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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Centers for Disease Control and Prevention

**[Docket No. CDC–2020–0046; NIOSH–233–C]**

### Hazardous Drugs: Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings and Managing Hazardous Drug Exposures: Information for Healthcare Settings

**AGENCY:** Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (HHS).

**ACTION:** General notice.

**SUMMARY:** The National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC), in the Department of Health and Human Services (HHS), announces the following final documents are available in the docket and on the NIOSH website: *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings* and *Managing Hazardous Drug Exposures: Information for Healthcare Settings*.

**DATES:** The documents announced in this notice are available on April 27, 2023.

**ADDRESSES:** The documents announced in this notice are available in the docket at *www.regulations.gov* and through the NIOSH Hazardous Drug Exposures in Healthcare website at *https://www.cdc.gov/niosh/topics/hazdrug/default.html*.

**FOR FURTHER INFORMATION CONTACT:** Jerald Ovesen, NIOSH, Robert A. Taft Laboratories, 1090 Tusculum Avenue, MS–C15, Cincinnati, OH 45226; Telephone: (513) 533–8472 (not a toll-free number); Email: *jovesen@cdc.gov*.

**SUPPLEMENTARY INFORMATION:** This notice is organized as follows:



## I. Public Participation

In a **Federal Register** notice published on May 1, 2020 (85 FR 25439), NIOSH invited the public to participate in the development of a suite of tools designed to assist with the identification of hazardous drugs and appropriate handling practices: (1) *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings*; (2) *NIOSH List of Hazardous Drugs in Healthcare Settings,* and (3) *Managing Hazardous Drug Exposures: Information for Healthcare Settings*.

The *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings* (*Procedures*) establish the NIOSH definition of a hazardous drug and a methodology for evaluating chemical properties, pre-clinical information, and available clinical information about each drug. The *Procedures* also clarify how

interested parties can ask NIOSH to reevaluate a determination to place or not to place a drug on the *NIOSH List of Hazardous Drugs in Healthcare Settings,* or a decision to place a drug on a particular table of the *NIOSH List of Hazardous Drugs in Healthcare Settings*.

The *NIOSH List of Hazardous Drugs in Healthcare Settings* (*List*) assists employers in providing safe and healthy workplaces by identifying drugs approved by the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) that meet the NIOSH definition of a hazardous drug and that may pose hazards to healthcare workers who handle, prepare, dispense, administer, or dispose of these drugs. In accordance with the *Procedures,* NIOSH's approach to evaluating information relevant to making determinations about placing drugs on the *List,* excluding drugs from the *List,* and removing drugs from the *List,* includes the following:

(1) regularly monitoring FDA databases to identify drugs that have the potential to meet the NIOSH definition of a hazardous drug;

(2) reviewing molecular properties and information in the manufacturer-provided drug package insert for each identified drug;

(3) assessing, integrating, and synthesizing evidence from human, animal, and in vitro studies of drug toxicity for each identified drug; and

(4) evaluating the totality of the evidence regarding the molecular properties and toxicity using the hazard characterization criteria in Sec. IV.C. of the *Procedures*.

The *List* creates no legal obligation for employers; it is advisory in nature and informational in content.

*Managing Hazardous Drug Exposures: Information for Healthcare Settings (Managing Exposures)* offers guidance to healthcare facilities regarding occupational exposure and risk assessments, risk management plans, waste and spill control, and control approaches for the safe handling of hazardous drugs by activity and formulation. *Managing Exposures* builds upon previous work by NIOSH including *NIOSH ALERT: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs* and the table *Personal Protective Equipment and Engineering Controls for Working with Hazardous Drugs in Healthcare Settings* (often referred to as ''Table 5''), published in previous iterations of the *List. Managing Exposures* creates no legal obligation for employers; it is advisory in nature and informational in content.

The public was invited to submit written comments regarding the three draft 2020 versions of these three documents, as well as views, opinions, recommendations, and/or data on any topic related to the drugs reviewed by NIOSH for possible placement on the *List*.

In addition, NIOSH invited comments specifically related to the following question and statement associated with this activity:

1. Which unique ingredient identifier is the most useful for users of the *List*?

2. Because there is conflicting evidence about the hazard posed by botulinum toxins to the workers who handle these drugs, NIOSH is not proposing the placement of botulinum toxins on the *List* at this time and invites additional studies, data, and expert opinions pertinent to this issue in order to evaluate the botulinum toxins more fully.

The public comment period for the May 2020 notice was initially open until June 30, 2020 (85 FR 25439), and later extended until July 30, 2020 (85 FR 37101), to ensure commenters had adequate time to comment.

One hundred thirty-two submissions were received from commenters in Docket CDC–2020–0046 (NIOSH–233–C). Commenters consisted of nurses; pharmacists; safety personnel; a veterinarian; healthcare, business, and government administrators and committees; and anonymous and unaffiliated individuals. The commenters represented a wide range of institutions, including academic and general medical centers and healthcare systems; hospital, commercial drug store, and compounding pharmacies; manufacturers of pharmaceuticals and medical devices; professional healthcare and veterinary organizations and associations; home infusion organizations; suppliers of cleanroom products; boards of pharmacy; and consultant companies for healthcare improvement and the performance of healthcare facilities, risk assessment, and waste management. Public comments on the documents discussed in the May 2020 notice are available for review at *www.regulations.gov* (Docket CDC–2020–0046). NIOSH also conducted a peer review, with four independent reviewers, of the draft *Managing Exposures Drug Exposures: Information for Healthcare Settings*.

NIOSH carefully considered all public comments and peer reviews resulting from the 2020 notice and determined that some clarifications and changes should be made to the draft *Procedures, List,* and the *Managing Exposures* documents. These changes are reflected in the two final documents described in this notice. Publication of the *NIOSH List of Hazardous Drugs in Healthcare Settings, 2023* (2023 *List*) will be announced in a forthcoming **Federal Register** notice. The 2023 *List* is not discussed further in this notice.

Public comments on the draft *Procedures* are summarized and answered by NIOSH in Sec. III of this notice and significant peer review and public comments on *Managing Exposures* are summarized and answered in Sec. IV. The changes to both documents are summarized in Sec. V.

Final versions of the *Procedures* document [1] and *Managing Exposures* are available on the NIOSH website and in the docket for this activity.[2]

## II. Background

In 2004, NIOSH published the *NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings (Alert),* which contained a compilation of lists of drugs considered to be as hazardous to workers' health. NIOSH periodically updates this list, now named the *NIOSH List of Hazardous Drugs in Healthcare Settings,* to assist employers in providing safe and healthful workplaces by identifying drugs that meet the NIOSH definition of a hazardous drug.

In 2017, NIOSH began developing a document to make the process used to guide the addition of hazardous drugs to the *List* more transparent, entitled the *Policy and Procedures for Developing the NIOSH List of Antineoplastic and Other Hazardous Drug in Healthcare Settings (Policy and Procedures)*. The *Policy and Procedures* document was created to formalize NIOSH's methodology and establish a process for requesting the addition of a drug to, the removal of a drug from, or relocation of a drug within the *List*. This document was reviewed by four peer reviewers and eight interested parties before NIOSH made the document available for public comment in a February 14, 2018

[1] NIOSH [2023]. *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings*. By Whittaker C, Ovesen JL, MacKenzie BA, Hartley T, Berry KA, Piacentino J. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication Number 2023–129, *https://wcms-wp.cdc.gov/niosh/docs/2023-129/default.html*.

[2] NIOSH [2023]. *Managing Hazardous Drug Exposures: Information for Healthcare Settings*. By Hodson L, Ovesen J, Couch J, Hirst D, Lawson C, Lentz TJ, MacKenzie B, Mead K. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication 2023–130, *https://wcms-wp.cdc.gov/niosh/docs/2023-130/default.html*.

notice (83 FR 6563). The peer reviewers and interested parties also provided input on the drugs considered for placement on the *List*.

Consistent with the draft *Policy and Procedures,* NIOSH proposed the addition of 20 drugs and one class of drugs to the *List* in the framework for the draft *List* in the February 2018 notice. Public comments were invited regarding any topic related to drugs identified in the notice, the draft *Policy and Procedures,* and the framework for the February 2018 update to the *List,* as well as the following questions related to this activity:

1. Has NIOSH appropriately identified and categorized the drugs considered for placement on the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings,* 2018?

2. Is information available from FDA or other Federal agencies or in the published, peer-reviewed scientific literature about a specific drug or drugs identified in this notice that would justify the reconsideration of NIOSH's categorization decision?

3. Does the draft *Policy and Procedures for Developing the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* include a methodology for reviewing toxicity information that is appropriate for this activity?

Fifty-five public comments were submitted in response to the February 2018 notice and summarized with NIOSH responses in a May 2020 notice (85 FR 25439). Those comments are available in Docket CDC–2018–0004. The substantive input provided by peer reviewers, interested parties, and public commenters on the February 2018 notice caused NIOSH to reconsider certain aspects of the draft *Policy and Procedures* and the draft framework for the *List*. As a result, NIOSH revised and updated the draft *Policy and Procedures,* renamed ''*Procedures,*'' as well as the draft list of drugs proposed for placement on the *List*. This collective input also contributed to the development of the draft document *Managing Exposures,* also announced in the May 2020 notice. Comments resulting from the May 2020 notice are available at *www.regulations.gov* in Docket CDC–2020–0046.

## III. Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings

The public comments submitted in response to the May 2020 version of the draft *Procedures* have been organized in accordance with the sections of the *Procedures* document. Substantive public comments are summarized below, followed by NIOSH responses. Sec. I of the *Procedures* addresses the statutory authority for this activity; no public comments were received on this section, therefore Sec. I is not discussed below.

### *A. Section II. Purposes*

#### 1. Application to Occupational Settings

*Public comment:* One commenter suggested that NIOSH make it clear that the hazardous drug designations apply to occupational exposure rather than patient use. The concern was for pharmacies adding warning labels that patients may receive.

*NIOSH response:* NIOSH states throughout all three documents that they are intended to address occupational exposures, not patient use. NIOSH does not require specific labeling, nor can NIOSH control how individual facilities implement their risk management processes to protect workers. No change to the *Procedures* has been made in response to this comment.

#### 2. Coordination With U.S. Pharmacopeia (USP)

*Public comment:* Several commenters reflected on USP General Chapter <800> *Hazardous Drugs—Handling in Healthcare Settings* (USP <800>) [3] and how USP and NIOSH documents interrelate. USP has incorporated the NIOSH *List* into USP <800> and some states require compliance with USP <800>, the effect of which has been that certain healthcare settings in some jurisdictions are required to handle NIOSH-identified hazardous drugs in accordance with the standards in USP <800>.

Some commenters suggested close coordination of NIOSH and USP on the issues of hazardous drugs handling, as well as standardizing the language. Two commenters suggested that NIOSH specifically reference USP in its documents. A few commenters noted that compliance with USP <800> is burdensome if a drug is identified as hazardous. One commenter suggested dropping the descriptor ''antineoplastic'' from both USP and NIOSH documents as uninformative, acknowledging that cancer treatment drugs now have a wide variety of modes of action. Another commenter suggested limiting the scope of the hazardous drugs *List* to chemicals for which NIOSH had ''definitive proof'' of hazard because USP recommendations for application of the *List* may lead to overuse of personal protective equipment (PPE).

