confidential by the respondent (5 U.S.C. 552(b)(4)).

Current actions: The Board has temporarily revised the instructions to the FR Y–9C report to accurately reflect the revised definition of ''savings deposits'' in accordance with the amendments to Regulation D in the interim final rule published on April 28, 2020 (85 FR 23445). Specifically, the Board has temporarily revised the instructions on the FR Y–9C, Schedule HC–E, items 1(b), 1(c), 2(c) and glossary content to remove the transfer or withdrawal limit. As a result of the revision, if a depository institution chooses to suspend enforcement of the six transfer limit on a ''savings deposit,'' the depository institution may continue to report that account as a ''savings deposit'' or may instead choose to report that account as a ''transaction account.''

(3) *Report title:* Consolidated Report of Condition and Income for Edge and Agreement Corporations.

Agency form number: FR 2886b.

OMB control number: 7100–0086.

Applicable date: May 1, 2020.

Frequency: Quarterly and annually.

Respondents: Banking Edge and agreement corporations and investment (nonbanking) Edge and agreement corporations.

Estimated number of respondents: Banking Edge and agreement corporations (quarterly): 9; banking Edge and agreement corporations (annually): 1; investment Edge and agreement corporations (quarterly): 21; investment Edge and agreement corporations (annually): 7.

Estimated average hours per response: Banking Edge and agreement corporations (quarterly): 15.77 hours; banking Edge and agreement corporations (annually): 15.87; investment Edge and agreement corporations (quarterly): 11.81; investment Edge and agreement corporations (annually): 10.82.

Estimated annual burden hours: Banking Edge and agreement corporations (quarterly): 568; banking Edge and agreement corporations (annually): 16; investment Edge and agreement corporations (quarterly): 992; investment Edge and agreement corporations (annually): 76.

General description of report: The FR 2886b reporting form is filed quarterly and annually by banking Edge and agreement corporations and investment (nonbanking) Edge and agreement corporations (collectively, Edges or Edge corporations). The mandatory FR 2886b comprises an income statement with two schedules reconciling changes in capital and reserve accounts and a balance sheet with 11 supporting schedules. Other than examination reports, it provides the only financial data available for these corporations. The Federal Reserve is solely responsible for authorizing, supervising, and assigning ratings to Edges. The Federal Reserve uses the data collected on the FR 2886b to identify present and potential problems and monitor and develop a better understanding of activities within the industry.

Legal authorization and confidentiality: Sections 25 and 25A of the Federal Reserve Act authorize the Federal Reserve to collect the FR 2886b (12 U.S.C. 602, 625). The obligation to report this information is mandatory. The information collected on the FR 2886b is generally not considered confidential, but certain data may be exempt from disclosure pursuant to exemptions (b)(4) and (b)(7)(C) of FOIA, (5 U.S.C. 552(b)(4) and (b)(7)(C)). The information exempt from disclosure pursuant to (b)(4) consists of information provided on Schedule RC–M (with the exception for item 3) and on Schedule RC–V, both of which pertain to claims on and liabilities to related organizations. The information exempt from disclosure pursuant to exemption (b)(7)(C) is information provided in the Patriot Act Contact Information section of the reporting form.

Current actions: The Board has temporarily revised the instructions to the FR 2886b to update the definition of ''savings deposits'' in accordance with the amendments to Regulation D in the interim final rule published on April 28, 2020 (85 FR 23445). Specifically, the Board has temporarily revised the instructions on Schedule RC–E to remove the transfer and withdrawal limit from the definition of a savings deposit. Please note that this revision does not require any changes to the form itself. As a result of the revision, if a depository institution chooses to suspend enforcement of the six transfer limit on a ''savings deposit,'' the depository institution may continue to report that account as a ''savings deposit'' or may instead choose to report that account as a ''transaction account.''

Board of Governors of the Federal Reserve System, April 28, 2020.

Michele Taylor Fennell,

Assistant Secretary of the Board.

