A Call to Action for Hazardous Drug Safety: Where We Have Been and Where We Are Now

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**Background:** The dangers associated with handling hazardous drugs (HDs) have been well documented. Contamination of the healthcare environment, which can occur during compounding and administration, may lead to drug absorption by healthcare workers. Studies have proven that HD exposure causes numerous side effects and chromosomal aberrations.

**Objectives:** This article examines the complex issues surrounding HD safety, including workplace culture, current guidelines, and misconceptions regarding the risks associated with exposure. Discussions include suggestions for creating a workplace culture where HD safety is an expectation, along with an update on laws and significant impending changes.

**Methods:** Historical data and current research are presented.

**Findings:** Although improvements have been made in the use of personal protective equipment, studies indicate that nurses continue to be unnecessarily at risk. Inability to fully understand the dangers, a lack of organizational safety culture, and the general inability to enforce guidelines continue to be challenging. Fortunately, a number of upcoming changes will help to build momentum for increasing nursing safety.

The risks associated with hazardous drug (HD) handling have been well documented in the literature, dating back more than 35 years (Centers for Disease Control and Prevention, 2004; Crudi, Stephens, & Maier, 1982; Lorente et al., 2000; Sorsa, Hemminki, & Vainio, 1985). Although HD exposure has been linked to a number of acute side effects, most research has focused on the reproductive consequences. Figure 1 contains a summary of exposure side effects. Many HDs also are classified as carcinogens by the International Agency for Research on Cancer (2015). Known and probable carcinogens are listed in Figure 2.

**Mutagenicity**

McDiarmid, Oliver, Roth, Rogers, and Escalante (2010) examined damage to chromosomes 5, 7, and 11 in 109 hospital employees. These chromosomes were selected for analysis because they have been associated with therapy-related acute myeloid leukemia (Pedersen-Bjergaard, Andersen, Christiansen, & Nerlov, 2002; Rogers & Emmett, 1987). The study cohort included 63 oncology nursing and pharmacy employees, and 46 employees who did not handle HDs as a control group. Damage was detected on chromosomes 5 and 7 more often in staff who handled HDs versus those who did not (p = 0.01). The study also demonstrated that increased damage was associated with increased handling, particularly with alkylating agents, such as cyclophosphamide (Cytoxan®), where the risk of damage was 8.54 times greater than control (p = 0.01) (McDiarmid et al., 2010). Based on studies that have shown an increased risk of cancer (Blair et al., 2001; Escobar, Smith, Vasishtha, Hubbard, & Zhang, 2007; Fransman et al., 2014; Ratner et al., 2010), and considering one of the fundamental theories of oncogenesis rests on the development of genetic mutations (Eggert, 2010), it would seem prudent to do whatever is necessary to prevent mutations whenever possible.
Hazardous Drug Guidelines

Two years after Falck et al. (1979) published a landmark paper demonstrating mutagenic substances in the urine of nurses who handled chemotherapy, the first HD safety guidelines appeared (Harrison, 1981). The American Society of Hospital Pharmacists (now known as the American Society of Health-System Pharmacists [ASHP]) published their recommendations in 1983 (Stolar, Power, & Viele, 1983). ASHP subsequently published a Technical Assistance Bulletin (TAB) in 1985, which was updated again in 1990 (Power, 1990). A decision was made in that document to use the term hazardous drug instead of chemotherapy because a number of drugs meeting the criteria were not considered antineoplastic. The most recent TAB was revised in 2006 (ASHP, 2006).

The Occupational Safety and Health Administration (OSHA) published its first work-practice guidelines for personnel dealing with cytotoxic drugs in 1986 (Yodaiken & Bennett, 1986). The introduction states that the guidelines were not to be considered mandatory standards. OSHA guidelines were updated in 1996 and 1999. In 2004, the National Institute for Occupational Safety and Health (NIOSH), the research arm of the Centers for Disease Control and Prevention, issued an alert for best practice for handling HDs (Centers for Disease Control and Prevention, 2004). The introduction summarized decades of studies by stating: “Warning: Working with or near hazardous drugs in health care settings may cause skin rashes, infertility, miscarriage, birth defects, and possibly leukemia or other cancer” (p. 1).

The Oncology Nursing Society (ONS) guidelines were first published in 1984 and provided specific information for nurses. Subsequently, ONS has devoted a number of resources to the subject, including an online course and two publications (Polovich, 2011; Polovich, Olsen, & LeFebvre, 2014).

Current State of Hazardous Drug Safety

What Is in Your Hospital?