*NIOSH response:* While NIOSH and USP have continuing contact and stay informed of progress and potential areas of conflict in their respective documents, the respective missions of NIOSH and USP differ, and the NIOSH and USP document processes also differ. Therefore, standardized language, while convenient for the reader, may not be attainable. NIOSH works to ensure that the *List* and associated documents are consistent with relevant sources of information and guidance, including USP. However, the *List* is informational in nature and does not confer any requirements or legal obligations on users. Additionally, NIOSH does not specifically reference USP <800> in its *Procedures* and *List* documents because NIOSH intends the *List* and associated documents as stand-alone informational materials for employers in healthcare settings. NIOSH has also removed some references to USP from the *Managing Exposures* document, as discussed further below.

Regarding the descriptor ''antineoplastic,'' NIOSH agrees with the commenter that it is no longer useful for understanding the hazards posed by individual drugs and has dropped that nomenclature from the document title and table titles in the *List*.

Finally, NIOSH does not agree with the suggestion to limit the *List* to drugs for which there is ''definitive proof'' of hazard. NIOSH evaluates the evidence of toxicity to determine the potential for the drug to be hazardous to workers. This analysis does not consider dosage form (the physical form of the pharmaceutical drug, *e.g.,* coated tablet, capsule, liquid). Therefore, it is incumbent on employers in healthcare settings to evaluate how drugs are used in their facilities and what risks may ensue, given the dosage forms, procedures, and tasks undertaken. This is called a ''site risk assessment'' and is described further in *Managing Exposures*.

For questions or concerns about the implementation of USP <800>, commenters should contact USP directly.

*Public comment:* One commenter stated, ''. . . the explicit use of the NIOSH *List* by USP to enforce Chapter <800> makes the *List* regulatory. Facilities that do not comply with USP Chapter <800> standards, and thus the NIOSH *List* designation of hazardous drugs, can be cited and face regulatory and legal consequences.''

*NIOSH response:* NIOSH did not compile the *List* for standardized compliance purposes and the *List* creates no legal obligation for employers. The *List* is an advisory statement. NIOSH does not have statutory authority to enforce the

[3] *See https://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare.*

recommendations comprising the *List* and companion *Managing Exposures*.

Moreover, the *List* is intended to be a helpful reference tool for use in employers' own workplace assessments. As detailed in the *Procedures,* compilation of the *List* is a hazard identification process in which NIOSH considers the inherent hazard of the drug. As such, the *List* is intended solely as a first step for employers in conducting their own assessments of hazardous drug risks to their particular workers that might result from myriad drug formulations and exposure scenarios.

Additionally, NIOSH has no ability to direct USP or the State and local jurisdictions that have incorporated USP <800> into their own requirements. While NIOSH has no control over USP <800>, NIOSH has relayed commenters' concerns to the organization. No change to the *Procedures* has been made in response to this comment.

*B. Section III. Background*

1. Exposure to Drugs in Healthcare Settings

*Public comment:* One commenter expressed concern that NIOSH did not consider the impact of hazardous drugs on cleaning staff. Another requested that NIOSH explicitly state that this applied to all pharmacies, including compounding pharmacies and mail-order pharmacies.

*NIOSH response:* NIOSH considers all workers who come into contact with hazardous drugs in healthcare settings as within the scope of the *Procedures, List,* and *Managing Exposures* documents, no matter the type of workplace. Accordingly, Sec. III.A of the *Procedures* addresses the tasks that workers undertake (*e.g.,* receipt, storage, preparation, compounding, manipulation, cleanup, and disposal of drugs and patient waste), rather than specific types of facilities. No change to the *Procedures* has been made in response to this comment.

*C. Section IV. NIOSH Definition of a Hazardous Drug*

*Public comment:* NIOSH received many comments on the NIOSH definition of hazardous drugs in Sec. IV of the draft *Procedures*. Specifically, many comments were received from parties that did not approve of the change in definition from previous versions of the *Procedures*. There were several issues raised objecting to the changes. Some public commenters and one *Managing Exposures* peer reviewer objected to NIOSH changing the hazardous drugs definition from the original 2004 definition of a hazardous drug, alleging that NIOSH made the change in its definition without the consensus of all interested parties. (Note: the *Managing Exposures* peer review comment is addressed in this section because it relates to the hazardous drugs definition in the *Procedures* document.)

Other commenters objected to specific wording changes in the definition. Some of these commenters objected to language that specifies how NIOSH considers drugs with high molecular weight, citing the potential for increased risks to workers. However, there was also some support among commenters for the NIOSH perspective, including one commenter who noted ''. . . the procedure should be refined from a system that focuses primarily on the intrinsic hazards of a drug to one that considers the occupational relevance of the intrinsic hazard.'' Commenters also objected to language indicating that NIOSH was limiting consideration of drugs to those approved by FDA CDER. These commenters recommended that, in addition to FDA CDER approval, NIOSH also fully consider all drugs approved by FDA Center for Biologics Evaluation and Research (CBER) to assess all potentially hazardous drugs in the workplace more fully. Other commenters disapproved of how NIOSH intended to consider drugs with insufficient toxicity data as not meeting the NIOSH definition of hazardous drugs. They recommended that NIOSH consider to be hazardous any drugs with insufficient toxicity data to meet the definition of hazardous drugs.

*NIOSH response:* The original 2004 definition of hazardous drug was based on an American Society of Health-System Pharmacists (ASHP) definition developed in 1990 and revised by NIOSH in collaboration with a large group of interested parties. NIOSH has used that definition as the basis for the *List* since 2004. In the *Policy and Procedures* described in the February 2018 notice, NIOSH proposed revising the definition to ''those drugs approved for use in humans by the FDA, not otherwise regulated by the U.S. Nuclear Regulatory Commission and either contains special handling information for workers handling the drug in the package insert or exhibits one of the six toxicity criteria.'' In the revised *Procedures* described in the May 2020 notice, NIOSH proposed further revisions, such as specifying drugs approved by FDA CDER. In addition, the definition included evaluating molecular properties that may limit the potential for adverse health effects for the exposed worker.

NIOSH notes that the definition in the final *Procedures* is still based largely on the 2004 definition. The *Procedures* document makes explicit the steps in evaluating the drugs that were not fully described in earlier versions of the *List,* although they have been NIOSH's long-standing practices. Except for considering molecular properties of drugs, the definition in the *Procedures* reflects how NIOSH has been implementing the 2004 definition to make decisions about hazardous drugs. Therefore, NIOSH did not consider it necessary to engage a large group of interested parties to make minor changes in the definition as the underlying foundation of the definition remains the same. In addition, NIOSH believed that the peer review and public comment processes provided ample opportunity for such interested parties to provide input on the changes to the definition.

Since the inception of the *List* in 2004, NIOSH practice is to only consider drugs approved by CDER to be included in the *List*. Therefore, to be transparent, one change from the 2004 definition includes the clarification that only FDA CDER-approved drugs are considered for the *List*. Drugs on the *List* that had been approved by CBER were part of the initial compilation of lists only; however, no drugs have been added to the *List* in intervening years that were subject to CBER approval. In addition to adopting the new language to the definition of ''hazardous drug'' in the final version of the *Procedures* Sec. IV, NIOSH has also added the language to footnote 12 to clarify that only CDER-approved drugs are included on the 2023 *List*. Similarly, it has not been a NIOSH practice to consider drugs approved by the Nuclear Regulatory Commission and this is also specified in the definition in the *Procedures*.

The six toxicity endpoints—carcinogenicity; teratogenicity or other developmental toxicity; reproductive toxicity; organ toxicity at low dose; genotoxicity; and structure and activity profiles of drugs that mimic existing drugs determined hazardous by the above criteria—in the definition of a hazardous drug remain unchanged from 2004. However, one caveat was added to the definition to clarify that a drug may be found not to be a hazard if it also exhibits a molecular property that may limit the potential for adverse health effects from exposure in healthcare workers. Such molecular properties typically include chemical, physical, and structural properties that affect the drug's absorption, (*e.g.,* chemical structure, molecular weight, or mass).

NIOSH has always emphasized that identification of potential hazards does not equate to occupational risks. In the 2004 *Alert,* NIOSH stated that drugs may be hazardous in one exposure scenario but have much less risk associated with another. Specifically, NIOSH noted in 2004 that ''Physical characteristics of the agents (such as liquid versus solid, or water versus lipid solubility) also need to be considered in determining the potential for occupational exposure. Therefore, the caveat inserted into the current hazardous drugs definition clarifies and extends that consideration for specific scenarios. It recognizes that although a drug may meet the definition of a hazardous drug in other ways, if NIOSH determines that occupational risks are not significant because of the chemical and physical properties of the drug, that drug may be excluded from the *List.* The purpose of this exclusion is to focus the *List* on drugs that have a reasonable potential for toxicity after occupational exposure, so that workers' attention is focused on drugs that are likely to be hazardous in occupational settings. It is important to note that this is not an automatic exclusion. NIOSH has not established a specific molecular weight, for example, above which drugs are automatically excluded from the *List.* Instead, this is a guideline to alert NIOSH reviewers that they should look at the totality of the evidence, thoroughly consider the possible occupational exposure scenarios, and evaluate whether there is significant risk under those conditions. This would include assessing exposure by inhalation of dust, vapor or mist, dermal absorption (including through abraded or compromised skin), ingestion, contact with mucous membranes, and needle sticks (using ''worst case'' assumptions). This exclusion also does not apply to the dosage form of the drug. Specifically, the *Procedures* notes in Sec. V.C.4.b,

> NIOSH does not consider dosage form as a molecular property of a drug because the same active pharmaceutical product can be offered in several different dosage forms, new dosage forms can be offered later, and some dosage forms can be discontinued.

NIOSH has considered the public comments and remains supportive of the idea of examining molecular properties of drugs as a consideration of whether they should be included on the *List.* In addition, NIOSH has added a column to the tables that allows for identification of those drugs approved by CDER under a biologics license application. Unlike the biological products approved by CBER, those approved by CDER are often large, single-molecule protein/peptide-based drugs such as monoclonal antibodies, intended for therapeutic use.[4] Denoting these drugs in the *List* will make it easier for users to identify drugs that are large, single-molecule products and peptides in order to implement the appropriate risk management strategies. In Sec. IV of the *Procedures,* the final NIOSH definition of hazardous drug is a drug that is:

A. Approved for use in humans [a] by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER),[b]

B. Not otherwise regulated by the U.S. Nuclear Regulatory Commission,[c] and

C. Either

1. Is accompanied by prescribing information in the ''package insert'' [d] that includes a manufacturer's special handling information (MSHI),[e] or

2. Is determined to be a carcinogenic hazard, developmental hazard, reproductive hazard, genotoxic hazard, or other health hazard by exhibiting one or more of the following toxicity criteria in humans, animal models, or in vitro systems:

- Carcinogenicity;
- Developmental toxicity (including teratogenicity);
- Reproductive toxicity;
- Genotoxicity;
- Organ toxicity at low doses; [f] or a
- Structure and toxicity profile that mimics existing drugs determined hazardous by exhibiting any one of the previous five toxicity types.[g]

However, if a drug also exhibits a molecular property [h] that may limit the potential for adverse health effects from exposure to the drug in healthcare workers, it may be determined it is not a hazard.

