examinations?

Medical surveillance standard. Workplace occupational health programs in settings where hazardous drugs are handled should include policies and procedures demonstrated to effectively monitor hazardous drug contamination in the health care setting and to monitor individuals who have been involved in an acute exposure (eg, a spill). The role of routine ongoing medical surveillance programs that include medical screening, laboratory testing, or other biologic monitoring is unclear, because there are no published data to reliably inform a standard or best practice.

Qualifying statements.

- There are currently no data from well-designed programs to inform whether screening and monitoring within medical surveillance programs increase or decrease benefits or harms related to health outcomes for workers who handle hazardous drugs. In addition, there are a lack of valid tests or techniques for detecting early signs of disease, no established levels of exposure that have been linked to adverse health effects, and other limitations.
- As an alternative to routine ongoing medical surveillance programs, this ASCO standard endorses larger-scale data collection in the context of a registry of health care workers. This standard also endorses the collection of data to test research hypotheses, provided that the necessary sample size to detect significant differences can reasonably be achieved, that peer-reviewed publication plans are determined a priori, and that approval has been given by a research ethics board. Gathering data with the purpose of examining them periodically for a small alteration²⁵ is not recommended.

TABLE 1. Summary of Safe Handling Issues, Challenges, and Actions or Potential Solutions

Issue	Challenge	Action/Potential Solution
Whether and when to use CSTDs ²⁶	No standard testing protocols or certification process for CSTDs	Independent research into the effectiveness of CSTDS
	No data on impact of CSTDs on worker health outcomes	Incorporation of results from the NIOSH testing protocol Independent certification of effective CSTDs
Implementation of medical surveillance, including medical screening, biologic monitoring, and laboratory testing	Medical surveillance in the context of safe handling fails to meet several established criteria; there are no valid tests or techniques for detecting early signs of disease, no established levels of exposure that have been linked to adverse health effects, and no established actions in response to a particular result	Workers should be encouraged to report occupational health issues to employee health services at the time that they are experienced As an alternative to routine ongoing medical surveillance programs, ASCO endorses larger-scale data collection in the context of a registry of health care workers The collection of data to test research hypotheses, provided that the necessary sample size to detect significant differences can reasonably be achieved, that peer-reviewed publication plans are determined a priori, and that approval has been given by a research ethics board is also endorsed
Implementation of external ventilation of C-SECs or C-SCAs	HEPA filters are appropriate for capturing solid or aerosolized particulates but do not capture vaporized drugs	External ventilation may be viewed as part of a suite of protective measures that are designed to reduce the likelihood of exposure; institutions should assess current engineering controls and may choose to incorporate external ventilation where it has not already been implemented
	There are few data available on the ability of hazardous drugs to vaporize within the workplace environment	Preparing hazardous drugs off site and consolidating preparation activities in an externally ventilated location are alternative options that may be considered where external ventilation is not possible within existing facilities because of structural or other constraints More research is needed on the optimal environment for workers who handle hazardous drugs Research is needed into the ability of hazardous drugs to vaporize within the workplace environment
Options for alternative duties for workers who are actively trying to conceive, are pregnant, or are breastfeeding	There may be special burdens on small practices looking to implement alternative duty programs	The health care setting has a policy that identifies potential alternative work options, where possible, for workers who are actively trying to conceive, are pregnant, or are breastfeeding
	Little is known regarding the level of risk in current workplaces for workers who are actively trying to conceive, are pregnant, or are breastfeeding	Health care workers are given information at the time of hire regarding the capacity of the organization to reassign to alternative duty; reviewing the options for alternative work, where available, should be the shared responsibility of the employee and employer More research is needed into the level of risk associated with handling hazardous drugs for all workers and this specific population of workers

Abbreviations: C-SCA, containment segregated compounding area; C-SEC, containment secondary engineering control; CSTD, closed-system transfer device; HEPA, high-efficiency particulate air; NIOSH, National Institute for Occupational Safety and Health.

- Workers should be encouraged to report occupational health issues to employee health services at the time that they are experienced.
- The Expert Panel will continue to monitor the literature for robust studies of the link between biologic markers and health outcomes and for studies that assess the outcomes of medical screening and biologic monitoring programs that may already be in place within specific institutions.

Definitions.

- “Medical surveillance is the analysis of health information to look for problems that may be occurring in the workplace that require targeted prevention. Thus, surveillance serves as a feedback loop to the employer.