Acknowledging that HD exposure should be avoided, how do healthcare workers know that their environment is contaminated and, therefore, putting them at risk? Wipe kits provide the ability to detect HD residue on surfaces within the working environment. Kits are now available for obtaining wipe samples without the expense of a site visit by an industrial hygienist. However, once collected, the samples need to be sent to a specialized laboratory capable of providing detailed analysis. Examples of such laboratories include Bureau Veritas Laboratories (http://labs.us.bureauveritas.com), ChemoGLO LLC (https://chemoglo.com), and RG Lee Group (www.rjlg.com).

In the 1980s and 1990s, wipe tests in hospitals revealed widespread contamination attributed to using horizontal flow “hoods” during drug compounding, which blew contaminated air back at the pharmacists (Connor, Anderson, Sessink, Broadfield, & Power, 1999; McDevitt, Lees, & McDiarmid, 1993; Nygren et al., 2002; Sessink, Anzion, Van den Broek, & Bos, 1992; Sessink, Boer, Scheefhals, Anzion, & Bos, 1992; Sessink et al., 1994). Subsequent ASHP guidelines require the use of vented vertical flow biologic safety cabinets (BSCs), although evidence strongly suggests that even these devices cannot fully prevent contamination within the compounding area (ASHP, 2006; Merger, Tanguay, Langlois, Lefebvre, & Bussieres, 2014; Vyas, Yiannakis, Turner, & Sewell, 2013).

Contamination also extends beyond the pharmacy and into patient care areas. Avoiding surface contamination is important because HDs can be absorbed through the skin, which is considered the primary source of uptake (Fransman, Vermeulen, & Kromhout, 2005). This is the primary rationale for wearing personal protective equipment (PPE) during all stages of HD handling (Polovich, 2011).

One of the most comprehensive surface contamination studies involved three large institutions in the United States, in which 143 wipe samples for five different HDs were obtained. The study included 7 pharmacy and 10 nursing areas (Connor et al., 2010). All facilities were reportedly following current guidelines. Researchers also obtained urine samples from all study participants to check for potential HD excretion. Sixty percent of the wipe samples were positive for at least one HD. Remarkably, the highest concentration was not in the pharmacy but on the lid of a disposal container on one of the nursing units. Three employees tested positive for HD in their urine.

Surface contamination has been definitively linked to hand contamination. One study obtained wipe samples from the hands of employees in five hospitals and one outpatient center (Hon, Teschke, Demers, & Venners, 2014). Study participants included nurses, physicians, dietitians, transporters, and unit clerks. Of the 225 wipe samples, 20% were found to be posi-
tive, even after staff had reportedly washed their hands. The highest concentration was found on a worker who was not involved with the administration of chemotherapy whatsoever; that exposure was potentially related to insufficient training.

Absorption and subsequent urinary excretion of HDs has been well documented since the 1980s (Everson, Ratcliffe, Flack, Hoffman, & Watanabe, 1985; Hirst, Tse, Mills, Levin, & White, 1984; Labuhn, Valanis, Schoeny, Loveday, & Vollmer, 1998; Sessink, Wittenhorst, Anzion, & Bos, 1997). As a follow-up to their hand contamination study, Hon, Teschke, Shen, Demers, and Venners (2015) also looked at the urine of 103 employees from the same disciplines. They found that 55% of the samples collected during a 24-hour period were positive for cyclophosphamide. As with the hand wipe samples, high levels were found in workers who were not directly involved with handling chemotherapy.

Nursing Vulnerability for Exposure

The avenues for exposure during the administration of HDs are different from those associated with compounding. Compounding of drugs usually is a sequential operation during which the pharmacist or technician prepares multiple doses of HDs in succession. Nursing workflow, however, is notoriously nonsequential. Multitasking while caring for several patients is common, and a busy nurse is faced with frequent interruptions. Drug administration does not occur in an enclosed environment. A compounding spill inside the BSC is relatively contained, whereas spills at the bedside can contaminate a larger physical area and involve the patient, family members, and nonpatient care staff. Likewise, nurses do not have the engineering controls used for compounding and have been historically inconsistent in wearing PPE (Polovich & Clark, 2012) (see Table 1).

Topics of Concern

During the years since the first nursing guidelines were published, much of the emphasis has focused on three main areas: compounding, PPE, and spill management.

