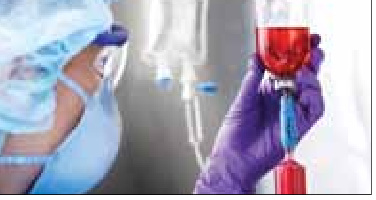

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By Thomas H. Connor, PhD, and Barbara A. MacKenzie, BS

2014 Updates to the NIOSH Hazardous Drug List

Due to concerns about exposure of health care workers to hazardous drugs, The National Institute for Occupational Safety and Health (NIOSH) convened a Hazardous Drug Working Group in 2000 in Washington, DC. The primary output of the group, which disbanded in 2007, was the 2004 publication of the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings.[1] This alert included a definition of hazardous drugs (see **FIGURE 1**) that was modified from a definition proposed by the American Society of Hospital Pharmacists (currently the American Society of Health-System Pharmacists).[2]

The 2004 alert included a sample, non-all-inclusive list of 136 drugs that should be handled as hazardous. It comprised lists being used at that time by four institutions: The National Institutes of Health, Johns Hopkins University, University of Michigan, and Northside Hospital in Atlanta. It also included a list generated by the Pharmaceutical Research and Manufacturers of America (PhRMA). At the time the 2004 Alert was published, NIOSH acknowledged that it would update the hazardous drug list as needed. After deciding on an approach and a mechanism to perform these updates, NIOSH reviewed all new drugs approved by the FDA and all new warnings on existing drugs from 2004 to 2007, to determine whether they qualified as hazardous under the NIOSH definition. This resulted in the official update that was published in 2010, which contained 31 additions to the original list.[3] The list was updated a second time in 2012 with 33 additions and 15 removals.[4]

The Latest Update

The process of updating the hazardous drug list includes a number of steps (see **FIGURE 2**) and takes about two years to complete; therefore, the list is about two to three years out of date when it is published. Currently, the expert review panel is made up of at least 10 members representing pharmacy and nursing organizations (ASHP, Hematology/Oncology Pharmacy Association, Oncology Nursing Society, American Nurses Association), government (Food and Drug Administration, Department of Veterans Affairs, Occupational Safety and Health Administration), industry (Biological Industry Organization, drug manufacturers), and academia.

For the 2014 update, the group reviewed approximately 250 potentially hazardous drugs; ultimately, 28 new drugs that met one or more of the NIOSH criteria for a hazardous drug were added to the list (see **TABLE 1**).[5] Of these additions, six had safe handling recommendations already established by the manufacturer; drugs that have safe handling guidance from the manufacturer are automatically listed by NIOSH as hazardous drugs. In the past, warnings located in the drug package insert have included references to several guidance documents,[1,6,7,8] but now they include only a link to the OSHA Web site (www.osha.gov/SLTC/hazardousdrugs/index.html) that links to the NIOSH Web site on hazardous drugs. The OSHA site serves as a hazardous drug and workers' rights information clearinghouse.

In addition to the new drugs listed for 2014, 11 drugs were removed from the original 2004 list based on their evaluation according to the NIOSH criteria (see **TABLE 2**).[5] One other drug, tetracycline, also was removed from the list based on stakeholder feedback and reevaluation.[5] In order to accommodate the needs of stakeholders and end users, NIOSH moved from a universal precautions approach to a user-based approach for the most recent update. The 2014 list delineates three classes of hazardous drugs: Group 1 includes 97 drugs that are classified as antineoplastic drugs by the American Hospital Formulary Service (AHFS)[9]; Group 2 includes 47 hazardous, non-antineoplastic drugs; and Group 3 includes 40 drugs that primarily have adverse reproductive effects. Some drugs in Group 2 also have reproductive effects and are identified as such.

New Additions

The 2014 list includes a new type of drug being used to treat certain cancers: two conjugated monoclonal antibodies—ado-trastuzumab emtansine and brentuximab vedotin—are listed automatically because of their manufacturer-provided safe handling recommendations. These drugs have a toxic compound

FIGURE 1

NIOSH Definition of a Hazardous Drug[1]

Any drug identified by at least one of the following six characteristics:

- Carcinogenicity
- Teratogenicity or developmental toxicity
- Reproductive toxicity in humans
- Organ toxicity at low doses in humans (<10 mg/day) or animals (<1mg/kg/day)
- Genotoxicity
- New drugs that mimic existing hazardous drugs in structure or toxicity

FIGURE 2

NIOSH Review Process for Hazardous Drugs

- Review all new FDA drug approvals
- Review all new warnings on existing drugs
- Review drug information (NIOSH internal committee)
- Meet with external expert and stakeholder panel
- Review by external expert and stakeholder panel
- Public comment period in Federal Register (60 days)
- Perform final review (NIOSH internal committee)
- Respond to comments from Federal Register Notice
- Obtain final approval by Office of Director
- Post in Federal Register and on NIOSH Web site

linked to the monoclonal antibody that delivers the compound to the tumor and releases it to kill the tumor cells. With more drugs of this type being developed, it is expected that others will be added to the list in future updates.