Surveillance may be based on a single case or sentinel event, but more typically uses screening results from the group of employees being evaluated to look for abnormal trends in health status. Surveillance can also be conducted on a single employee over time. Review of group results helps to identify potential problem areas and the effectiveness of existing worksite preventive strategies.”²⁷

- “Medical screening is a method for detecting disease or body dysfunction before an individual would normally seek medical care. Screening tests are usually administered to individuals without current symptoms, but who may be at high risk for certain adverse health outcomes.”²⁷

- Biologic monitoring is “the measure of a specific agent or its metabolite in a body fluid (such as a urine 5-FU [fluorouracil] level).”²²
- Laboratory testing in the context refers to the routine testing of blood samples from health care workers, which would include a complete blood count at minimum.

Literature search results and interpretation. The search for primary research found no studies that addressed Question 1, neither for the outcomes related to implementation of surveillance programs nor for optimal timing. Several studies were found that addressed the topic of medical surveillance in other workplace settings, such as exposure to lead, crystalline silica, and nanoparticles. These studies were too indirect to be considered relevant to inform Question 1. Given the lack of study of this intervention in the setting of potential exposure to hazardous drugs, the Expert Panel turned to published information outlining the important components of a medical surveillance program and assessed these against the conditions that are commonly found in workplaces where hazardous cytotoxic drugs are handled.

The stated goals of medical surveillance, which is classified as an administrative control (ONS), are to⁷: minimize adverse health effects in personnel potentially exposed to hazardous drugs, detect deviations in expected norms (from established baseline), detect health problems earlier, detect trends in groups of workers, and act as a check on the appropriateness of controls already in place.²⁵

Although these programs have been recommended by OSHA and others since 1995, the rate of implementation of medical surveillance programs for hazardous drugs has been low, with 46% of nurses at work sites in 2003 reporting some type of medical surveillance.²⁸ A recent survey of safe handling guidelines and practices across 24 countries found that medical surveillance was mandatory in one country, the Netherlands, but that there were no clear guidelines for how to perform surveillance or what was considered relevant.²⁹ Rather, the focus was on “prevention by area monitoring”^{29(p9)} and environmental wipe samples, as well as “contamination criteria after cleaning.”^{29(p9)} OSHA recommends baseline and periodic medical examinations annually or every 2 to 3 years.²² Lack of knowledge regarding expected level of risk and expected adverse health outcomes over and above those rates in the unexposed population presents a challenge when interpreting medical surveillance data.

Within the United States, USP,⁷ ONS,²⁵ and OSHA²² recommend medical surveillance. A Canadian guideline from Cancer Care Ontario⁴ did not endorse medical surveillance for several reasons; there are currently no established exposure limits for hazardous drugs and no established response protocols in the event of a health event among an exposed worker. An Irish guideline states that criteria for

establishment of medical surveillance are unlikely to be met for staff exposed to hazardous drugs.⁶ The sensitivity and specificity of medical surveillance questionnaires for the detection of adverse events associated with the handling of hazardous drugs are unknown. In addition, in the United States, there is no current registry of health care workers participating in medical surveillance programs, so it is difficult to gather data on a scale that would be useful for controlled comparisons, detection of trends over time, or facilitation of before and after studies of interventions.

Medical surveillance can include medical screening. Implementation of a medical surveillance program must consider the potential harms of screening, including overdiagnosis, misdiagnosis, anxiety regarding pending test results, and the potential to create a false sense of security. The World Health Organization has developed a list of established and emerging screening criteria³⁰ (Box 1). The Expert Panel also considered the assessment methods outlined by the Health and Safety Executive in the United Kingdom.³² This methodology begins with a risk assessment. After this, according to the Health and Safety Executive, if there is still a risk to health after all precautions have been put into place, medical health surveillance is required if the following criteria are met:

- There is an identifiable disease/adverse health effect and evidence of a link with workplace exposure
- It is likely the disease/health effect may occur
- There are valid techniques for detecting early signs of the disease/health effect
- These techniques do not pose a risk to employees

Given the lack of data on the effectiveness of medical surveillance programs and an analysis of the criteria commonly associated with implementation of surveillance and screening programs (Box 1), the ASCO standards do not recommend routine medical surveillance in workplaces where hazardous drugs are handled.

