By Thomas H. Connor, PhD

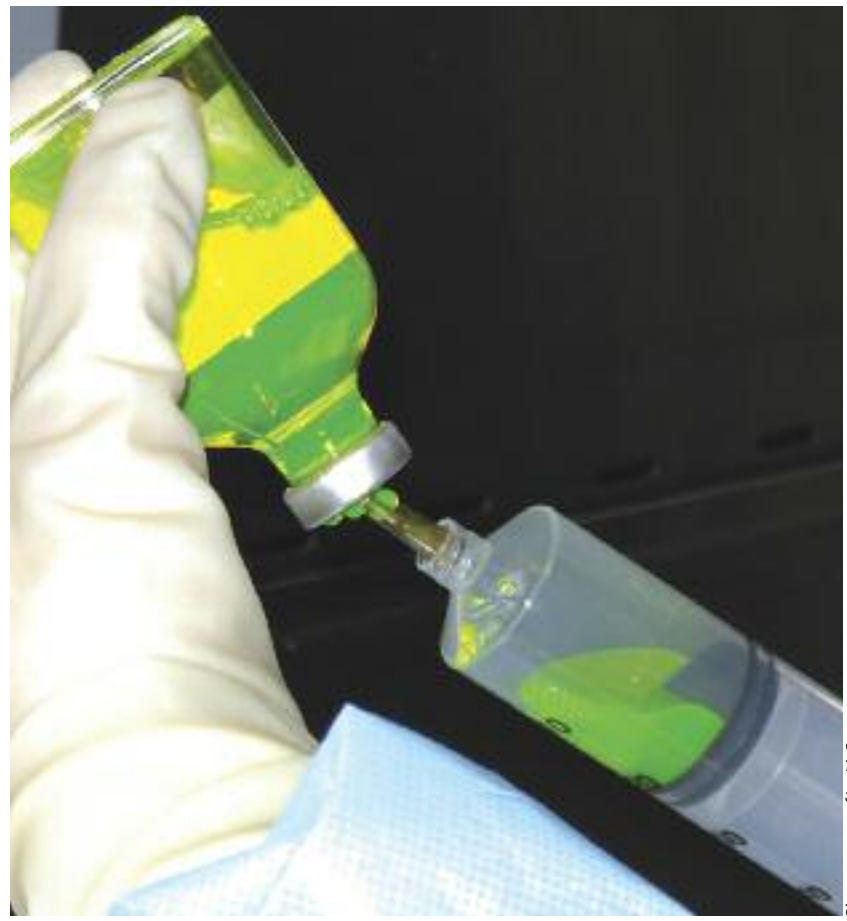
Identification and Safe Handling of **Hazardous Drugs**

In the fight against deadly diseases, we have long relied on powerful and dangerous substances as forms of treatment, the most obvious of these being chemotherapy. To use these medications safely and effectively, we must establish a clear definition of what constitutes a "hazardous drug."

Beginning over thirty years ago, when the development of secondary cancers in patients treated with chemotherapy drugs were observed, concerns arose as to whether similar cancers might develop in health care workers exposed to both the patients receiving these drugs and the drugs themselves. Although many chemotherapy drugs have been shown to be carcinogenic in both animal and human studies, no systematic study has been done to determine their carcinogenic impact on health care workers in general. The American Society of Health-System Pharmacists (ASHP), the Oncology Nursing Society (ONS), and the Occupational Safety and Health Administration (OSHA) all published guidelines for the safe handling of these drugs during the 1980s. In 1990, ASHP developed five criteria to help identify what constitutes a hazardous drug. In 2004, with the publication of the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs, NIOSH expanded the ASHP definition to include the following six criteria:

- Carcinogenicity
- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity
- Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria

If a drug meets one or more of these criteria, it is classified as a hazardous drug.



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Small leaks are common when using needles and syringes to either reconstitute powders and/or transfer liquids to a final container such as an IV bag or bottle.