[FR Doc. 2020–09342 Filed 4–30–20; 8:45 am]

BILLING CODE 6210–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

[CDC–2020–0046; NIOSH–233–C]

Hazardous Drugs: Draft NIOSH List of Hazardous Drugs in Healthcare Settings, 2020; Procedures; and Risk Management Information

AGENCY: Centers for Disease Control and Prevention, HHS.

ACTION: Notice and request for comment.

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 announces that the following draft documents are available for public comment: (1) *NIOSH Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings (Procedures);* (2) *NIOSH List of Hazardous Drugs in Healthcare Settings, 2020* (*List*), including those drugs proposed for placement on the 2020 *List,* and (3) *Managing Hazardous Drug Exposures: Information for Healthcare Settings.*

DATES: Comments must be received by June 30, 2020.

ADDRESSES: Comments may be submitted, identified by docket numbers CDC–2020–0046 and NIOSH–233–C, by either of the following two methods:

- *Federal eRulemaking Portal: www.regulations.gov* Follow the instructions for submitting comments.
- *Mail:* NIOSH Docket Office, Robert A. Taft Laboratories, MS–C34, 1090 Tusculum Avenue, Cincinnati, OH 45226–1998.

Instructions: All information received in response to this notice must include the agency name and the docket numbers (CDC–2020–0046; NIOSH–233–C). All relevant comments received will be posted without change to *www.regulations.gov,* including any personal information provided.

FOR FURTHER INFORMATION CONTACT: Barbara MacKenzie, NIOSH, Robert A. Taft Laboratories, 1090 Tusculum Avenue, MS–C26, Cincinnati, OH 45226, telephone (513) 533–8132 (not a toll free number), email:*bmackenzie@cdc.gov.*

SUPPLEMENTARY INFORMATION:

I. Public Participation

A. Request for Comments

Interested parties are invited to participate in this activity by submitting

written views, opinions, recommendations, and/or data. Comments are invited on any topic related to the procedures and drugs identified in this notice, including three draft documents: (1) *NIOSH Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings (Procedures);* (2) *NIOSH List of Hazardous Drugs in Healthcare Settings, 2020* (*List*), including those drugs identified in this notice as being proposed for placement on the *List;* and (3) *Managing Hazardous Drug Exposures: Information for Healthcare Settings.* All three draft documents are available in the docket for this activity. NIOSH also invites comments specifically on the following questions related to 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.

B. February 2018 **Federal Register** *Notice*

In a **Federal Register** notice (FRN) published on February 14, 2018 (83 FR 6563), NIOSH invited the public to participate in the development of the *List* and the procedures used to develop the *List* by submitting written views, opinions, recommendations, and/or data. Comments were invited on any topic related to the drugs reviewed by NIOSH for possible placement on the planned 2018 version of the *List.* NIOSH also sought comment on a draft *Policy and Procedures for Developing the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings (Policy and Procedures).*[1]

Fifty-seven submissions were received in docket CDC–2018–0004 (NIOSH–233–B) from 55 commenters (one commenter sent three separate submissions to the docket). Commenters included pharmacists, professional organizations and associations, pharmaceutical manufacturers, medical centers and/or health systems, individuals who provided their names but not their affiliations, a company that provides risk assessments, a drug database, an insurance company, a medical school professor, a neurologist, and an anonymous commenter. NIOSH also conducted a peer review, with four independent reviewers, of the draft *Policy and Procedures.*[2]

Significant peer review and public comments on the draft *Policy and Procedures* are summarized and answered below in Section II; public comments on specific drugs are summarized and answered below in Section III.

NIOSH carefully considered all of the peer reviews and public comments and determined that significant, substantial changes should be made to the draft *Policy and Procedures,* the list of drugs proposed for placement on the *List,* and also to the organization of the *List* itself. The new drafts, entitled the *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings (Procedures)* and the *NIOSH List of Hazardous Drugs in Healthcare Settings, 2020* (*List*) are found in the Supplemental Materials tab of the docket and are available for public comment, as discussed above.

Public comments on the draft *Policy and Procedures* and the drugs proposed for placement on the *List* and peer review summaries on specific drugs proposed for placement on the *List* are available in dockets CDC–2018–0004 and NIOSH–233–B.