Standard 3: CSTDs

Question 2. What are the incidence rates of relevant health outcomes for workers who use CSTDs to prepare or administer hazardous drugs, compared with health outcomes for workers who do not use CSTDs to prepare or administer hazardous drugs?

CSTD standard. To inform a standard on this topic, a testing protocol for CSTDs is needed. In addition, there is a need for a process to identify and certify effective CSTDs.

Qualifying statements.

- Within a recent systematic review,³³ the quality of the published literature on CSTDs was rated as low quality and at high risk of bias using the GRADE methodology.³⁴ After implementation of CSTDs, some studies have noted a decrease in the percentage of surface sampling wipes that have detectable levels of antineoplastic drugs and/or a decrease in the percentage of workers who have detectable levels of antineoplastic

BOX 1. WORLD HEALTH ORGANIZATION SUMMARY OF CLASSIC AND EMERGING SCREENING CRITERIA

Wilson and Jungner³¹ classic screening criteria

1. The condition sought should be an important health problem.
2. There should be an accepted treatment of patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once-and-for-all project.

Synthesis of emerging screening criteria proposed over the past 40 years³⁰

1. The screening program should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening program effectiveness.
5. The program should integrate education, testing, clinical services, and program management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The program should ensure informed choice, confidentiality, and respect for autonomy.
8. The program should promote equity and access to screening for the entire target population.
9. Program evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

Reprinted from Bulletin of the World Health Organization, 86 (4), Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years, 317-8, Copyright 2008.

drugs in their urine. There are no short- or long-term data to inform whether specific CSTDs have an impact on health outcomes.

- NIOSH recommends using CSTDs when transferring hazardous drugs from primary packaging to infusion bags, bottles, or pumps.¹⁹ USP 800 requires use of CSTDs for nursing administration of hazardous drugs and recommends use for sterile product compounding of hazardous drugs.⁷
- At this time, there is no standardized testing protocol to assess the performance of available CSTDs. NIOSH is in the process of developing an independent vapor containment performance protocol for CSTDs in health care settings.³⁵ These ASCO standards will be revised to incorporate the NIOSH CSTD testing protocol when it becomes available.
- We encourage NIOSH to develop a certification process so that practices can identify effective CSTDs.

Literature search results and interpretation. CSTDs are devices that are intended to “mechanically prohibit transfer of environmental contaminants into the system and the

escape of hazardous drug or vapor concentrations outside the system.”^{19(p44)} The review of the evidence for CSTDs did not find any published studies that evaluated health outcomes but rather found studies of surrogate markers such as presence of antineoplastic drugs in urine, surface contamination, and containment levels of drugs in controlled laboratory settings. Review authors concluded that the largely industry-sponsored body of evidence was of low quality and that there is a need for a third party to develop a neutral testing method to determine the efficacy of CSTDs. Another recent systematic review³³ using the GRADE methodology³⁴ concluded that the quality of the published literature on CSTDs was low and at high risk of bias.

There are currently no established performance or evaluation standards for CSTDs. A protocol being developed by NIOSH for this purpose underwent a public comment period that was completed in February 2018.³⁵ Presently, OSHA recommends that CSTDs be used when compounding or administering hazardous drugs and recommends that manufacturers’ performance claims be carefully evaluated when selecting a CSTD. A health

technology assessment conducted by the Canadian Agency for Drugs and Technology in Health (CADTH) concluded that CSTDs “appear to reduce environmental contamination of hazardous drugs and consequently workers’ exposure to these drugs, but it is not clear whether or not this translates to a reduction in clinical harms to the health care staff preparing these medications.”^{36(p6)} CADTH review noted that with respect to surrogate outcome studies, “although urine samples may give an idea of exposure, they do not necessarily extrapolate to harms.”^{36(p6)} This review found no new studies of health outcomes with the use of CSTDs. This standard is made in the context of NIOSH currently developing a protocol for CSTDs.

Standard 4: External Ventilation of C-SECs or C-SCAs

Question 3. Do workers who practice drug compounding in an environment that is externally ventilated have fewer adverse health effects resulting from vapors from hazardous drugs, compared with workers who practice drug compounding in an environment that does not have external ventilation and where air is recirculated using a HEPA filtration system?