Recently, more oral medications belonging to two groups of drugs have been added to the list: oral cancer drugs that are often taken for months or years, and non-antineoplastic drugs or drugs with reproductive effects that also meet the NIOSH criteria for a hazardous drug. Some are human carcinogens or animal carcinogens at low doses, while others have serious adverse reproductive effects, often at low doses.

TABLE 1
2014 Additions to NIOSH Hazardous Drug List[5]

Drug	AHFS Classification
Group 1: Antineoplastic Drugs	
Abiraterone	10:00 antineoplastic agents
Ado-trastuzumab emtansine*	10:00 antineoplastic agents
Brentuximab vedotin*	10:00 antineoplastic agents
Cabazitaxel*	10:00 antineoplastic agents
Crizotinib	10:00 antineoplastic agents
Eribulin	10:00 antineoplastic agents
Erlotinib	10:00 antineoplastic agents
Omacetaxin	10:00 antineoplastic agents
Vandetanib*	10:00 antineoplastic agents
Vemurafenib	10:00 antineoplastic agents
Group 2: Non-Antineoplastic Drugs	
Abacavir	8:18.08.20 nucleoside and reverse transcriptase inhibitors
Apomorphine	28:36.20.08 nonergot-derivative dopamine receptor agonists
Deferiprone	64:00 heavy metal antagonists
Dexrazoxane*	92:56 protective agents
Fingolimod	92:20 biologic response modifiers
Fosphenytoin	28:12.12 hydantoins
Liraglutide recombinant	68:20.06 incretin mimetics
Nevirapine	8:18.08.16 nonnucleoside reverse transcriptase inhibitors
Phenytoin	28:12.12 hydantoins
Propylthiouracil	68:36.08 antithyroid agents
Spironolactone	24:32.20 mineralocorticoid receptor antagonists
Group 3: Drugs with Reproductive Effects	
Fluconazole	8:18.08 azoles
Icatibant	92:32 complement inhibitors
Misoprostol	56:28.28 prostaglandins
Topiramate	28:12.92 anticonvulsants, miscellaneous
Ulipristal	68:12 contraceptives
Voriconazole	8:14.08 azoles
Warfarin	20:12.04.08 coumarin derivatives

*Safe handling recommendations from manufacturer

Conclusion

For the benefit of health care workers, NIOSH also provides guidance on engineering controls and personal protective equipment for handling hazardous drugs in a number of the more common scenarios that might be encountered in health care settings (see **TABLE 3**). Furthermore, during the past few years, several states have adopted the NIOSH Alert and the NIOSH hazardous drug list into their state regulations and others are considering similar legislation. The first to do this was Washington, followed by California and North Carolina. However, California's and North Carolina's rules refer only to antineoplastic drugs and not to the entire list. Other states are considering whether to follow suit. Presently, NIOSH is in the process of evaluating new drugs and drugs with new warnings for the next update to the list scheduled for 2016.

In the meantime, health care institutions that handle hazardous drugs should review the 2014 list and determine which drugs on the list are used in their facility. Once that is established, the next step is to assess the risk to employees and determine what type of engineering controls and personal protective equipment are required to protect employees from exposure. ■


Thomas H. Connor received his BS and MS in microbiology from the University of Rhode Island, and his PhD in environmental toxicology from The University of Texas Medical Branch, Galveston. Tom 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.

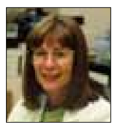
Barbara A. Mackenzie has been an employee of NIOSH for 36 years. She received her BS from the University of Cincinnati. Barbara was the co-lead on the Hazardous Drugs List project, coordinating meetings with both the public and expert reviewers, collecting and correlating all review comments, and coordinating and tracking the project through all phases of approval.