Effects of Exposure and Surface Contamination Issues

Early reports documented headaches, nausea, dizziness, skin rashes, hair loss, and other acute effects from exposure to hazardous drugs—mainly chemotherapy agents. Several studies have identified developmental and reproductive effects in pregnant workers related to exposure, including malformations, low birth weight, and spontaneous abortions. A number of studies have reported significant increases in measures of genetic damage in workers handling these drugs compared with reference populations. Chromosomal aberrations, sister chromatid exchange, DNA damage, and other genetic endpoints have been used to demonstrate the negative effects of these drugs on workers who handle them. Similar study results continue to be reported worldwide, primarily from countries where safety conditions are not as stringent as in the United States or most European countries. There is some limited evidence indicating increased cancers in workers exposed to hazardous drugs, but this specific issue has not been studied in depth.

Numerous studies from many countries have documented workplace contamination from a number of these drugs. Although there are more than 100 drugs used in cancer treatment, only a few have been studied to assess workplace contamination. Cyclophosphamide is most commonly used for evaluating workplace contamination due to the fact that it is used in several treatment protocols, is a known human carcinogen, is easily sampled and measured, and appears to be quite stable in a normal work environment. In these studies, both pharmacy and nursing/patient areas have shown contaminaion with cyclophosphamide, as well as several other chemotherapy drugs.

Generally, exposure is measured by determining whether the parent drug or drug metabolites are found in workers' urine. Although the results have varied considerably, a number of studies have documented the presence of several chemotherapy drugs in the urine of health care workers. Most studies have examined environmental contamination or worker exposure, yet few have considered both measures. Because of several variables, including differences in technique, work practices, and PPE usage, little correlation has been drawn between the drug amounts measured in the environment and in the urine of workers.

Work Practices that Present Exposure Risk

Unfortunately, the exterior of many drug vials are contaminated with the vial contents before they even reach the pharmacy, thus the basic task of receiving and storing the drugs can potentially spread contamination to the workplace. Some pharmacies rinse the vials at receiving or before use, but given the diverse chemical nature of the drugs, there is no universal solvent that will remove all residue from all types of vials.

Studies published since the early 1990s have shown that small leaks are common when using needles and syringes to either reconstitute powders and/or transfer liquids to a final container such as an IV bag or bottle. Wipe samples taken from work areas such as biological safety cabinets (BSCs), counters, floors, trays, gloves, and IV bags have shown that contamination is common in the pharmacy, which invariably leads to contamination in nursing and patient areas. From these areas, contamination can then spread to other areas of the hospital, and drips and spills from IV tubing during administration can contribute to further contamination. It is imperative that IV lines be primed in the pharmacy or primed with a non-drug solution so that priming is not done in the patient area with the drug solution.

Most body fluids and wastes (vomit, sweat, urine, and feces) have been shown to contain drugs and/or their metabolites. Typically, urine from treated patients is considered hazardous for 48 to 72 hours post-treatment, although some drugs may take longer to be excreted. Therefore the patient's body fluids and waste should be handled with the same precautions as hazardous drugs.

Identify and Reduce Risk

Based on studies from the early 1980s, recommendations to use Class II BSCs instead of horizontal laminar flow cabinets greatly reduced worker exposure during the preparation of hazardous drugs, while still maintaining a sterile environment. NIOSH recommends Class II, type B2 BSCs that are 100% vented to the outside of the building. However, several studies have shown that pharmacy areas still demonstrate contamination when this type of BSC is used. Factors that contribute to environmental contamination include:

- Contaminated drug vials received and stored in the pharmacy area
- Overcrowding items within the BSC, or the simple act of moving hands and arms in and out of the cabinet, which disrupts airflow and allows contaminated air to leave the opening of the cabinet
- Removing contaminated gloved hands, IV bags, or other end products, and/or waste materials to counter tops, trays, and other surfaces

With the finalization of USP Chapter <797> in 2008, many institutions that prepare hazardous drugs have adopted cleanroom technology. Along with improving cleanroom design, some institutions have implemented isolators. For hazardous drug preparation, only a compounding aseptic containment isolator (CACI) is appropriate to protect both the worker and the sterility of the product. USP <797> also contains specific requirements for the quality of air in cleanrooms and isolators.