[a] Although only drugs approved by FDA for use in humans are included in the definition of hazardous drug, some of those drugs may be used in veterinary settings for treatment of animals and may be a hazard for veterinary care workers.

[b] Although biological products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, recombinant therapeutic proteins, are included in FDA definition of a drug, they are not included in the drugs that NIOSH evaluates for potential inclusion on the *List* because they are approved for use by FDA's Center for Biologic Evaluation and Research (CBER), not by FDA's CDER. This provision makes clear NIOSH's long-standing practice of only considering drugs approved by FDA CDER.

[c] 10 CFR parts 19, 20, and 35. *See https://www.nrc.gov/materials/miau/med-use.html.* Drugs regulated by the Nuclear Regulatory Commission are not included on the *List.*

[d] *See* Drug Advertising: A Glossary of Terms at *https://www.fda.gov/drugs/resourcesforyou/consumers/prescriptiondrugadvertising/ucm072025.htm.* ''Prescribing information is also called product information, product labeling, or the package insert (''the PI''). It is generally drafted by the drug company and approved by FDA. This information travels with a drug as it moves from the company to the pharmacist. It includes the details and directions healthcare providers need to prescribe the drug properly. It is also the basis for how the drug company can advertise its drug. The prescribing information includes such details about the drug as: its chemical description; how it works; how it interacts with other drugs, supplements, foods, and beverages; what condition(s) or disease(s) it treats; who should not use the drug; serious side effects, even if they occur rarely; commonly occurring side effects, even if they are not serious; effects on specific groups of patients, such as children, pregnant women, or older adults and how to use it in these populations.''

[e] MSHI includes language that informs those handling the drug of the need to follow heightened handling and disposal procedures. For example, language such as ''follow special handling and disposal procedures'' or ''procedures for proper handling and disposal of anticancer drugs should be considered'' is frequently used in package inserts. However, NIOSH does not consider language pertaining to packaging and temperature controls as MSHI.

[f] All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less). For example, a daily therapeutic dose of 10 milligrams per day (mg/day) or a dose of 1 milligram per kilogram (mg/kg) per day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 micrograms per cubic meter (µg/m3) after applying appropriate uncertainty factors. See Naumann BD, Sargent EV [1997]. Setting occupational exposure limits for pharmaceuticals. Occup Med 12(1):67–80; Sargent EV, Kirk GD [1988]. Establishing airborne exposure control limits in the pharmaceutical industry airborne exposure control limits in the pharmaceutical industry, Am Ind Hyg Assoc J 49(6):309–313; Sargent EV, Naumann BD, Dolan DG, Faria EC, Schulman L [2002]. The importance of human data in the establishment of occupational exposure limits. Hum Ecol Risk Assess 8(4):805–822]. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry.

[g] NIOSH [2004]. NIOSH Alert: preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. By Burroughs GE, Connor TH, McDiarmid MA, Mead KR, Power LA, Reed LD, Coyle BJ, Hammond DR, Leone MM, Polovich M, Sharpnack DD. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety

[4] *See* FDA, *Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research. https://www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research.*

and Health, DHHS (NIOSH) Publication No. 2004–165, available at *https://www.cdc.gov/niosh/docs/2004-165/*.

[h] Properties of a drug molecule that may limit adverse effects in healthcare workers are typically chemical, physical, and structural properties that affect its absorption (ability to enter the cells of the body), *e.g.,* chemical structure, molecular weight, or mass. *See* Clementi F, Fumagalli G [2015]. Molecular pharmacology. Hoboken, NJ: Wiley & Sons; Di L, Kerns EH [2016]. Drug-like properties: concepts, structure, design, and methods. Oxford, UK: Elsevier; Mattson P, Kihlberg J [2017]. How big is too big for cell permeability? J Med Chem *60*(5):1662–1664, *https://doi.org/10.1021/acs.jmedchem.7b00237*.

1. Investigational Drugs

*Public comment:* Two commenters remarked on the exclusion of investigational new drugs from the definition of ''hazardous drug'' in Sec. IV. One commenter sought guidance in how to handle those drugs, while the second commenter supported the idea that drugs with inadequate safety information not be automatically added to the *List*.

*NIOSH response:* Although the NIOSH *Procedures* are focused on drugs that have received FDA CDER approval, and do not consider investigational drugs, NIOSH has addressed this issue in the document *Managing Exposures*. Guidance for employers developing a facility-specific hazardous drug list is found in Ch. 3, Sec. 3.1 of that document, Developing a Facility-Specific Hazardous Drug List, which now states:

> Toxicological data may be incomplete or unavailable for some drugs, specifically investigational drugs. Until adequate information becomes available, it is prudent to handle investigational drugs as hazardous if the mechanism of action suggests that there may be a concern.

2. Over-the-Counter Drugs

*Public comment:* One commenter indicated that it was unclear why over-the-counter drugs were excluded from the definition of a hazardous drug in Sec. IV of the *Procedures*.

*NIOSH response:* Over-the-counter (OTC) drugs are not evaluated by NIOSH because FDA regulations at 21 CFR 330.10 require OTC drugs to meet a safety standard that includes:

> . . . a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability.[5]

NIOSH acknowledges that this does not mean these drugs are always safe and there are circumstances under which there may be risks to workers who handle OTC drugs. However, to focus resources on the most hazardous drugs, NIOSH has decided to exclude drugs with an OTC form from consideration for the *List*. No change to the *Procedures* has been made in response to this comment.

3. Veterinary Drugs

*Public comment:* One commenter on the *List* requested that NIOSH consider including veterinary drugs in the *List* because these drugs are often approved first for veterinary uses and later approved for human therapies.

*NIOSH response:* At this time the *List* is compiled from drugs approved by CDER. The veterinary drugs prescribing insert often does not include information about the toxicity criteria that NIOSH considers. NIOSH may consider developing further resources related to the handling of drugs approved by the FDA Center for Veterinary Medicine in the future. No change to the *Procedures* has been made in response to this comment.

*D. Section V. Identifying, Screening, Evaluating, and Reviewing a Drug for Placement on the List*

1. Section V.A. Step 1: Identifying Potentially Hazardous Drugs

*Public comment:* One commenter was concerned that the NIOSH *List* might be inconsistent with FDA labeling requirements, specifically questioning whether NIOSH is considering individual branded product labeling and how the criteria for carcinogenicity are applied when the information is derived from the package insert.

*NIOSH response:* In developing the *List,* NIOSH considers the toxicity of the drug, not a specific brand or dosage form. Regarding the concerns about how the information on the package insert is used to support a carcinogenicity determination, NIOSH notes that a mention of tumors or malignancies does not automatically result in a NIOSH determination that there is an occupational cancer hazard in handling the drug. NIOSH takes all the available information into consideration including therapeutic dose, carcinogenic dose in any animal studies, and other factors in making its determination. Mention of carcinogenicity on a package insert is insufficient to automatically meet the NIOSH criteria for carcinogenicity. No change to the *Procedures* has been made in response to this comment.

2. Section V.B. Step 2: Screening Potentially Hazardous Drugs

*Public comment:* Some commenters expressed concern regarding *Procedures* Sec. V.B.2.b, which describes screening outcomes when there is ''insufficient information in the drug package insert to suggest that the drug exhibits any one of the toxicity criteria in the NIOSH definition of hazardous drug.'' The text of the *Procedures* indicates that for those drugs for which NIOSH has determined that there is insufficient toxicity information to suggest that the drug exhibits any one of the toxicity criteria, NIOSH will not propose to add that drug to the *List.* Commenters were concerned that this decision would increase worker hazards. Specifically, one commenter stated, ''[w]e suggest that NIOSH consider additional parameters to ensure that any drug that could potentially pose a hazard to employees not fall through the cracks.''

*NIOSH response:* NIOSH understands the concern that it appears that drugs that have been insufficiently studied might be removed from consideration. However, unlike other workplace chemicals, pharmaceuticals are subject to rigorous, required toxicity testing to merit approval by FDA. NIOSH understands that there is a difference in the focus of the two agencies. NIOSH notes that the FDA-required toxicity tests, which are based on the mode of action and potential toxicity of the drug at treatment exposure levels, provide sufficient information for NIOSH to identify potential hazards at the levels of occupational exposure expected in healthcare settings. In Sec. V.B.2.b of the *Procedures,* NIOSH now states:

> If there is insufficient information in the drug package insert to suggest that the drug exhibits any one of the toxicity criteria in the NIOSH definition of hazardous drug, then NIOSH will not propose to add the drug to the *List.*

This does not mean that the drug has been insufficiently tested to determine potential toxicity. Instead, it indicates that in some cases, in its review of all available information, FDA did not find a concern for toxicity of a particular type and such tests were not required or that the available toxicity data are insufficient to meet the NIOSH criteria for a hazardous drug. NIOSH has added footnote 29 with this explanation to the *Procedures* in response to this comment.

3. Section V.C. Step 3: Evaluating Potentially Hazardous Drugs

a. Toxicity Criteria

*Public comment:* One commenter asked NIOSH to clarify whether drugs

[5] 21 CFR 330.10(4)(i).

are placed on the *List* solely based on in vitro studies.

*NIOSH response:* NIOSH examines the totality of the evidence from the specified sources described in the *Procedures.* In Sec. V.C.3.e, NIOSH specifies the use of in vitro studies in genotoxicity determinations as those toxicity tests are the most common tests for that toxicity endpoint. However, NIOSH also notes in multiple places in the *Procedures* that human data are preferred over animal data and both human and animal data are preferred over in vitro toxicity data. In Sec. V.C.3.e.(1) of the *Procedures,* regarding genotoxicity data, NIOSH states:

> Human genotoxicity studies are not commonly available for evaluation. If available, NIOSH gives preference to human genotoxicity studies over animal and in vitro studies. However, NIOSH considers all relevant information in its evaluation.

*Public comment:* One commenter questioned the NIOSH use of animal toxicity data and in vitro data in making a hazardous drug determination. In particular, the commenter expressed concern that the inclusion of data from animal models or in vitro systems in defining a hazardous drug may not be relevant to hazard risk in human exposure. The commenter further recommended that drugs placed on the *List* solely due to animal or in vitro toxicity data should be so identified.

*NIOSH response:* NIOSH notes in the *Procedures* that human data are preferred over both animal and in vitro data for making determinations about the hazardous nature of drugs. Data from animal and in vitro studies designed to predict human toxicities contain valuable information about the potential toxicity of drugs. Therefore, NIOSH fully evaluates all available relevant scientific information regarding the potential toxicity of hazardous drugs and does not separately identify which determinations have been made based solely on animal and/or in vitro data. Doing so might give an erroneous impression of less concern for certain drugs based on the type of information available.