TABLE 2
Drugs Deleted from the 2004 Hazardous Drug List for Not Meeting the NIOSH Criteria for Hazardous Drugs[5]

Drug	AHFS Classification
Aldesleukin	10:00 antineoplastic agents
Asparaginase	10:00 antineoplastic agents
Denileukin	10:00 antineoplastic agents
Estrone	68:16.04 estrogens
Nilutamide	10:00 antineoplastic agents
Pegaspargase	10:00 antineoplastic agents
Pentamidine isethionate	8:40 miscellaneous anti-infectives
Podofilox/podophyllum resin	84:36 miscellaneous skin and mucous membrane agents (mitotic inhibitor)
Testolactone	10:00 antineoplastic agents
Trifluridine	52:04.06 antivirals
Vidarabine	52:04.06 antivirals
Tetracycline	8:12.24 tetracyclines

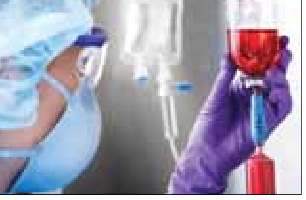

TABLE 3

Personal Protective Equipment and Engineering Controls for Working with Hazardous Drugs in Health Care Settings[5*]

Formulation	Activity	Double gloves	Protective gown	Eye protection	Respiratory protection	Ventilated engineering controls
Intact tablet or capsule	Administration from unit-dose package	no (single glove should be used)	no	no	no	N/A
Tablets or capsules	Cutting, crushing, or otherwise manipulating tablets or capsules	yes	yes	no	yes, if not done in a control device	yes[†]
	Administration	yes	yes	no	yes, if powder generated	N/A
Oral liquid drug	Compounding	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes[†]
	Administration	yes	yes	no[‡]	no[‡]	N/A
Topical drug	Compounding	yes	yes	yes	yes, if not done in a control device	yes[†]
	Administration	yes	yes	yes, if liquid that could splash[‡]	yes, if inhalation potential	N/A
Ampule	Opening	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes, BSC or CACI
Subcutaneous, intramuscular injection	Preparation (withdrawing from vial or ampule)	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes, BSC or CACI
	Administration from prepared syringe	yes	yes	yes, if liquid that could splash[‡]	yes, if inhalation potential[‡]	N/A
Intravenous solution	Compounding	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes, BSC or CACI; recommend use of CSTD
	Administration of prepared solution[§]	yes	yes	yes, if liquid that could splash[‡]	yes, if inhalation potential[‡]	N/A; recommend use of CSTD
Solution for irrigation	Compounding	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes, BSC or CACI; recommend use of CSTD
	Administration (bladder, HIPEC, limb perfusion, etc)	yes	yes	yes	yes	N/A
Powder/solution for inhalation	Inhalation	yes	yes	yes	yes	yes, when applicable

*The table provides general guidance for some of the possible scenarios that may be encountered in health care settings, but cannot cover all possible situations.

[†]For nonsterile preparations, an engineering control, such as a fume hood or Class I BSC, is sufficient. It is recommended that these activities be carried out in a control device, but it is recognized that under some circumstances, it is not possible. If the activity is performed in an engineering control that is used for sterile intravenous preparations, a thorough cleaning is required following the activity.

[‡]Required if patient may resist (infant, unruly patient, veterinary patient) or if administered by feeding tube. [§]Intravenous tubing already attached and primed.

HIPEC=hyperthermic intraperitoneal chemotherapy.

References

1. NIOSH. NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication no. 2004-165. http://www.cdc.gov/niosh/docs/2004-165/. Accessed October 2, 2014.
2. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990;47:1033-1049.
3. NIOSH. NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2010. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication no. 2010-167 (Supersedes 2004-165). http://www.cdc.gov/niosh/docs/2010-167/pdfs/2010-167.pdf. Accessed October 2, 2014.
4. NIOSH. NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2012. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication no. 2012-150 (Supersedes 2010-167). http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf. Accessed October 2, 2014.
5. NIOSH. NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2014. By Connor TH, MacKenzie BA, DeBord DG, et al. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication no. 2014-138 (Supersedes 2012-150). http://www.cdc.gov/niosh/docs/2014-138/pdfs/2014-138_v3.pdf. Accessed October 19, 2014.
6. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health Syst Pharm.* 2006;63:1172-1191.
7. Polovich M, Bolton DL, Eisenberg S, et al. *Safe Handling of Hazardous Drugs.* 2nd ed. Oncology Nursing Society; 2011.
8. US Department of Labor. Occupational Safety and Health Administration. Hazardous Drugs. https://www.osha.gov/SLTC/hazardousdrugs/index.html. Accessed October 19, 2014.
9. ASHP/AHFS 2014. American Hospital Formulary Service Drug Information. [2014]. AHFS drug information online updates. http://www.ahfsdruginformation.com. Accessed October 10, 2014.