The Importance of Proper Training and Work Practices

The safe handling of hazardous drugs requires knowledge of the hazards of a

drug, as well as the proper work practices to ensure protection of the drug, the work environment, and all workers potentially exposed to it. Safe handling procedures must be followed in the receiving area, the pharmacy, the clinic or patient room, and during cleaning and disposal of hazardous waste. In addition to training staff at the time of hire, periodic retraining and testing should be a common practice. With the introduction of new techniques, procedures, equipment, and drug delivery systems, it is imperative that workers be trained and kept up-to-date on all new implementations.

Several organizations have published recommendations for proper practices when working with hazardous drugs. In addition, there is organizational consistency in recommendations concerning the use of PPE. These include use of the following:

- Double gloves—for drug preparation and administration
- Non-absorbent, single-use protective gowns—as opposed to lab coats or scrubs
- Respiratory protection, as needed—when a splash or inhalation exposure is possible, use of a NIOSH-certified N-95 or better respirator is recommended
- Eye protection—when a splash is possible, goggles are preferable to glasses with side shields
- Shoe covers—as required in the cleanroom

Use of Closed System Transfer Devices and Novel Drug Forms

Several studies have demonstrated a significant reduction in surface contamination and/or worker exposure (as measured by the presence of drugs in the urine) when a closed system transfer device (CSTD) is used. Typically, the use of CSTDs has shown a reduction in surface contamination, but not a total elimination. This could be due to the presence of contamination on the vials or the fact that some drug residue has been demonstrated to persist for months on work surfaces and floors. While not a foolproof system, the reduction in contamination demonstrated by the use of CSTDs makes them a valuable tool for mitigating risk.

The adoption of oral chemotherapy products is expected to increase significantly in the future, and patients are expected to remain on oral chemotherapy for many years. This new practice poses a different exposure scenario than those of IV medications. Although the risk of exposure from drug preparation will decrease, the venue of administration may change from the hospital pharmacy to the retail pharmacy. The dust from uncoated tablets, for example, poses an inhalation risk for those who count or dispense them. Coated and uncoated tablets create exposure risks when they have to be cut or crushed for pediatric patients or others who cannot swallow intact tablets.

Conclusion

Over the past 30 years, we have been investigating the risks hazardous drugs pose to health care workers to determine how to minimize them. With current analytical techniques, we can assess the level of environmental contamination for about 10% of the hazardous drugs currently in use. Several dozen studies have shown that workplace contamination is common with these drugs. We can extrapolate that the other 90% of hazardous drugs handled in the same manner, although not yet measured, probably pose the same risk. Until safer drugs become the

Hazardous Drug Handling Recommendations

- **OSHA** has not recently updated its recommendations, but its standing recommendations are still applicable in many cases.
- **ONS** updates its safe handling procedures every few years.
- **NIOSH** published guidelines in 2004, and updates its list of hazardous drugs periodically.
- **ASHP** published its most recent update in 2006.
- **The International Society of Oncology Pharmacy Practitioners** published international standards in 2007.
- **USP Chapter <797>** was finalized in 2008 and covers hazardous drug preparation.
- **Many health systems** publish their own guidelines for handling hazardous drugs. It is worthwhile to investigate these through professional networking.

mainstay, health care workers need to be vigilant about their work practices for their protection and the protection of their coworkers. ■

Thomas H. Connor, PhD, joined NIOSH in 2001 as a research biologist focusing on occupational exposure to hazardous drugs. He was the lead author on the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs, along with other related NIOSH documents. In 2008, he received the ASHP Board of Directors Award of Honor recognizing almost 30 years of research involving the protection of health care workers from hazardous drug exposures.

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