Compounding: In the 1980s and 1990s, nurses often prepared their own chemotherapy (Crudi et al., 1982). Accordingly, ONS included information on compounding in their guidelines. How many nurses are still mixing HDs is unknown, although a 2007 study that looked specifically at spills in an ambulatory setting reported four spills in a six-month period involving nine employees (Friese et al., 2015). Of the 40 study participants, eight had detectable levels of HD in their urine, including four who had not been involved with a spill. In addition, 60% of the participants reported in a follow-up questionnaire that they were either “not concerned” or had a “low level of concern” about the spill. This speaks to the apparent lack of awareness that still exists among nurses who administer HDs.

Neutralizing

Based on wipe test studies, it is known that contamination exists (Bigelow, Schulz, Dobish, & Chambers, 2009; Connor, 2006; Connor et al., 1999; Odraska et al., 2013) and persists throughout many hospitals (Roberts, Khammo, McDonnell, & Sewell, 2006). HDs can linger on surfaces for long periods of time (Connor, Anderson, Sessink, & Spivey, 2002; Hansel et al., 1997), are difficult to remove (Anderson, Connor, Power, & Dorr, 2001; Gonzalez & Massoomi, 2010), and cannot be neutralized by alcohol. Studies have shown that a 5.25% concentration of sodium hypochlorite (approximately equal to household chlorine bleach) can neutralize some HDs (Benvenuto et al., 1993; Castegnaro et al., 1997; Roberts et al., 2006); however, that concentration is highly corrosive and impractical to use in a healthcare setting because of the generation of noxious fumes.

ONS cautions against using chemicals that have not been tested against chemotherapeutic drugs for neutralization because of the potential generation of unknown toxic compounds (Polovich, 2011). Two commercial products are available that do neutralize some HDs, and a summary can be found in Table 2. Although both products are beneficial and should be considered as part of a spill kit, the small size of the packets limits the effective area that can be neutralized, making them impractical for large-volume spills. This poses a significant challenge. A survey by Boiano et al. (2014) found that 9% (n = 190) of the reported spills were not cleaned at all. Therefore, it becomes even more imperative that every precaution is taken to prevent spills from occurring.

Guideline Adherence

A number of explanations have been proposed for the lack of consistent adherence to guidelines, including practice setting, workplace culture, and number of patients per nurse (Polovich

<table>
<thead>
<tr>
<th>Article</th>
<th>N</th>
<th>Gloves (%)</th>
<th>Gowns (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiano et al., 2014</td>
<td>1,954</td>
<td>85</td>
<td>58</td>
</tr>
<tr>
<td>Oncology Nursing Society, 2008*</td>
<td>661</td>
<td>94</td>
<td>51</td>
</tr>
<tr>
<td>Massachusetts Nursing Association, 2007</td>
<td>400</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td>Polovich &amp; Martin, 2011</td>
<td>324</td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td>Martin &amp; Larson, 2003</td>
<td>236</td>
<td>94</td>
<td>31</td>
</tr>
</tbody>
</table>

*Data on file

TABLE 1. Summary of Personal Protective Equipment Compliance Surveys
& Clark, 2012). Workplace culture, in particular, sets the tone for how organizations view safety and hazards (Sherwood & Zomorodi, 2014) and is directly influenced by policies and procedures, expectations from staff and management, and how outcomes are achieved (Gershon et al., 2000). Polovich and Clark (2012) noted that policies and procedures, ostensibly intended to safeguard staff, failed to coincide with current guidelines in 25% of the 165 facilities surveyed, and 75% did not have an official system to monitor policy compliance. Surprisingly, 25% of the organizations also did not provide gowns for staff, indicative of a larger problem related to guidelines versus regulations.

### Guideline Violations

The 1970 OSHA general duty clause states that “employers are responsible for providing safe and healthful workplaces for their employees” (p. 1). However, the clause is not specific to nursing, HD handling, or PPE use. In 2010, it was reported that OSHA had cited only one healthcare facility during the prior 10 years for violating the clause (Smith, 2010).

Although no published surveys describe the number of nurses who may have reported their employers to OSHA for not providing PPE, nurses in one Florida oncology clinic filed a complaint that subsequently resulted in a NIOSH site visit (Couch, West, & Niemeier, 2013). Safety improvements occurred as a result, and the authors encouraged other nurses to contact NIOSH if safety hazards have not been adequately addressed by management. Although that is a sound recommendation, oncology nurses may be afraid to report their employer for fear of retribution and, therefore, may remain silent.