*Public comment:* The same commenter was concerned that the language in Secs. V.C.3.a.(5)(c), V.C.3.b.(4)(b), and V.C.3.c.(4)(b) of the *Procedures,* regarding adverse effects observed in toxicity studies at doses near, at, or below the maximum recommended human dose, indicated that NIOSH would use such findings to support a hazardous drug determination, even when the adverse effect may not be related to a toxic effect.

*NIOSH response:* The language cited by the commenter is from the *Procedures* and is parallel to language in sections on carcinogenicity, reproductive toxicity, and developmental toxicity. The adverse effects observed would be those associated with the specific toxicity resulting from administration of the drug to experimental animals. The occurrence of these effects below or near the maximal recommended human dose clarify that they are occurring at a dose level of concern. In considering the potential occupational hazard, it is important for NIOSH to consider when effects occur only at doses much higher than the human therapeutic dose, as workers are unlikely to be exposed to drugs at those therapeutic dose concentrations or higher doses. NIOSH has used the maximal recommended human dose as a benchmark to indicate the high end of doses of concern. Typically, NIOSH would be most concerned with toxic effects that occurred below this level.

*Public comment:* One commenter stated that the toxicity criteria in Sec. V.C.3 should be clarified and further defined. According to the commenter, ''unclear terms include 'serious organ toxicity,' 'low doses,' and 'generally support.' ''

*NIOSH response:* While NIOSH appreciates the desire to have more explicit language in describing the toxicity criteria, the broad spectrum of drugs covered makes it difficult to precisely define the criteria in a way that will apply to both all drugs and all modes of action considered. Language that would be precise for a particular drug may create a situation where, when applied to another drug, is inadequate to protect workers or results in over-protection. The remedies for this are to either have precise language with an exhaustive list of exceptions (assuming one could know all the potential exceptions that are possible) or to provide as much indication of how NIOSH views toxicity as possible, knowing that there are exceptions that will arise. NIOSH chose the latter strategy, but notes that for any particular drug consideration, NIOSH relies on the professional judgement of NIOSH staff scientists, conducts rigorous peer review of the determinations, and provides an opportunity for public comment on how that language was applied to that drug. No changes to the *Procedures* have been made in response to this comment.

b. Developmental and Reproductive Toxicity

*Public comment:* Two commenters suggested that NIOSH may not want to use developmental and reproductive hazards as inclusion criteria, citing concerns that drugs contraindicated in pregnancy may be automatically included in the *List* as reproductive or developmental hazards. The commenters also stated that the risks were easily mitigated with normal drug handling procedures.

*NIOSH response:* The *List* is intended to identify potential hazards in the healthcare workplace so that workplaces can further consider what risk management strategies are appropriate for their specific needs. This includes, but is not limited to, reproductive and developmental hazards. Drugs that pose developmental and reproductive hazards are identified to protect workers, both male and female, who may be pregnant or trying to become pregnant.

Contraindication during pregnancy is not enough for NIOSH to consider a drug to be a developmental or reproductive hazard. *See Procedures,* Sec.V.C.3.b and c. No change to the *Procedures* has been made in response to this comment.

c. Organ Toxicity at Low Dose

*Public comment:* One commenter expressed concern with the language regarding low dose toxicity in Sec. V.C.3.d of the draft *Procedures.* Specifically, the commenter did not agree with the toxicity level of 10 milligrams per day (mg/day) in human adults or 1 milligram per kilogram per day (mg/kg/day) in laboratory animals as proposed by NIOSH. The commenter used the drugs clonazepam and olaparib as examples of drugs for which these criteria should not be used.

*NIOSH response:* NIOSH uses a dose 10 mg/day in an adult human or 1 mg/kg/day in animals as one consideration in evaluating potential hazards related specifically to organ system toxicity at low doses. NIOSH also may consider the human recommended dose as a threshold for some effects. This is because occupational exposure is expected to be lower (and therefore, less potentially hazardous) than therapeutic exposure. NIOSH does not usually use a lethality measure ($LD_{50}$) when assessing potential hazards. In general, if the effect of concern occurs at or below the human treatment dose, then it would likely be considered a hazardous drug. Clonazepam is on the *List* because it has developmental and reproductive effects at lower than the

maximum human recommended dosage. Olaparib is also on the *List* because of the potential reproductive and developmental hazards at less than the human dosage. Therefore, NIOSH does not agree with the commenter's recommendation and has made no change in the *Procedures.*

d. Tabular Arrangement of Hazardous Drugs on the List

*Public comment:* Several commenters questioned the use of manufacturer's MSHI as a criterion for placement in Table 1 of the NIOSH *List.* Table 1 contains drugs that have MSHI in the package insert and/or meet the NIOSH definition of a hazardous drug, and are classified by the National Toxicology Program (NTP) as *known to be a human carcinogen* and/or classified by the International Agency for Research on Cancer (IARC) as *carcinogenic to humans* (Group 1) or *probably carcinogenic to humans* (Group 2A). The commenters indicated that, because MSHI is not a part of the package insert required by FDA, linking the MSHI to placement on Table 1 would provide a disincentive to manufacturers to provide MSHI.

*NIOSH response:* The MSHI is directly relevant to worker protection from hazardous drugs and often cites the Occupational Safety and Health Administration (OSHA) hazardous drug guidance website.[6] Manufacturers have provided MSHI to alert workers to how their drug can be safely handled. By placing drugs with MSHI into Table 1, NIOSH is acknowledging and amplifying what manufacturers, who are in the best position to know the toxicity information for their drugs, have already determined to be the best way to handle their product. Manufacturers do not provide MSHI lightly and NIOSH believes it is in the manufacturers' interest to continue to provide information to protect workers handling their drugs. Accordingly, the Table 1 MSHI criterion has been retained. No change to the *Procedures* has been made in response to this comment.

*Public comment:* Commenters also weighed in on the carcinogen classifications by the IARC and NTP required for placement in Table 1. One commenter suggested that when drugs are identified by IARC as known human carcinogens ''only after prolonged exposure,'' NIOSH should consider moving them to Table 2 of the *List.* Table 2 contains drugs that meet the definition of a hazardous drug but do not have MSHI and are not classified as human carcinogens by NTP or IARC. The commenters also indicated that NIOSH should look carefully at the drug's mode of action when making that determination. Another commenter noted that NIOSH placed drugs that NTP classified as ''known to be carcinogenic in humans'' in Table 1 but did not do so with drugs that were classified as ''reasonably anticipated to be carcinogenic in humans.''

*NIOSH response:* To simplify the criteria for Table 1, NIOSH is retaining the criteria proposed in the May 2020 notice, so that ''[d]rugs that have MSHI in the package insert and/or meet the NIOSH definition of a hazardous drug and one or more of the following criteria: are classified by NTP as *known to be a human carcinogen,* or are classified by IARC as Group 1 *carcinogenic to humans* or Group 2A *probably carcinogenic to humans*'' are included in Table 1. Drugs classified by NTP as reasonably anticipated to be carcinogenic to humans are evaluated by NIOSH and may be placed on Table 2; the designation of reasonably anticipated alone is not sufficient to place a drug in Table 1. However, NIOSH acknowledges that the context of the carcinogenicity and the mode of action are important information to consider when employers are evaluating the potential risk to workers related to this hazard.

Table 2 of the *List* includes ''[d]rugs that meet the NIOSH definition of a hazardous drug and do not have MSHI, are not classified by NTP as *known to be a human carcinogen,* and are not classified by IARC as Group 1, *carcinogenic to humans,* or Group 2A, *probably carcinogenic to humans.* (Some may also have adverse developmental and/or reproductive effects.)'' Of note, Table 2 includes those drugs that meet the NIOSH definition of a hazardous drug and exhibit carcinogenicity in humans but have not been evaluated by IARC or NTP or have been classified by NTP as *reasonably anticipated to be carcinogenic to humans* or by IARC as *possibly carcinogenic to humans* (Group 2B). No change to the *Procedures* has been made in response to this comment.

4. Section V.D. Step 4: Peer Review of Potentially Hazardous Drugs and Section V.E. Step 5: Public Review of Potentially Hazardous Drugs

*Public comment:* One commenter stated that the process would be improved with an opportunity for manufacturers (called ''sponsors'' in some comments) to provide input early in the screening process described in Sec. V of the *Procedures.* Specifically, the commenter suggested that

> . . . NIOSH could include an additional step in the screening process of drugs being considered for inclusion on the *List.* This step would involve notifying sponsors when their drug(s) is/are being considered for inclusion on the *List.* NIOSH would then have an opportunity to request sponsor input on inclusion of specific products, and sponsors could choose to submit additional data regarding the potential hazards (or lack thereof) that could be useful to the peer review committee in their review activities.

*NIOSH response:* NIOSH finds the current process utilizing peer review and public comment provides ample opportunity for interested parties to participate in development of the *List.* Manufacturers (sponsors) and others are welcome to provide relevant data and information that may not be already available. In addition, there is a formal reevaluation process through which manufacturers can provide additional data for reevaluation of a drug, described in Sec. VI of the *Procedures.* NIOSH notes that, to date, interested parties have provided only limited additional toxicology information in response to publication of the draft *List* in the May 2020 notice, and much of that data was provided as part of the reevaluation process. No change to the *Procedures* has been made in response to this comment.

*Public comment:* One commenter indicated that the peer reviewers who reviewed the draft *Procedures* in 2018 were inadequately identified and their credentials were not clear.

*NIOSH response:* The peer reviewers, their credentials, and the charge to reviewers can be viewed on the NIOSH web page, Peer Review Plan for the Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings, available at *https://www.cdc.gov/niosh/topics/hazdrug/peer-review-plan.html.*

## IV. Managing Hazardous Drug Exposures: Information for Healthcare Settings

In addition to the *Procedures* and *List* documents, NIOSH solicited feedback on the guidance document, *Managing Hazardous Drug Exposures: Information for Healthcare Settings.* Four peer reviewers, whose names and credentials are available on the NIOSH Peer Review web page,[7] *reviewed the draft.* Public comments follow the peer review responses below, along with NIOSH responses. Overall, peer reviewers and public commenters were supportive of

[6] *See http://www.osha.gov/SLTC/hazardousdrugs/index.html.*

[7] *https://www.cdc.gov/niosh/review/peer/isi/healthsafetyrisks.html.*

this new resource and offered many suggestions for its improvement.

*A. Peer Review*

The charge given to the peer reviewers for the *Managing Exposures* document is available on the NIOSH Peer Review web page.[8] Peer review questions are listed below with the peer reviewer responses summarized beneath each question.

Reviewers' concerns that focused on issues in other documents (for example, the definition of hazardous drugs or the organization of the tables in the *List*) are included under the NIOSH responses to comments for those documents.