External ventilation standard. External ventilation of containment secondary engineering controls or containment segregated compounding areas may be viewed as part of a suite of protective measures that are designed to reduce the likelihood of exposure. Institutions should assess current engineering controls and may choose to incorporate external ventilation where it has not already been implemented.

Qualifying statements.

- Although there is no long-term clinical evidence to inform a standard, engineering controls such as barriers, enclosures, negative pressure, contaminant capture, and elimination (eg, use of external venting) are protective measures that may be used to potentially reduce health care workers’ risk of exposure to hazardous drugs. None of these controls are expected to eliminate the risk of exposure to workers as standalone measures.
- External ventilation of C-SECs or C-SCAs is required by USP 800.⁷
- Preparing hazardous drugs off site and consolidating preparation activities in an externally ventilated location are alternative options that may be considered where external ventilation is not possible within existing facilities because of structural or other constraints.
- More research is needed on the optimal environment for workers who handle hazardous drugs.

Literature search results and interpretation. Among the various routes of exposure to hazardous drugs, contact with skin is considered to be the most common and likely³⁷; however, exposure may also occur through inhalation of aerosols (solid or liquid particles suspended in air) or gaseous vapors resulting from evaporation of hazardous drugs that are in solid or liquid form. Previous standards

issued by USP (USP 797) recommended HEPA filtration and ideally venting to the outside of the building.^{38(p19)} Newer standards (USP 800,⁷ OSHA²²) for sterile hazardous drug compounding require external ventilation of containment primary engineering controls (ie, biologic safety cabinets), whether the configuration is an ISO Class 7 air quality buffer room with an ISO Class 7 anteroom or an unclassified containment segregated compounding area that is considered acceptable for low- and medium-risk hazardous drugs.⁷

The literature search did not locate any studies that addressed Question 3, and in general, little research has been conducted on the topic of hazardous drug vaporization. Two studies conducted in 2000 and 2002, respectively, found that commonly used hazardous drugs did have the potential to vaporize during compounding, although in the latter study, there was no evidence of hazardous drugs in the workers’ urine samples, and health outcomes were not included in the scope of the studies. It is possible that acute symptoms such as lightheadedness, dizziness, nausea, and headache, which were reported after working with hazardous drugs in unventilated areas in an early study³⁹ and in studies conducted in Turkey⁴⁰ and in Greece,⁴¹ may be related to the presence of vapors. No vaporization studies of drugs that have been approved within the last 15 years have been conducted.

HEPA filters are designed to capture particles, but they do not trap vapors or gases. Therefore, the requirement in recent hazardous drug handling guidance for external ventilation addresses the potential for hazardous drugs to produce vapors that are not eliminated when HEPA-filtered air is internally vented and recirculated into the compounding area. More research is needed to determine the potential for drugs that are currently in use to vaporize, the health effects associated with exposure to vapors, and whether the currently recommended hierarchy of controls is effective in reducing exposure to vapors from hazardous drugs.

Standard 5: Alternative Duty

Alternative duty standard. The health care setting has a policy that identifies potential alternative work options, where possible, for workers who are actively trying to conceive, are pregnant, or are breastfeeding. Health care workers are given information at the time of hire regarding the capacity of the organization to reassign to alternative duty. Reviewing the options for alternative work, where available, should be the shared responsibility of the employee and employer.

Literature search results and interpretation. During the development process for these standards, the Expert Panel endorsed the standard practice of informing health care workers that they may request alternative duty assignments while they are trying to conceive, are pregnant, or are breastfeeding. The Expert Panel also puts forward a

standard requiring that workers receive information on the risks of working with hazardous drugs, as well as the need for more research in this area to more accurately characterize the level of risk (Table 1).

OPEN COMMENT

Summary of Responses

The draft standards were posted online for an open comment period from April 6 to 20, 2018. Potential respondents were asked to comment on the draft standards only; background information and standard development methodology were not included in the open comment survey. Potential respondents were required to complete a nondisclosure agreement, but conflict-of-interest disclosures were not a requirement of participation. Ten external responses to the comment period were received. Respondents reported affiliations with professional societies, pharmacy, academia, USP, and hospital/medical centers. Respondents were asked to rate their level of agreement with each of the four standards and optionally to provide comments and feedback.