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

NIOSH created and periodically updates the *List* to assist employers in providing safe and healthful workplaces by offering a list of drugs that meet the NIOSH definition of a hazardous drug. In the February 2018 Request for Comment, NIOSH requested comment on a draft *Policy and Procedures* for developing the *List.* The draft *Policy and Procedures* document was developed to formalize the methodology NIOSH uses to guide the addition of hazardous drugs to the *List* and create a process for requesting the removal from or placement of drugs on the *List.* Four independent peer reviewers and 55 public commenters offered input on the draft *Policy and Procedures;* their substantive comments are summarized below, followed by NIOSH responses.

A. Peer Review Summaries and NIOSH Responses

NIOSH consulted four independent peer reviewers, who were asked to consider the following questions:

- Does the draft policy and procedures clearly describe the process used by NIOSH to screen and evaluate drugs?
- Are the screening and evaluation categorization processes described by the draft policy and procedures scientifically sound?
- Is the set of information sources used for classifying drugs sufficient to identify relevant hazards? Are there other information sources that should be included?
- Is the threshold of information required to move from the screening process to the full evaluation process clearly described? Is the information threshold scientifically sound?
- Is the reconsideration process for addition or deletion of a drug to/from the hazardous drug list adequately described?
- Are there any issues not considered by the charge questions that should be addressed?

Overall, the independent peer reviewers found the draft *Policy and Procedures* to be clearly written and supported by the available science and the reconsideration process (now referred to as ''reevaluation'') to be adequate. Two reviewers had questions about the information thresholds required to evaluate drugs, and all reviewers had editorial suggestions for improving the clarity of the draft. Peer reviews on the draft *Policy and Procedures,* as well as NIOSH's responses, are discussed below.

Scientific Approach

Peer review comment: Some paragraphs in the section entitled, ''Evidence of Health Effects in Workers from Handling Hazardous Drugs'' do not belong in the scientific approach section and should be moved to be part of section B ''Systematic and Sequential Methodology'' section.

Peer review comment: The frequency of review of the FDA database should be specified earlier in the draft.

NIOSH response: Although NIOSH typically reviews the FDA database on a monthly basis, the draft *Procedures* no longer specifies or indicates a frequency of database review to allow for flexibility in the event of unforeseen circumstances.

Peer review comment: NIOSH's discussion of an employer-performed site-based risk assessment to control the risk of exposure is confusing when placed in a document describing NIOSH's hazard identification procedures. The *Procedures* should state ''that this list is [a] hazard identification and not a risk assessment exercise. The subsequent description of a site risk

[1] As discussed later in this notice, NIOSH has revised the draft *Policy and Procedures* based on peer reviews and public comments. The new iteration is now referred to as ''draft *Procedures*'' throughout this notice.

[2] *See https://www.cdc.gov/niosh/topics/hazdrug/peer-review-plan.html* for the peer review plan for the draft *Policy and Procedures.*

assessment does not seem appropriate here. The last paragraph of this section is particularly confusing to the reader. . .''

NIOSH response: NIOSH is reorganizing and streamlining the document to make it more easily understood and to move information on site risk assessment to a separate draft document, *Managing Hazardous Drug Exposures: Information for Healthcare Settings.* The draft *Procedures* document is now focused on NIOSH's procedure for identifying hazardous drugs and no longer discusses managing the risk of exposure.

Peer review comment: NIOSH should add ''administrative controls'' when discussing engineering controls, personal protective equipment, and other steps to manage the risk of exposure, because of their significance ''in the well-accepted hierarchy of controls for minimizing exposure to workplace hazards.''

Peer review comment: NIOSH should list further tools to aid employers to protect workers.

NIOSH response: In streamlining the document to make it more focused on NIOSH's procedures for identifying hazardous drugs, information on controlling the risk of hazardous drug exposure in the workplace was moved to the draft NIOSH document *Managing Hazardous Drug Exposures: Information for Healthcare Settings.*

Application

Peer review comment: NIOSH should mention ''some other common healthcare job categories that are likely to be exposed . . . From my perspective, as a minimum, this should include porters, ward aides and unit clerks.''