1. Charge 1.a. What additional information would improve [the document's] usefulness and why?

*Peer review:* One peer reviewer suggested additional helpful references to ''. . . resources developed by professional organizations regarding safer handling of hazardous drugs.'' In addition, multiple reviewers suggested more extensive referencing of USP <800>.

*NIOSH response:* Additional links to helpful resources were added to the document. However, regarding USP <800>, NIOSH notes that many of the references circle back to NIOSH recommendations, so in those instances reference to USP <800> was not made. However, some references to USP <800> were added into the text where the recommendations were not originally from NIOSH guidance. A link to USP <800> has also been added to the document's Resources section.

2. Charge 1.b. What changes could be made to improve the utility of the information?

*Peer review:* One reviewer expressed concern that the definition of hazardous drug was changed without input from a much larger and international group of interested parties.

*NIOSH response:* This comment is addressed with the public comments received in the response to comments in Sec. II of the *Procedures* document.

*Peer review:* Another reviewer suggested that the information be distilled into a fact sheet or job aid to encourage implementation.

*NIOSH response:* NIOSH has reformatted the Table of Control Approaches for Safer Handling of Hazardous Drugs, by Activity and Formulation (Table of Control Approaches) in *Managing Exposures,* Ch. 8, to make it easy to reproduce. NIOSH is also considering the development of additional materials to summarize the information in *Managing Exposures* and help employers implement the NIOSH guidance.

3. Charge 1.c. What information is redundant, incorrect, missing, or not needed? Please Explain

*Peer review:* One reviewer suggested that the narrative immediately following the Table of Control Approaches did not add substantive information and could be removed.

*NIOSH response:* Since no other peer or public comments identified this as a problem, and in recognition that people absorb information in different ways, NIOSH has decided not to revise or remove the narrative following the table. No change to *Managing Exposures* has been made in response to this comment.

*Peer review:* One reviewer noted some differences between the Oncology Nursing Society (ONS) recommendations and the NIOSH recommendations in the Table of Control Approaches. These included recommendations for the use of double versus single gloves when handling manufacturer prefilled syringes and the double flushing of toilets.

*NIOSH response:* NIOSH reviewed the risks addressed in the ONS recommendations and adjusted the text throughout the *Managing Exposures* document as necessary, emphasizing that facilities are responsible for conducting site risk assessments and developing standard operating procedures (SOPs). The NIOSH recommendation for single gloves in handling prefilled syringes has been retained. The recommendation for flushing twice has been removed, specifying that a plastic-backed absorbent pad should be placed over toilets without lids during flushing.

*Peer review:* One reviewer noted that NIOSH should clarify that the controls were in descending order of effectiveness in the Table of Control Approaches.

*NIOSH response:* NIOSH has clarified the hierarchy of controls with additional text in Ch. 6, stating, ''[t]he controls at the top of the hierarchy are the most effective and provide the best business value.''

*Peer review:* The same reviewer asked whether medical surveillance was part of administrative controls.

*NIOSH response:* Medical surveillance is part of a comprehensive exposure control program complementing engineering controls, safe work processes (administrative controls), and use of PPE. In response to the peer reviewer's query, NIOSH has rearranged *Managing Exposures* and moved the section on medical surveillance into Ch. 6 to clarify that this consideration should be a part of the workplace's risk management plan.

4. Charge 2. Please Provide Any Additional Studies or Scientific Information That Evaluate or Validate Engineering, Work Practice, or Administrative Controls To Reduce Exposures to Hazardous Drugs in Healthcare Settings

*Peer review:* Reviewers commented on including references to USP <800> and provided additional links to resources and additional citations.

*NIOSH response:* As discussed above, links to suggested resources and suggested citations have been added to the document where appropriate.

*Peer review:* One reviewer requested that a citation be added regarding the insufficient protection offered by surgical masks during compounding.

*NIOSH response:* NIOSH agrees; this reference was included in the May 2020 notice draft *Managing Exposures. See* Ch. 6, Sec. 6.4, Personal Protective Equipment, in which NIOSH states:

> Surgical masks that are not labeled as N95 are not NIOSH-approved, do not provide respiratory protection, and should not be used to compound or administer fine powders which may result from handling hazardous drugs [citations omitted].

*Peer review:* Reviewers suggested specific risk mitigation strategies, such as requiring that all employees handling hazardous drugs wear PPE; having written policies to govern spill cleanup; requiring the availability of spill kits; having written policies that address medical surveillance; specifying that training should happen prior to working with hazardous drugs and annually thereafter; and that demonstrating and documenting annual competency were warranted.

*NIOSH response:* NIOSH recommends that workers performing any task involving hazardous drugs, including all compounding, administration, waste handling, and spill response, wear all assigned PPE to reduce the exposure and provide a barrier of protection. The recommendations on spill cleanup and spill kits, written policies on medical surveillance, training prior to working with hazardous drugs, and competency being determined and documented have been added to *Managing Exposures.*

[8] *Id.*

5. Charge 3. Please Provide Any Additional Studies or Scientific Information That Support or Validate the Use of the NIOSH Recommended Control Strategies or Alternative Strategies To Control Exposures to Hazardous Drugs

*Peer review:* One reviewer suggested including a reference on spills and PPE use and another on the hierarchy of controls and PPE use.

*NIOSH response:* In response to the peer reviewer, NIOSH has added references to *Managing Exposures* to support the use of the hierarchy of controls when PPE is inconsistently used (Friese *et al.* 2011) [9] and during spill response (Friese *et al.* 2020) [10] were added to document.

6. Charge 4. Please Provide Any Additional Studies or Scientific Information That Support or Validate Evidence-Based Strategies or Approaches for Controlling Exposures to Hazardous Drugs That Are Different From Those That NIOSH Has Proposed

*Peer review:* Reviewers suggested language clarifications and additional references for NIOSH consideration.

*NIOSH response:* NIOSH agrees with many of the suggestions and references offered by peer reviewers and has revised the final *Managing Exposures* accordingly.

*Peer review:* Reviewers questioned the location and composition of the recommendations for medical surveillance.

*NIOSH response:* As discussed above, in response to the peer reviewer, the topic of medical surveillance was moved into Ch. 6, Risk Management Plan. Medical surveillance should be included as a part of a comprehensive exposure control program to protect the health of workers. This section now includes the following recommendation:

> Elements of a medical surveillance program for workers exposed to hazardous drugs should include the following:
>
> • Consideration of a baseline clinical evaluation to allow for an individualized point of comparison should adverse health effects of exposure to hazardous drugs be suspected in the future. Whether a worker should undergo baseline clinical evaluation should be based on the availability of clinical examinations and tests which can be targeted toward specific hazardous drugs and health endpoints, as well as their corresponding performance characteristics, such as sensitivity, specificity, and predictive value. If a baseline clinical evaluation is performed, it can include a targeted (1) medical history, (2) physical examination, and (3) laboratory testing. Selection of baseline evaluation components should be informed by the toxicities of the hazardous drugs to be handled.
>
> • Health questionnaires administered by a healthcare professional at the time of hire and periodically. The questionnaires should include information about relevant symptoms and medical events. Reproductive outcomes such as miscarriage should be included whenever anticipated as an adverse outcome of hazardous drug exposure because their occurrence may go unreported.
>
> • History of drug handling as an estimate of prior and current exposure, including dates of duty assignment related to hazardous drugs and similar types of information.
>
> • A follow-up plan, as needed, for workers who have had health changes suggesting toxicity or have experienced acute exposure (for example, from substantial skin contact or inhalation or from cleaning a large spill [a broken IV bag, leaking IV line, etc.]) [citation omitted].

*Peer review:* One reviewer suggested a reference describing controls in urological procedures.

*NIOSH response:* This reference has not been included because NIOSH determined it is a general paper and does not address specific worker exposure from the medical procedure, bladder installation. No change to *Managing Exposures* has been made in response to this comment.

7. Charge 5.a. What additional information would improve the usefulness of [the Table of Control Approaches in Chapter 8] and why?

*Peer review:* One reviewer suggested adding a statement indicating that compounding and manipulating oral hazardous drugs should be done in a compounding area, and not a patient care area, and to alert medical personnel of the hazards.

*NIOSH response:* NIOSH has provided separate recommendations for compounding and administering in the Table of Control Approaches. It would be impractical to try to identify all actions that would fall under a ''do not do this'' recommendation. No change to *Managing Exposures* has been made in response to this comment.

*Peer review:* Another reviewer mentioned that a job aid or standard operating procedure would be of particular help associated with the Table of Control Approaches.

*NIOSH response:* The Table of Control Approaches is meant to stand alone without a standard operating procedure. NIOSH is developing a shorter fact sheet to assist employers. No change to *Managing Exposures* has been made in response to this comment.

8. Charge 5.b. What structural or format changes could be made to improve the utility of [the Table of Control Approaches]?

*Peer review:* Two reviewers noted that the format of the Table of Control Approaches should be considered for potential use as a stand-alone document and maximized for searching online.

*NIOSH response:* NIOSH agrees and has developed the final Table of Control Approaches with those considerations in mind.

9. Charge 5.c. What information is redundant, incorrect, missing, or not needed [in the Table of Control Approaches]? Please Explain

*Peer review:* One reviewer suggested reference to the 2018 Oncology Nursing Society's Safe Handling of Hazardous Drugs, 3rd edition (ONS 2018) as an additional resource for exposure control approaches and recommended a specific control strategy when attaching needles to closed system transfer devices (CSTDs). The same reviewer mentioned that double flushing was no longer recommended.

*NIOSH response:* NIOSH agrees and has added a citation to ONS 2018 to provide an additional resource for exposure control strategies. NIOSH has also included a link to a NIOSH topic page on CSTDs to further describe the appropriate controls needed when using CSTDs. The suggested revision, however, is too specific for this general recommendation document. NIOSH concurs that double flushing was not recommended and has revised the document to update the recommendations.

*Peer review:* Another reviewer stated that the content of the Table of Control Approaches was overwhelming and suggested a bullet point summary. The reviewer also suggested linking to the USP Reference Standards Mobile App.

*NIOSH response:* NIOSH is developing a shorter fact sheet to present a summary of the information. A reference to USP <800> has been added to the document's Resources section. However, NIOSH has not provided a link to a for-purchase product.

[9] Friese CR, Himes-Ferris L, Frasier MN, McCullagh MC, Griggs JJ [2011]. *Structures and Processes of Care in Ambulatory Oncology Settings and Nurse-Reported Exposure to Chemotherapy.* BMJ Qual Saf. 21(9):753–759.

[10] Friese CR, Wong M, Fauer A, Mendelsohn-Victor K, Polovich M, McCullagh MC [2020]. *Hazardous Drug Exposure: Case Report Analysis from a Prospective, Multisite Study of Oncology Nurses' Exposure in Ambulatory Settings.* Clin J Oncol Nurs. 24(3):249–255.

10. Charge 6. What improvements could be made to this risk management information to make it more useful to employers and healthcare workers? Please Provide Specific Examples

*Peer review:* Two reviewers suggested that NIOSH recommend alternative duty for pregnant women or individuals trying to conceive to further reduce potential worker risks and advocated expanding the Medical Surveillance section with specific requirements.