### Changes

At a meeting of Safe Handling of Hazardous Drugs Association stakeholders, Polovich (2015) was quoted as saying, “Nurses should not have to risk their health and safety when caring for patients who are receiving chemotherapy. Yet, health care is the only industry in the United States where protection against exposure to carcinogens is optional” (p. 1). The meeting included members from the American Society of Clinical Oncology, ASHP, the Association of Community Cancer Centers, the Association of Pediatric Hematology/Oncology Nurses, and the Hematology/Oncology Pharmacy Association. A position paper was issued by ONS (2015), which underscores a small but definitive shift in HD safety paradigms. This document marks the strongest and most explicit declaration to date on HD safety.

### State Legislation

Lacking the ability to enforce NIOSH guidelines at the federal level, several states (Washington, California, Maryland, North Carolina, and Michigan) have recently passed or have pending HD safety legislation. Washington state’s landmark legislation (Smith, 2010) stemmed from the death of a Seattle pharmacist from pancreatic cancer after many years of compounding chemotherapy under unsafe conditions. Her daughter raised the issue of “voluntary” safety guidelines to two state senators and the law was passed in 2011.

### Joint Commission

In the March 2014 EC News, the Joint Commission (JC) addressed hospitals’ responsibilities in protecting workers. In addition to reiterating established recommendations, their Environment of Care Standard EC 02.02.01 states, “The hospital manages risks related to hazardous materials and waste . . . [and] minimizes the risks associated with disposing of hazardous medications” (JC, 2014, p. 8). Another JC publication covered the purchasing of HD-tested gloves, and described the problem of using gloves that have not been tested against HDs using the appropriate American Society for Testing and Materials standard as a “sobering and valid concern” (JC, 2015, p. 6). Whether the JC will get as deeply involved with HD safety as it has in preventing central venous catheter infections is unclear. However, JC Resources, an affiliate of the JC, is developing a training toolkit on the topic, indicating a further commitment to HD safety.

### U.S. Pharmacopeial Convention

The mission of U.S. Pharmacopeial (USP) Convention is to set standards “for the identity, strength, quality, and purity of medicines” (USP, 2015b, p. 1). Many of their practice standards have focused on compounding. However, in February 2016, USP released the final version of chapter 800 (referred to as USP<800>), a well-organized although highly controversial

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### TABLE 2. Products Used to Neutralize Chemotherapy

<table>
<thead>
<tr>
<th>Product</th>
<th>Pad 1</th>
<th>Pad 2</th>
<th>Drugs Neutralized</th>
<th>Area of Coverage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDClean™</td>
<td>Proprietary quaternary amm-</td>
<td>Alcohol</td>
<td>6</td>
<td>8 square feet</td>
<td>Low odor</td>
</tr>
<tr>
<td></td>
<td>nonium compound</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SurfaceSafe™</td>
<td>2% sodium hypochlorite and</td>
<td>1% sodium thiosulfate and</td>
<td>More than 14</td>
<td>2 square feet</td>
<td>Bleach odor</td>
</tr>
<tr>
<td></td>
<td>detergent</td>
<td>alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from ChemoGLO, 2016; Covidien, 2012; Robert Dorr, personal communication.
standard that covers HD handling from delivery to the pharmacy through waste disposal (USP, 2015a). Most relevant to nurses are the sections that will mandate nursing practice. Organizations will have until July 1, 2018, to comply.

Nursing Implications of USP<800>

Some nurses may find that implementing USP<800> will require little or no changes to their current practice. However, based on the results of previously described surveys, most will need to make significant modifications. A summary of USP<800> nursing requirements is found in Figure 3. What makes USP different from NIOSH, ASHP, or ONS is that enforcement is carried out by each state’s Board of Pharmacy. Although not every state adheres to USP, for the majority that do, the impact will be a monumental step forward in protecting nurses from HD exposure.

Closed-System Transfer Device

One specific USP<800> requirement will be the use of a closed-system transfer device (CSTD) for the administration of all HDs. Although recommended in guidelines and literature for a number of years (ASHP, 2006; Polovitch et al., 2014; Vyas et al., 2013), CSTDs have, to date, not been required. A detailed discussion of CSTDs is beyond the scope of this article, but a number of variables need to be considered when choosing a CSTD, including integration with existing pumps and tubing and specific pharmacy requirements. A brief comparison of devices can be found in Table 3.

One challenge to choosing a CSTD has been the lack of a standardized test for comparing effectiveness of these devices. A test was recently designed by NIOSH with the intent of providing an unbiased method for comparing devices. However, concerns were noted during the public comment period and NIOSH is determining whether the test protocol should be modified. No CSTD is 100% foolproof, and they are not intended as a substitute for PPE (Connor et al., 2002; Harrison, Peters, & Bing, 2006; Sessink, Connor, Jorgenson, & Tyler, 2011; Wick, Slasson, Jorgenson, & Tyler, 2003). However, regardless of which CSTD is chosen, using any device is better than using no device at all (Davis, McLauchlan, & Connor, 2011).