NIOSH response: Because the draft *Procedures* document only addresses NIOSH's procedure for identifying hazardous drugs, the ''Application'' section is removed. Information about the application of the *List* can be found in the introduction of the draft *Managing Hazardous Drug Exposures: Information for Healthcare Settings.* However, rather than identifying job-specific titles, the document focuses on workplace activities.

Definitions

Peer review comment: NIOSH did not include a mechanism to place investigational drugs on the *List.* There seems to be no ''mechanism in place for labeling investigational (*i.e.,* non-FDA approved drugs used in preclinical and clinical research prior to submission of an NDA [new drug approval]) drugs as potential human health hazards. Although such drugs are not in widespread clinical use, personnel in academic and research-oriented facilities are potentially at risk from exposure to these drugs. . . . the document speaks to the need for individual healthcare workplaces to create their own lists of hazardous drugs, but this places the burden of regulation on these institutions themselves, or more likely individuals within these institutions. I wonder whether the current regulatory climate permits NIOSH any level of control over the handling of drugs in this category.''

NIOSH response: Drugs still under investigation are not included on the *List* because no scientific information, including information normally provided in package inserts, is available for NIOSH review. Accordingly, the *List* is derived only from drugs approved by FDA's Center for Drug Evaluation and Research. For this reason, NIOSH encourages individual healthcare settings to develop their own formulary-specific lists of hazardous drugs, which could include investigational drugs that have not yet been approved by FDA.

Identifying, Screening, Evaluating, and Reviewing a Drug for Placement on the *List:* Screening Potentially Hazardous Drugs

Peer review comment: It may be inappropriate for NIOSH not to place drugs on the *List* when NIOSH has determined there is insufficient information to support the placement. According to the reviewer, ''[t]his approach may not be appropriate if indeed the purpose of the screening is to protect the health and well-being of workers who may be exposed to hazardous drugs. From an occupational hygiene perspective, if there is no existing occupational exposure limit or threshold limit value for a chemical hazard, the best practice is to ensure that worker exposure to the chemical remains As Low As Reasonably Achievable (ALARA). This is because there is insufficient information to establish an exposure limit and, therefore, one should err on the side of caution and apply the ALARA principle. Employing this same train of thought to the draft policy and procedures, it would, in my opinion, be a best practice to add the drug that has insufficient information to the *List* until suitable scientific evidence demonstrates that it should not be included.''

NIOSH response: FDA-approved drugs generally have a reasonable body of toxicity information because the manufacturers are required by FDA to provide this information to ensure patient safety when seeking approval for their drugs. The FDA requirements for tested and reported endpoints generally overlap with the NIOSH definition of a hazardous drug. The fact that FDA has requirements for reporting of relevant safety related data supports the NIOSH presumption that a lack of information on an endpoint indicates a lack of concern for a specific type of hazard.

Peer review comment: A statement about the evaluation procedures in the draft *Policy and Procedures* indicates that NIOSH would only consider human studies. '''When available, published, peer-reviewed scientific literature about the hazard potential of a particular drug, including any studies cited in the package insert that are relevant to workers in a health care setting.' This clearly infers human studies only. However, the remaining parts of the draft policy and procedures mentions that animal studies should be reviewed . . . . It is unclear why animal studies were not included as a source of evaluating potentially hazardous drugs. In my opinion, a review of any animal studies should be conducted as they may offer insight regarding the potential risk posed by a drug. As such, the use of animal studies to evaluate the hazardous nature of a drug should be explicitly stated.''

NIOSH response: The reviewer has interpreted the NIOSH statement differently than what the agency intended. Animal studies, where available, are also used in our evaluations. The draft *Procedures* document is being reorganized to clarify the information NIOSH considers in its evaluations, including relevant animal studies.