*NIOSH response:* NIOSH has determined that the employer is in the best position to ascertain the utility and feasibility of alternative duty as a control strategy in their workplace. As discussed above, the components and timing of medical surveillance should be determined by the licensed healthcare professional conducting the medical evaluation. No change to *Managing Exposures* has been made in response to this comment.

*Peer review:* Another reviewer suggested visual abstracts and graphics to better convey concepts and summarize key points referenced in a 2019 study by Friese *et al.,* entitled *Randomized Controlled Trial of an Intervention to Improve Nurses' Hazardous Drug Handling,* published in the Oncology Nursing Forum.[11]

*NIOSH response:* The visual aspect of Friese *et al.* 2019 is inspiring. NIOSH is considering reviewing the documents to look for opportunities to create shorter fact sheets with meaningful graphics to improve understanding. In addition, a NIOSH visual communication team has worked to make the Table of Control Approaches in the *Managing Exposures* document easier to read and reproduce.

*Peer review:* One reviewer suggested adding a section on home veterinary care, recommending information from a specific reference.

*NIOSH response:* The NIOSH document is geared towards employees in healthcare settings, including veterinarians and veterinary staff, but not pet owners doing home veterinary care. However, the veterinary resource suggested was a ''consensus opinion'' about protecting both veterinary workers and owners so it was added to the document's Resources section.

11. Charge 7. Please Provide Information About Your Professional Experience, if Any, of Implementing Control Strategies for Exposures to Hazardous Drugs in Healthcare or Similar Settings. Please Describe What You Found to Be Most or Least Effective and Why. Include Relevant Publications if Available

*Peer review:* One reviewer indicated that there is a need for increased signage for all staff, family, and visitors in contact with patients receiving hazardous drugs. References were suggested outlining the scope of the problem.

*NIOSH response:* The recommendation for signage has been added to the document.

*Peer review:* Another reviewer asked why recommendations were made to protect veterinary patients but not humans in veterinary practices.

*NIOSH response:* NIOSH has clarified that the recommendations are designed to protect veterinary workers not the veterinary patients.

*Peer review:* One reviewer was concerned with potential hazardous drugs exposures from patient or general public exposure to toilets in outpatient settings and suggested the addition of the following reference: Walton A, Bush MA, Douglas C, Allen DH, Polovich M, Spasojevic I [2020], *Surface Contamination with Antineoplastic Drugs on Two Inpatient Oncology Units,* Oncol Nurs Forum 47(3):263–272.

*NIOSH response:* NIOSH determined the reference cited contained useful information pertaining to identification of potentially contaminated areas and has added it to the section on surface contamination.

*Peer review:* One reviewer was concerned that wipe testing be conducted where hazardous drugs should not be found as an important exposure control.

*NIOSH response:* Ch. 6, Sec. 6.5, Surface Contamination, has been edited to include sampling where hazardous drugs are prepared, administered to patients, or otherwise handled (*i.e.,* receiving areas, transit routes throughout the facility, and waste storage areas).

*Peer review:* One reviewer recommended NIOSH add references on the persistence of contamination even when workplace controls are used (*i.e.,* Kopp B, Schierl R, Nowak D, 2013; and Walton A, Bush MA, Douglas C, Allen DH, Polovich M, Spasojevic I, 2020).

*NIOSH response:* Ch. 6, Sec. 6.5 has been edited to include the suggested references as well as others to support the premise that workplace contamination with hazardous drugs continues to be an issue in the United States.

*Peer review:* One reviewer suggested that *Managing Exposures* recommend ''spill drills'' to train and refresh training for employees.

*NIOSH response:* NIOSH concurs and has added language to the document recommending that workplaces practice for spills.

12. Charge 8. Please Provide Any Additional Comments or Suggestions Either as a List Below or Using Track Changes in the Attached Draft Document

*Peer review:* One reviewer suggested that *Managing Exposures* include guidance from ONS 2018 regarding the use of chewing gum and tobacco and the application of cosmetics in the areas where hazardous drugs are handled; written policies that address spill cleanup and medical surveillance; and the availability of spill kits.

*NIOSH response:* NIOSH concurs and has added language to the final document pertaining to the suggestions. Additionally, ONS 2018 has been both cited and listed as an additional resource.

*Peer review:* One reviewer recommended changing ''nurses' aides'' to ''nurses' assistants.''

*NIOSH response:* NIOSH concurs with the suggested change and has revised the final *Managing Exposures* accordingly.

*Peer review:* One reviewer suggested that ''large spill'' be defined.

*NIOSH response:* NIOSH concurs this should be clearer, and in the recommendation regarding a follow-up plan for workers who have experienced acute exposures from large spills has clarified that large spills may result from a broken IV bag, leaking line, or similar event. NIOSH has determined that defining ''large spill'' would be too prescriptive because ''large'' is subjective and may depend on such factors as the concentration of the drug and the amount of surface area upon which it may be spilled. Accordingly, the definition of ''large spill'' should be defined by each facility according to its own needs.

*Peer review:* One reviewer requested more specific language in the recommendations for training.

*NIOSH response:* NIOSH agrees and has added information about providing training frequently and when there are new hazardous drugs brought into the facility. Workers should be trained prior to beginning work with hazardous drugs and should demonstrate competency before they handle a hazardous drug, clean an area where hazardous drugs are

[11] Friese CR, Yang J, Mendelsohn-Victor K, McCullagh M [2019]. *Randomized Controlled Trial of an Intervention to Improve Nurses' Hazardous Drug Handling.* Oncol Nurs Forum. 46(2):248–256.

used, and perform work tasks that will potentially expose them to the body fluids of a patient who is taking hazardous drugs.

*Peer review:* One reviewer requested more clarity about signage.

*NIOSH response:* NIOSH agrees and has clarified that signage should be placed where the hazardous drugs are used and stored.

*Peer review:* One reviewer requested additional information about handling contaminated excreta.

*NIOSH response:* NIOSH agrees and has added language about handling of drug contaminated excreta.

*Peer review:* Two reviewers commented that *Managing Exposures* should specify the types of gloves that should be used for different hazards, and that NIOSH should clarify how often PPE should be changed and the order of doffing PPE.

*NIOSH response:* NIOSH disagrees that the document should provide specifics on the type of glove to be used since different glove types offer different protection from dermal exposure to hazardous drugs. NIOSH does agree that providing information on when to change PPE and the order of doffing PPE is important and has added the recommendation ''[r]emove PPE in the following order: shoe covers, sleeve covers, outer gloves, face shield, gown, respirator/mask, inner gloves'' to Sec. 6.4, Personal Protective Equipment. No change to *Managing Exposures* has been made in response to this comment.

*Peer review:* One reviewer had specific suggestions regarding controls for CSTDs, specifically regarding double gloving when using prefilled syringes and when plastic-backed pads should be used.

*NIOSH response:* NIOSH agrees with the suggestion about the use of plastic-backed pads and new language has been added to the existing discussion on CSTDs in Ch. 6, Sec. 6.2, Engineering Controls. NIOSH disagrees that double gloves are needed when using prefilled syringes and has made no changes in response to this recommendation.

*Peer review:* One reviewer commented that eyewash stations should be mentioned, exposure assessment through wipe sampling (at baseline and routine intervals) could be clarified, and the heading for Sec. 8.3 could be made more explicit.

*NIOSH response:* NIOSH agrees and has added information to Sec. 6.5 Surface Contamination, on wipe sampling, and to Sec. 7.2, Spill Control, on eyewash stations. The heading for Sec. 8.3 in the 2020 draft *Managing Exposures* has been changed to ''Additional Considerations for Handling Hazardous Drugs'' and the section was turned into a new Ch. 9.

*B. Public Comments*

1. Glossary

*Public comment:* NIOSH received comments from five commenters related to definitions in the Glossary. The following definitions were suggested:

- *Biological safety cabinet (BSC):* ''laboratory'' may be confusing; consider instead ''an enclosed, ventilated workspace . . .''
- *Cleaning:* Removal of organic and inorganic material from objects and surfaces using water, detergents, surfactants, solvents, and/or other chemicals.
- *Decontamination:* Inactivating, neutralizing, or physically removing hazardous drug residue from non-disposable surfaces and transferring it to absorbable, disposable materials appropriate to the area being cleaned.
- *Deactivation:* To render a compound inert or inactive.
- *Disinfection:* A process of inhibiting or destroying microorganisms.

*NIOSH response:* NIOSH has added the suggested definitions for ''deactivation'' and ''disinfection'' in the final *Managing Exposures.*

2. Chapter 1.0 Purpose and Scope

*Public comment:* A commenter asked for clarity on recommendations for retail pharmacies.

*NIOSH response:* NIOSH notes that retail facilities should perform the appropriate risk assessments. The assessments may show, due to limited handling or manipulation of open containers, that the risks of exposure are limited. However, the assessment of potential handling scenarios in the facility should still be performed to determine what those risks are. No change was made to the final *Managing Exposures* in response to this comment.

*Public comment:* A commenter suggested NIOSH highlight potential exposures to hazardous drugs through handling of human fluids and wastes.

*NIOSH response:* NIOSH agrees and has edited Ch. 4.0, Occupational Exposure Assessment, to highlight the potential risk from exposure to human waste products (*i.e.,* urine, feces, vomit).

3. Chapter 6.0 Risk Management Plan

*Public comment:* Several commenters on both the *Managing Exposures* draft and the *List* draft mentioned specific issues regarding the assessment of risk discussed in Ch. 6.0. Several asked for more specific guidance for site risk assessments, particularly surrounding administration and compounding.

*NIOSH response:* NIOSH disagrees that *Managing Exposures* should provide more specific guidance for risk assessments. Each facility should conduct its own risk assessment to determine which tasks within the facility would be considered administration or compounding. In response to these comments, NIOSH has revised the language in the final document to specify that each facility should conduct its own risk assessment and develop SOPs specific to its use of hazardous drugs.

a. Section 6.2 Engineering Controls

*Public comment:* Seven comments were received on engineering controls discussed in Sec. 6.2 (in addition to comments related to CSTDs, which are considered below). Commenters suggested adding information about engineering controls, such as uninterrupted power supply, negative pressure, and unidirectional flow of air. Some commenters also suggested specific recommendations regarding use of BSCs and compounding aseptic containment isolators (CACIs), clarification of the recommendations regarding nonsterile preparations in footnote 4 of the Table of Controls in Ch. 8, use of glove bags and suggestions for various updated references. One commenter noted that cleaning is not the only step needed to ensure the BSC or CACI is in optimal condition to compound drugs. Proper use also includes processes to deactivate (*i.e.,* render a compound inert or inactive), decontaminate (*i.e.,* remove hazardous drug residue), and disinfect (*i.e.,* destroy microorganisms).