Conclusion

Although the dangers of HDs have been known for more than 30 years, the goal of ensuring the safety of all nurses who handle these agents has not yet been reached. A multi-pronged approach is needed to significantly reduce the risk of exposure for oncology nurses and other members of the healthcare team.

Every nurse needs to understand the issues because safety cannot evolve in an environment where there is no perceived danger (Lusardi, 2012). Administrators must be committed to promoting safety to facilitate change and maintain standards (Raso & Gulinquello, 2010). To achieve this, HD education should continue to be a priority for ONS and other professional nursing organizations. Nurses need to be reached via different mediums and methods (i.e., journal articles, case studies, webinars, dinner lectures for nursing organization chapters, national and regional symposiums, and online courses) in addition to making the topic an annual staple of ONS Congress. All nurses need to receive accurate information and understand requisite precautions.

Interdepartmental collaboration is crucial for success (Sherwood & Zomorodi, 2014). Oncology nurses must partner with their pharmacy departments to ensure HDs are compounded.

### TABLE 3. Comparison of Closed-System Transfer Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Type</th>
<th>Aerosol/Vapor Vial Containment System</th>
<th>Luer Adaptor</th>
<th>Needle</th>
<th>Administration Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>B Braun OnGuard™ closed medication system with Tevadaptor® components</td>
<td>Membrane</td>
<td>Activated charcoal matrix and 0.2 micron hydrophobic filter</td>
<td>Yes</td>
<td>Vial; yes; male connector: no</td>
<td>Dry spike Spike secondary</td>
</tr>
<tr>
<td>BD Phaseal™</td>
<td>Membrane</td>
<td>External expansion chamber</td>
<td>Yes</td>
<td>No</td>
<td>Dry spike Extension tubing Secondary sets</td>
</tr>
<tr>
<td>CareFusion/BD Chemotherapy Safety System: Teixium®, SmartSite® Vialshield®</td>
<td>Luer</td>
<td>External balloon</td>
<td>No</td>
<td>Yes</td>
<td>Dry spike Secondary sets Primary sets Bonded syringes</td>
</tr>
<tr>
<td>Equashield LLC Equashield II®</td>
<td>Membrane</td>
<td>Internal closed pressure equalization</td>
<td>Yes</td>
<td>No</td>
<td>Dry spike Spike adaptor Spike secondary Custom build sets Bonded syringes</td>
</tr>
<tr>
<td>ICU Medical ChemoClave®, Genie®, Spiros®, ChemoLock™</td>
<td>Luer</td>
<td>Internal balloon</td>
<td>No</td>
<td>Yes</td>
<td>Dry spike Custom build sets</td>
</tr>
<tr>
<td></td>
<td>Membrane</td>
<td>Internal balloon</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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</tbody>
</table>

*Note. Based on information from B Braun Medical, 2016; Becton, Dickinson and Company, 2016a, 2016b; Equashield, 2016; ICU Medical, 2016.*
Implications for Practice

- Increase nursing awareness of the risks associated with hazardous drugs through multiple mediums and methods.
- Change the safety culture within organizations by using scientific evidence and fostering the development of hazardous drug safety champions.
- Adopt a zero-tolerance approach to preventing exposure within the workplace.

using CSTDs to prevent contamination on the exterior of bags and syringes, which can lead to environmental contamination. The use of CSTDs at the bedside will help mitigate spills and leakage during administration and disposal. Regardless of brand, they should become the norm for compounding and administration.

HD safety champions are needed on every oncology unit, infusion center, and private practice to set the standards for their peers and ensure the promotion of safety (Ibitayo, Baxley, & Bond, 2014; Walton et al., 2012). If not already in place, annual HD education should be implemented (Sottani, Porro, Comelli, Imbriani, & Minoia, 2010). Nurses can no longer be complacent when PPE is not available, when risky behaviors are considered acceptable, and when policies are vague or unenforceable.

The nursing profession must work with state legislators to enact laws requiring healthcare facilities to follow the latest guidelines and standards. Although significant inroads have been made, 90% of states still do not have laws to enforce HD safety. USP<8000> will require significant changes in many workplaces, and a gap analysis should be performed to determine what changes will be necessary to meet the deadline. HD safety is entering a new era, but it will require a commitment from nurses at every level to ensure its success.

References