Peer review comment: NIOSH should consider a more detailed process when evaluating study quality because ''[t]he issue related to the quality of a study and, in turn, the strength of data *i.e.* relative risk, odds ratios, *etc.* is not clearly outlined with respect to the evaluation process. Drawing conclusions from a methodologically flawed paper can lead to misclassification of a drug. In addition, having an algorithm to determine the strength of a paper will also aid in minimizing any potential inter- and intra-reviewer differences. Although there is currently some guidance in the footnotes, it may be worthwhile to consider a more detailed evaluation process of relevant studies and place it in a more prominent location in the document or possibly as an Appendix.''

NIOSH response: The majority of drug evaluations are based on information provided in the drug package insert; NIOSH relies on the quality of science

generated by a drug manufacturer, subsequently reviewed by FDA during the drug approval process, and then published in the drug package insert. Peer-reviewed, published studies are usually not available and therefore evaluating the quality of studies is not typically possible. When studies are available for review of a drug being considered for placement on the *List* or for the reevaluation of a drug already on the *List,* quality may be evaluated by NIOSH scientists and independent peer reviewers on a case-by-case basis. In the case of a drug being reevaluated, conclusions about study quality would be discussed in a notice published in the **Federal Register**.

Peer review comment: NIOSH should provide ''a more robust description of the evaluation criteria to include that these are shared across a number of other professional organizations and panels which also endorsed these same criteria.''

NIOSH response: The NIOSH *List* is adopted, endorsed, and/or referenced by a number of non-governmental organizations, including the American Society of Health-System Pharmacists (ASHP), The Joint Commission, and the Oncology Nursing Society.

Because the organizations that may endorse the evaluation criteria may change, NIOSH declines to identify them in the *Procedures* document.

Peer review comment: NIOSH should offer an example of why a drug identified as a hazardous drug because it poses as carcinogenic hazard might not be a classified as a carcinogen pursuant to the NIOSH *Chemical Carcinogen Policy.*

NIOSH response: A drug may be considered a hazardous drug but not a chemical carcinogen if, for example, a drug manufacturer includes a carcinogenicity warning in the drug's package insert but the evidence for carcinogenicity has not been reviewed by the International Agency for Research on Cancer (IARC); the National Toxicology Program (NTP), within the U.S. Department of Health and Human Services; the U.S. Environmental Protection Agency (EPA); or independently by NIOSH. In that case, NIOSH may consider it to be appropriately grouped with carcinogenic drugs, although it would not necessarily meet the criteria for an occupational carcinogen according to the NIOSH *Chemical Carcinogen Policy.*

Peer review comment: NIOSH should clarify ''how the threshold dosages (10 mg/day or 1 mg/kg/day) for defining organ toxicity at 'low doses' . . . were derived. . . . Are these standard or commonly accepted definitions of 'low dose' exposure? Is there a scientific justification for them? If so, perhaps this could be referenced with a footnote.''

NIOSH response: The daily therapeutic dose at which serious organ toxicity, developmental toxicity, or reproductive toxicity occurs (10 mg/day in human adults and 1 mg/kg per day in laboratory animals) has long been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 μg/m^3 after applying appropriate uncertainty factors.[3] OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. NIOSH is adding text in footnote 16 of the draft *Procedures* to clarify and emphasize the derivation.

Peer review comment: NIOSH should clarify a sentence concerning NIOSH's preference for human genotoxicity data which states: ''If available, NIOSH gives preference to those studies. . .''

NIOSH response: This refers to human genotoxicity studies, which are rarely available. If available, NIOSH would give preference to them over animal and in vitro studies. NIOSH is adding text to clarify the agency's intent.

Peer review comment: ''Following the 60-day period to allow for public and stakeholder consultations, it is unclear if NIOSH will be responding to any parties that have provided comments. On the contrary, if a party submits a written request for reconsideration, NIOSH will be responding in these instances. One would assume that, in both instances, a great deal of time and thought is expected to provide feedback to NIOSH. It would presumably be courteous to respond to any party that has provided comments for consideration.''