*NIOSH response:* BSC selection should be based on a risk assessment of the hazardous drugs in use at each facility and be flexible enough to allow for evolving equipment types and performance specifications. In response to comments, NIOSH has clarified the language in the document as follows:

> Class II BSCs that exhaust filtered cabinet air to the outdoors are recommended. BSCs that exhaust cabinet air back into the segregated engineering control (SEC) are discouraged. When the work activity requires handing volatiles, a risk analysis should be conducted to identify the appropriate Class II BSC selection to ensure that any air recirculation internal to the BSC does not result in vapor accumulation.

NIOSH provides recommendations related to the proper use of ventilated cabinets, and, in response to comments, NIOSH has revised one of the recommendations to clarify that proper use requires users to ''[i]nstall, maintain, deactivate, decontaminate, clean and disinfect the BSC.'' Another

recommendation has been revised to read ''[h]ave readily available or display a current field-certification label prominently on the ventilated cabinet.'' NIOSH has also added recommendations for negative pressure and an uninterrupted power source.

In response to comments, NIOSH has defined the terms ''deactivate,'' ''decontaminate,'' and ''disinfect'' in the Glossary to improve clarity.

In reference to the comment on nonsterile preparations in the Table of Control Approaches footnote 4, the footnote is only intended for nonsterile preparations, as stated. It should not be taken to suggest that NIOSH recommends that sterile compounding does not need to be performed in a sterile ventilated engineering control as long as the person compounding is wearing appropriate respiratory protection. This document addresses worker safety. In the interest of patient safety and drug safety all appropriate USP guidelines should be followed. No change to the document was made in response to this comment.

Regarding the comment on glove bag use, NIOSH is unaware of any reason why a small sterile glove bag that does not deflect airflow to outside of the direct compounding area could not be used inside a BSC. NIOSH is also unaware of any confusion or conflicts created by past glove bag recommendations. In NIOSH's experience, these are only rarely used but they could indeed be used as described and would also be protective. NIOSH is unaware of a unidirectional airflow requirement. Even if used under unidirectional airflow, if the glove bag interior and inserted supplies were all sterile, and the glove bag placed beneath a laminar flow of ISO 5 air, NIOSH believes this still would meet the intent of the recommendation. Of course, each facility should conduct their own risk assessment and develop SOPs specific to their use of hazardous drugs. No change to *Managing Exposures* has been made in response to this comment.

Closed System Transfer Devices

*Public comment:* One commenter suggested removing or altering images that reference proprietary names in Figures 4 and 5. Particularly in Figure 5, which includes a photograph of a robotic drug preparation system with the manufacturer's name in the photo credit. This device is ''not yet fully functional in the United States'' and should not be part of the NIOSH informational document. In general, such images may not be representative of the numerous products available on the U.S. market for safely compounding hazardous drugs and demonstrates bias.

*NIOSH response:* Regarding the figures, NIOSH has decided to keep them in the final *Managing Exposures.* However, in Figure 4, NIOSH has substituted more non-specific images of two types of CSTDs that are representative of those available in the U.S. market rather than photographs. The following Disclaimer continues to be included on the title page: ''[m]ention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH).''

*Public comment:* A commenter suggested the removal of references to robotic systems.

*NIOSH response:* NIOSH has not changed the document in response to this comment, noting that the text already states ''robotic systems are considered supplemental controls that should only be used in combination with primary engineering controls (*i.e.,* BSCs and CACIs) to further protect against worker exposures to hazardous drugs.''

*Public comment:* One commenter requested clarification in the wording related to priming IV tubing.

*NIOSH response:* In response to the comment, NIOSH has reworded the sentence to state, ''[c]ompounding personnel should prime the IV tubing and syringes inside the ventilated cabinet or prime them in-line with nondrug solutions or by use of a CSTD to prevent the escape of hazardous drugs.''

*Public comment:* Five comments were received on recommendations regarding CSTDs, all specifically focused on issues of compatibility with the drug product.

*NIOSH response:* Each facility should conduct its own risk assessment and develop SOPs specific to its use of hazardous drugs. NIOSH states in Sec. 8.1 that the MSHI should be consulted. However, in response to comments, NIOSH has added the language ''when dosage form allows'' in every case where a CSTD is recommended in the Table of Control Approaches.

b. Section 6.3 Administrative Controls

Alternative Duty

*Public comment:* Two commenters made suggestions on alternative duty. Both proposed including recommendations on the importance of alternative duty for healthcare workers who are pregnant, trying to conceive, or who are breastfeeding.

*NIOSH response:* NIOSH recognizes that alternative duty is one method to control hazardous exposures to healthcare workers who are pregnant, trying to conceive, or who are breastfeeding. However, NIOSH has determined that the specific control strategies should be left up to the employer who is in the best position to conduct an in-depth individual facility risk assessment. No change to *Managing Exposures* has been made in response to this comment.

Cleaning

*Public comment:* One commenter requested clarification of the terms associated with cleaning activities.

*NIOSH response:* In response to the comment, NIOSH has edited Sec. 6.3 to clarify the difference between cleaning and decontamination. In Sec. 6.3, NIOSH has replaced the term ''rags'' with ''disposable wipes'' and has clarified that ''[w]ork surfaces should be deactivated, decontaminated, and cleaned before and after each activity and at the beginning and end of the work shift.'' The terms ''deactivation'' and ''decontamination'' have been added to the Glossary.

Counting Tablets

*Public comment:* Four commenters had questions on counting tablets, discussed in Sec. 6.3. Specifically, the comments questioned whether the information was considered to establish requirements or merely recommendations, and how the recommendation to limit the use of automated counting machines should be implemented.

*NIOSH response:* In this document, NIOSH is issuing recommendations not requirements. The document is informational in nature and creates no legal obligation. Regarding counting tablets, NIOSH has clarified the language in Sec. 6.3 of the document recommending that automated counting machines be prohibited for hazardous drugs unless the machine has been evaluated and found to not release powders.

*Public comment:* One commenter suggested changing the NIOSH recommendations for use of automated counting machines.

*NIOSH response:* In response to the comment, NIOSH has revised the recommendations on the use of counting machines to include the following text and references:

> Tablet and capsule forms of hazardous drugs should not be placed in an automated counting machine unless a facility risk assessment validates that the specific machine does not introduce dust and contamination; most counting machines can stress tablets and capsules thereby introduce

powdered contaminants into the work area [citations omitted].

c. Section 6.4 Personal Protective Equipment

Use of Gloves

*Public comment:* Fourteen comments were received about the recommendations on glove use discussed in Sec. 6.4. The comments specifically addressed the use of single versus double gloves during shipping and receiving and while handling prefilled syringes. There were also comments on the use of spray alcohol on gloves and the use of sleeve covers with gloves.

*NIOSH response:* In response to several comments, the recommendation for receiving, unpacking, and placing in storage has been changed to single glove. Although NIOSH already recommends employers ''ensure that the selected gloves are not degraded by the alcohol,'' the recommendation for use of spray alcohol was removed. NIOSH is retaining the recommendation of a single glove for manufacturers' prefilled syringes as it is anticipated that they have less of a chance for exterior contamination. Facilities should conduct their own risk assessment to determine gloving requirements for their specific situations.

Use of Gowns, Sleeve Covers, and Head Covers

*Public comment:* Seven reviewers suggested that the recommendation for sleeve covers should be removed or modified.

*NIOSH response:* In response to the comment, NIOSH has turned the recommendation for the use of sleeves into a consideration: ''[c]onsider using sleeve covers if there is a gap between the gown and the glove.''

*Public comment:* One commenter suggested that NIOSH state that gowns be shown to resist permeation by hazardous drugs. Another reviewer suggested that information about the frequency of changing gowns be added.

*NIOSH response:* NIOSH has added language clarifying that gowns should be shown ''to resist permeation by the types of hazardous drugs used'' to Sec. 6.4, Gowns. Language has also been added to recommend changing gowns after one use or at a frequency determined by the employer and immediately after a spill or splash and disposing of in an appropriate waste container.

*Public comment:* One commenter suggested that NIOSH should define the term ''face shield'' to reduce the risk of confusion.

*NIOSH response:* Because face shields are very common in healthcare (and the general public) the term is generally understood and no further definition was required. No change to *Managing Exposures* has been made in response to this comment.

Use of Respirators

*Public comment:* Five comments were received on respirator use. Some requested detailed guidance for spill and cleaning activities. Other comments included a request for guidance during compounding and clarification on respirator selection when using volatile hazardous drugs. One comment suggested that the powered air-purifying respirator (PAPR) depicted in Figure 6 is not appropriate for use with drugs that are volatile.

*NIOSH response:* Regarding the comments for specific guidance, NIOSH reiterates that each facility should conduct its own risk assessment and develop SOPs for specific scenarios. NIOSH has clarified its guidance on respirator use with volatile hazardous drugs by adding the recommendation: ''[u]se a full-facepiece combination particulate/chemical cartridge-type respirator or a powered air-purifying respirator (PAPR) whenever handling volatile hazardous drugs or aerosolizing hazardous drugs for inhalation or nebulized therapy.'' The images in Figure 6 were used as examples of the types of respirators that could be used. to protect workers from hazardous drug exposures. The type of PAPR in Figure 6 may not be the correct PAPR for every situation. Facilities should choose the correct device that fits their specific needs and as stated in the disclaimer, ''[m]ention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH).'' Changes were made to the text to indicate a variety of potential respirators for different needs.

d. Section 6.5 Surface Contamination

*Public comment:* One comment suggested expanding the section on monitoring surface contamination. Another noted that there was no mention of assessing environmental contamination by surface wipe sampling, and that this technique has become a sophisticated and useful tool in other countries but not yet adopted by U.S. facilities handling hazardous drugs.

*NIOSH response:* NIOSH has revised the document to include additional references to support the recommendations on wipe testing for contamination.

e. Section 6.6 Medical Surveillance

*Public comment:* NIOSH received several comments on medical surveillance. Two comments mentioned the difficulty and burden of instituting a medical surveillance program in a mobile workforce and in small businesses. Another asked for clarity on the recommended frequency of clinical follow-up. One commenter stated that clinical exams and labs for medical surveillance of workers exposed to hazardous drugs be curtailed until positive evidence was available to demonstrate the usefulness of the practice. Conversely, a different commenter called for the establishment of a national registry to capture the exposures and outcomes from exposure to hazardous drugs.

*NIOSH response:* Regarding the difficulty, burden, and potential lack of data showing the efficacy of a medical surveillance program, NIOSH notes that ONS, OSHA, and USP all recommend medical surveillance for workers in contact with hazardous drugs. Surveillance can identify sentinel adverse health effects among workers suggesting failures in controlling exposures and thus identify the need for improvements in workplace controls, such as engineering or administrative controls or personal protective equipment. Also, individual workers may benefit from detection of disease in early stages when it may be more treatable with better clinical outcomes. No change has been made to *Managing Exposures* in response to this comment. NIOSH has no plans to recommend a national registry at this time.

4. Chapter 7.0 Waste and Spill Control

a. Section 7.1 Hazardous Drug Waste and Section 7.2 Spill Control

Waste Designation and Handling

*Public comment:* One commenter requested clarification of the difference between trace and overtly contaminated items and the procedures for disposal of contaminated items.