The level of agreement with the standards as written with no suggested modifications ranged from 20% to 40%, and most respondents provided written feedback and suggested modifications. There was agreement across respondents that it is desirable to create an environment that maintains a level of risk that follows the principle of ALARA (ie, as low as reasonably achievable)²²; however, what this means in practice was a point of contention, and several respondents raised concerns that these standards differ from USP 800⁷ and other standards. The ASCO response outlined in the Data Supplement attributes this discrepancy to the quality of the evidence base, which is low to very low for several of the standards; in this scenario, it is more likely that consensus-based recommendations will differ across groups. It was suggested by some respondents that surrogate outcomes such as genetic markers provide strong evidence to underpin a mandate for standards such as external ventilation. This point of view is in contrast with the position taken by the Expert Panel members for these standards, who agree that flexibility is necessary in situations where only surrogate outcomes are available and where significant uncertainty exists regarding the potential for benefit or risks of harm associated with an intervention.

Modifications made in response to the feedback received via the open comment process included improved clarity around the definition of medical surveillance and related terminology, alternatives to medical surveillance programs and external ventilation where they are not feasible, incorporation of data from a new meta-analysis of CSTDs,³³ and further direction within the standard for alternative duty. It is hoped that these modifications improve the clarity of the standards and provide more detailed description of

the combination of evidence and considered judgment that was used in their development. In addition, the variability of feedback received during the open comment period reinforced the need for further independent research in several areas, as outlined in the Discussion. Detailed results of the open comment process and ASCO responses are outlined in the Data Supplement. Some comments have been edited and condensed for clarity and to avoid repetition.

DISCUSSION

Recently, considerable activity has taken place in the United States at the state and national levels to articulate best practices for safe handling of hazardous drugs. Updated standards have been issued by OSHA,²² USP,⁷ and ONS.²⁵ These ASCO standards largely endorse the guidance contained within those standards and include a search for evidence in three key areas: medical surveillance, external ventilation of C-SECs or C-SCAs, and CSTDs. These searches were conducted as part of an evidence-based development framework and also served to identify areas of priority for future research.

Given the lack of recent data on the health outcomes associated with exposure to hazardous oncology drugs and the near absence of data on the impact of controls to mitigate exposure and risk, standards to date have been consensus rather than evidence based. These ASCO standards used an evidence-based methodology and combined systematic searches for evidence with expert consensus. Using established guideline development methodology, the Expert Panel determined that conditional rather than strong standards would be appropriate for the areas outlined here, based on the absence of evidence of benefit, but recognizing that most of these interventions have minimal potential for harm to health care workers. Potential benefits include the avoidance or mitigation of adverse health outcomes, while potential harms include implementation of unnecessary or uncertain procedures or technologies, inconvenience, anxiety, a false sense of security, overdiagnosis or misdiagnosis, and cost and physical constraints.

Lack of data on the effectiveness of controls is an indicator of the need for more research to develop an evidence base for standards, including the establishment of the baseline risk of harms in current workplace settings, as well as the prevalence of adverse health effects associated with hazardous drugs that are currently in use, barriers to implementation of the hierarchy of controls, and the effectiveness of various interventions.

Where USP 800 has been officially adopted within certain states, users of these standards should refer to the requirements contained within USP 800 and outlined within the relevant qualifying statements in the Bottom Line Box.

Although the ASCO standards differ in some ways from the USP 800 standards, existing standards are largely endorsed by ASCO, and we hope to reinforce the hierarchy of controls that provides protection for workers. We strongly encourage workplaces to follow a philosophy of ALARA²² with respect to exposure, and we endorse efforts that will reduce the barriers to implementation of effective controls.

ASCO will assess the 2018 Safe Handling Standards for potential inclusion in the ASCO Quality Oncology Practice Initiative certification process and will work with state affiliates to raise awareness regarding all of the available worker safety standards and legislation regarding the safe handling of hazardous drugs. In addition, ASCO plans to

reach out to other societies to collaborate on tools and resources for implementation and explore workshops and other strategies for education, dissemination, and implementation of the standards to promote the safe handling of hazardous drugs.

The evolution of oncology care as well as publication of new evidence will trigger periodic updating of and revisions to these standards. The standards were created with applicability in mind; that is, the standards need to be as applicable in the small practice setting as they are in a comprehensive cancer center. In addition, the standards can serve as the foundation for best practices, which are evidenced-based processes that help ensure safe handling in a strong culture of safety and quality.

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Safe Handling of Hazardous Drugs: ASCO Standards

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