NIOSH response: It is NIOSH practice to respond to all stakeholder and public comments and peer reviews in a **Federal Register** notice or in a document posted in the relevant NIOSH docket, to maintain a transparent and thorough administrative record.

Reconsideration (Reevaluation) of NIOSH Decisions to Place and Remove Drugs

Peer review comment: NIOSH should clarify whether a drug may be removed from the *List* based on changes to the package insert, ''or if written requests from interested parties to the NIOSH Director are the only mechanism for consideration of a drug for deletion from the *List* (the reconsideration process as described). If the latter is the case, could a sentence be added to clarify that?''

NIOSH response: A drug may be removed from the *List* based on either a written request from an interested party or a change to the package insert. Although rare, NIOSH notes any labeling changes that could affect the status of a drug that has been previously classified as hazardous. No labeling change has ever resulted in the removal of a drug from the *List,* but labeling changes that demonstrate a lack of evidence of toxicity would be dealt with in the regular *List* updates.

Only when a labeling change results in the addition of MSHI to a package insert will NIOSH automatically consider the drug to be a hazardous drug and add it to the *List.*

B. Public Comment Summaries and NIOSH Responses

The public comments have been organized into the following topic areas: organization of the *List* and impact of *United States Pharmacopeia (USP) Compounding Compendium* chapter <800≤ Hazardous Drugs—Handling in Healthcare Settings; the nature of the *List*—exposure/hazard characterization; monoclonal antibodies; periodicity; methodology/process; criteria clarification; and editorial suggestions.

Organization of the *List* and Impact of USP <800≤ Hazardous Drugs—Handling in Healthcare Settings

Seven commenters expressed concern about the impact of USP <800≤ on the NIOSH *List,* and, in turn, the effect on small pharmacies that compound pharmaceutical drugs. USP <800≤ incorporates by reference the NIOSH *List* and imposes certain requirements on its users when handling certain drugs on the *List.* The individuals and organizations who commented on this issue felt that USP's use of the NIOSH *List* raises the *List* to the level of a regulatory action, and should include only antineoplastic drugs on Table 1.

Comment: Prior to USP <800≤, the NIOSH *List* was considered a ''precautionary recommendation.'' But the USP <800≤ standards are too restrictive and overreaching, and the chapter's incorporation into state law places facilities at legal risk if they fail to comply. The ordering of the tables in the *List* implies risk stratification; USP <800≤ supports this impression by requiring heightened handling requirements for Table 1 drugs. Because

[3] Sargent EV and Kirk GD [1988], *Establishing Airborne Exposure Control Limits in the Pharmaceutical Industry,* Am Ind Hyg Assoc J 49(6):309–13; Naumann BD and Sargent EV [1997], *Setting Occupational Exposure Limits for Pharmaceuticals,* Occup Med 12(1):67–80; 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.

Table 1 includes drugs identified as antineoplastic, NIOSH should clarify the rationale and intent of Table 1, since drugs used as antineoplastics, but which are not cytotoxic or genotoxic, as traditional antineoplastics are, have been included. Moreover, USP <800≤ requires the use of personal protective equipment for Table 1 drugs, which may delay care or undermine patient safety. NIOSH should collaborate with healthcare to better understand the implications of identifying certain drugs as hazardous and the cost to implement USP <800≤.

NIOSH response: The NIOSH *List* creates no legal obligation for its users; it is informational, not regulatory, in content. USP added clarification about the application of chapter <800≤ to hazardous drugs, which can be found on its FAQ page.[4]