*NIOSH response:* A new Sec. 7.1, Hazardous Drug Waste, has been added which describes the 3 types of waste streams: hazardous waste, as defined by the Resource Conservation and Recovery Act (RCRA);[12] trace chemotherapy waste; and nonhazardous pharmaceutical waste. The new section also includes a description of disposal containers. A site-specific assessment of risk should be performed to determine facility SOPs.

*Public comment:* NIOSH received eight comments on waste designation

[12] 42 U.S.C. 6901 *et seq.,* 40 CFR 261.

and handling. Several specific recommendations were offered on how to handle waste contaminated with hazardous drugs. Several commenters asked for clarification of terms, specifically differentiating between waste contaminated with trace amounts of hazardous drugs and hazardous waste.

*NIOSH response:* NIOSH appreciates the clarification and suggestions regarding waste management. Several revisions to address these comments have been made throughout the document. However, a comprehensive list of waste handling procedures is beyond the scope of this document. The narrative section on waste handling was expanded to clarify trace waste from hazardous waste to address some of these concerns.

5. Section 8.0 Control Approaches for Safe Handling of Hazardous Drugs by Activity and Formulation

a. Section 8.1 Introduction to Table of Control Approaches

*Public comment:* One commenter suggested deleting the Table of Control Approaches, noting that it was unnecessary and overly conservative. In particular, the table does not appropriately differentiate between control measures (*e.g.,* ventilation, respiratory protection) based on factors such as dosage forms of hazardous drugs (*e.g.,* intact tablet and capsules vs. bulk active pharmaceutical ingredients), types of hazardous drugs (antineoplastic vs. non-antineoplastic), and other important factors that affect how medications are handled in healthcare facilities and the degree to which workers may be exposed. In this way, the Table of Control Approaches is inconsistent with the risk assessment procedures outlined in USP <800>.

*NIOSH response:* NIOSH disagrees, finding that the Table of Control Approaches has broad support among peer reviewers and public commenters who provided input on the May 2020 draft and is foundational to this activity. *Managing Exposures* lays out information regarding risk management strategies. Exposure assessments that include consideration of many facilities' specific factors such as dosage forms and each individual drug's potential hazards to determine the best control measures are part of the strategies discussed in this document. The table represents common handling situations in healthcare workplaces and should be considered within the broader framework the document provides. While NIOSH is independent from USP, the use of the Table of Control Approaches within the framework of this document is consistent with the use of risk assessment procedures laid out in USP <800>. No change has been made to *Managing Exposures* in response to this comment.

*Public comment:* One commenter suggested considering reformatting the Table of Control Approaches. Another commenter suggested that gloves should be American Society for Testing and Materials (ASTM) rated and that gowns should be impervious and single use.

*NIOSH response:* In response to the comment, NIOSH revised the table to clarify that gloves should be ASTM rated and gowns should be impervious and single use. A new line was added to the table to include the headers Engineering Controls and PPE.

b. Section 8.2 Control Approaches by Activity and Formulation

Receiving and Packaging

*Public comment:* Two comments were received on recommendations surrounding receiving and packaging, discussed in Sec. 8.2. One comment suggested that single gloves were appropriate for unpacking, and the other asked if repackaging was considered compounding.

*NIOSH response:* NIOSH agrees that single gloves for receiving and unpacking were appropriate and has changed the recommendations in Sec. 8.2 and in the Table of Control Approaches accordingly. Repackaging would not typically be considered compounding if it does not change the final dosage form.

Transportation

*Public comment:* One commenter suggested that gloves did not provide protection during transportation, but that they could actually increase the hazard by spreading potential exposure.

*NIOSH response:* NIOSH has retained the recommendation, discussed in Sec. 8.2, that gloves should be worn during transport of hazardous drugs in a facility. Each facility should conduct its own risk assessment and develop SOP specific to its use of hazardous drugs. No change has been made to *Managing Exposures* in response to this comment.

Compounding of Drugs

*Public comment:* Four commenters commented on the recommendations regarding drug compounding, discussed in Sec. 8.2. Commenters requested that tablet or capsule crushing not be included in compounding, questioned whether prefilled IV bags needed to have tubing attached and be primed, and requested guidance on pouring liquids from one container to another.

*NIOSH response:* In *Managing Exposures,* NIOSH has moved tablet crushing to the administration recommendations to be consistent with USP guidance which does not consider crushing or splitting tablets as ''compounding.''

Regarding precautions with IV bags, this would not be considered compounding under the FDA definition, as the final formulation is unchanged. Pouring from one container to another also would not be considered compounding under the FDA definition. No change has been made to *Managing Exposures* in response to these comments.

Administration

*Public comment:* Six comments were received on administering drugs in the Table of Control Approaches. Two commenters questioned the distinction between prefilled and in-house prepared syringes. Other commenters asked about vented filters to remove bubbles in IV tubing, ophthalmologic application, and procedures to minimize risks from crushing tablets.

*NIOSH response:* An in-house prepared syringe may contain trace contamination and a manufacturer's prefilled syringe can be assumed to be clean. Accordingly, NIOSH has maintained the subsections of the Table of Control Approaches distinguishing between prefilled and in-house prepared syringes. The use of vented filters allows bubbles to be eliminated from infusion lines. When inline vented filters use is suggested for compounds prone to outgassing, an assessment of the risk of exposure would be appropriate. It is expected that the level of drug vapor released during infusion will be miniscule and the level of dilution once passing through the vent into the room air would limit the hazard posed by outgassing during infusion.

Regarding ophthalmic application, NIOSH agrees with the commenter and has added information on ophthalmologic applications to the Table of Control Approaches and Sec. 8.2. Regarding minimizing risks to workers for specific scenarios, an intact coated tablet or capsule will have a coating preventing the release of dusts/powders or liquids; and a cut, crushed or uncoated tablet will provide a possible source of dusts/powders or liquids that could expose the workers. Similarly, an in-house prepared syringe may contain trace contamination and a manufacturer's prefilled syringe can be assumed to be clean and would have less likelihood of exposing the worker to hazardous drugs. Each facility needs to conduct its own risk assessment and

develop SOPs specific to its use of hazardous drugs.

6. USP <800>

*Public comment:* Several commenters offered suggestions on the document's use of USP <800>. Most were concerned that USP should be cited more often.

*NIOSH response:* In response to commenters, USP <800> has been cited in the document where it could be determined that it could provide new information that did not originate with NIOSH (thus avoiding circular references).

*Public comment:* NIOSH should be differentiating between controls for antineoplastics and other hazardous drugs.

*NIOSH response:* NIOSH reaffirms that this document is intended to apply to all drugs on the 2023 *List* and not just antineoplastics. No change to *Managing Exposures* has been made in response to this comment.

*Public comment:* One commenter suggested that guidance on performing an individual drug risk assessment that meets the USP <800> standard would be helpful as alternative containment strategies and/or work practices for specific dosage forms weren't included.

*NIOSH response:* NIOSH disagrees with providing guidance for ''specific dosage forms'' as that is beyond the scope of this general guidance document. However, the text ''[t]he risk assessment should include evaluating the dosage form and identifying the probability of exposure'' has been added to Sec. 5.0 Risk Assessment, for clarity.

7. Other Topics

*Public comment:* One commenter noted that the term ''pills'' is referred throughout the document, for example, on pages 38 and 66. According to the commenter, ''pill'' is a nonspecific, outdated term and should be replaced with the word ''tablet'' instead.

*NIOSH response:* NIOSH agrees and has made this change throughout the final *Managing Exposures.*

*Public comment:* Several commenters noted spelling mistakes, errors in tables, and other editorial improvements.

*NIOSH response:* NIOSH thanks the commenters for pointing out these errors. NIOSH has accepted all appropriate editorial, spelling, and correction comments in its revision of *Managing Exposures.*

**V. Summary of Changes to Documents**

*A. Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings*

As described in the responses to comments above, only limited clarifications were made in the *Procedures* document. Notable changes include a revision to footnote 12 to clarify that only CDER-approved drugs are included on the *List* and the addition of a new footnote 29 to clarify NIOSH's intent regarding drugs with insufficient information in the package insert to determine whether the drug meets the NIOSH definition of a hazardous drug. Other changes comprised only minor editorial improvements.

*B. Managing Hazardous Drug Exposures: Information for Healthcare Settings*

Changes were made to the document, *Managing Exposures,* in response to comments received. There were some reorganizations, added references and information, and clarification of recommendations, as follows:

- In response to commenters, USP <800> was cited in document where it could be determined that it had new information that did not originate with NIOSH (thus avoiding circular references). ONS 2018 was cited and listed as an additional resource.
- The language in the document was clarified to specify that each facility should conduct their own risk assessment and develop SOPs specific to their use of hazardous drugs.
- Under Administrative Control recommendations, the language was clarified that automated counting machines should be prohibited unless the automated counting machine has been evaluated and found to not release powders.
- In the recommendations on PPE, several changes were made in response to comments:
  - Gloving recommendations for receiving and unpacking were changed to a single glove.
  - Recommendation to ''spray'' sterile alcohol on gloves was removed.
  - Recommendation for the use of sleeves was changed to ''Consider using sleeve covers if there is a gap between the gown and the glove.''
- In the Table of Control Approaches:
  - Ophthalmologic administration guidance was added.
  - Recommendation for double flushing of toilets in homes was removed and replaced with new guidance that states ''Close toilet lid or use a plastic-backed absorbent pad placed over the toilet without a lid during flushing.''
  - ''Crushing or manipulating tablets or capsules'' was moved from the compounding activity formulation column to the administering activity formulation column.
- The document was edited to highlight the potential risk from exposure to human waste products (urine, feces, vomit). The topic of Medical Surveillance was moved forward in the document under Risk Management for clarity. Three new sections were added to increase the clarity and utility of the recommendations:
  - Section 6.5 Surface Contamination
  - Section 7.1 Hazardous Waste
  - Section 7.2 Spill Control
- Chapter 9 was created to reorganize information in the previous draft for clarity:
  - Chapter 9.0 Additional Considerations for Handling Hazardous Drugs
  - Section 9.1 Home Healthcare
  - Section 9.2 Veterinary Clinics (formerly Section 8.3 Steps to reduce potential exposure to hazardous drugs)

Additional references were added as suggested by commenters and peer reviewers to provide additional resources for readers.

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Administration for Children and Families

**[CFDA Number: 93.647]**

### Announcement of the Intent To Award Single-Source Cooperative Agreements to Approved but Unfunded Diaper Distribution Pilot Applications From FY2022

**AGENCY:** Office of Community Services (OCS), Administration for Children and Families (ACF), Department of Health and Human Services (HHS).

**ACTION:** Notice of issuance of single-source awards.

**SUMMARY:** The ACF, OCS, Division of Community Discretionary and Demonstration Programs (DCDDP) announces the intent to award seven single-source cooperative agreements in the aggregate amount of up to $8,181,779 to approved but unfunded applications submitted to the Diaper Distribution Demonstration and Research Pilot (DDDRP) Notice of Funding Opportunity HHS–2022–ACF–OCS–EDA–0161.