In response to peer reviews and public comments, NIOSH proposes a reorganization of the tables in the draft 2020 *List* in a manner that may address at least some of the concerns expressed. Because the way cancer is treated therapeutically has changed, and the classes of drugs used to fight cancer have changed, antineoplastic drugs are no longer all cytotoxic or genotoxic. Furthermore, some drugs carry multiple American Hospital Formulary Service (AHFS) code classifications and are not solely used as antineoplastic drugs. Therefore, when antineoplastic drugs are grouped as they were in earlier versions of Table 1 of the *List,* an appearance that these drugs pose the same hazard was inadvertently created (*i.e.,* non-cytotoxic drugs with cytotoxic drugs). NIOSH determined that grouping all antineoplastic drugs together in one table is no longer the most useful or informative for the user. In light of these changes, NIOSH proposes a new *List* structure, described in the preamble to the draft *List,* which is available for review in the docket for this activity. Changes to the *List* structure would place all drugs that meet the NIOSH definition of a hazardous drug and contain MSHI in the package insert and/or are classified by the National Toxicology Program (NTP) as ''known to be a human carcinogen,'' or classified by the International Agency for Research on Cancer (IARC) as ''carcinogenic'' or ''probably carcinogenic'' on Table 1. Table 2 would now contain drugs that meet one or more of the NIOSH hazardous drug criteria and may be developmental and/or reproductive developmental toxins but are not drugs which have MSHI or are classified as carcinogens or probable carcinogens by NTP or IARC. Table 3 would be removed and the drugs formerly placed in that table placed into Table 1 or 2, accordingly.

Realistic Risk of Occupational Exposure

Nine commenters expressed the sentiment that the *List* would be more useful if it identified drugs that pose a realistic risk to healthcare workers.

Comment: NIOSH should identify those drugs that pose a realistic risk to healthcare workers by considering such occupation exposure factors as drug type (*e.g.,* small molecule, biologic), stability, dosage form, and route of exposure, and then evaluating them against the toxicity criteria. Not refining the *List* to identify real risks of occupational exposure could lead to ''overwarning'' for drugs that present little or no workplace risk.

NIOSH response: Compilation of the *List* is a hazard identification and hazard characterization process, as described in the draft *Procedures.* The draft *Procedures* considers the toxicity criteria in the definition of a hazardous drug to identify the hazard and some intrinsic molecular properties to characterize the hazard [5] when determining the potential for adverse health effects of hazardous drugs in healthcare workers. Risks associated with how and how often a hazardous drug is used in a particular setting, and evaluation of exposure factors for all occupational exposures is beyond the scope of the *List.* The draft *Managing Hazardous Drug Exposures: Information for Healthcare Settings,* which is in the docket for this activity, is intended to assist employers in establishing their own hazardous drugs management procedures specific to their workplace.

Monoclonal Antibodies

Seven commenters opposed the inclusion of biological drug products (monoclonal antibodies) on the *List.*

Comment: The language in the section titled ''Application'' indicates that the draft *Policy and Procedures* do not apply to healthcare workers who handle recombinant therapeutic proteins. Therefore, all recombinant therapeutic proteins should be excluded from the *List* unless ''science-based or product-specific circumstances dictate otherwise.''

Comment: Monoclonal antibodies (*i.e.,* therapeutic proteins) are of such a large molecular weight that they do not pose a realistic risk to healthcare workers. For example, monoclonal antibodies ''are too large to be absorbed through skin contact, and if ingested, they would be destroyed by digestion; if inhaled, the pulmonary system would prevent absorption. Consequently, these drugs are all administered by injection. The only potential risk to healthcare workers is of an accidental needle stick, which would not inject a pharmacologically active dose.'' Accordingly, the monoclonal antibodies bevacizumab, blintumomab, and trastuzumab should not be placed on the *List,* and pertuzumab should be removed from Table 1.

Comment: The draft *Policy and Procedures* should include a methodology describing how NIOSH evaluates monoclonal antibodies.

NIOSH response: NIOSH applies the same methodology for evaluating each drug approved by the FDA Center for Drug Evaluation and Research, regardless of class. The definition of a hazardous drug in the draft *Procedures* recognizes that the molecular properties of a drug, such as the molecular weight, may substantially limit the potential for adverse health effects. NIOSH may consider molecular weight along with the other intrinsic molecular properties of a drug that affect the hazard a drug poses. While some large molecular weight drugs may have low bioavailability by relevant routes of exposure, other factors in the characterization of the hazard are considered as well. Therefore, in accordance with the draft *Procedures* some monoclonal antibodies may not meet the NIOSH definition of the term ''hazardous drug.'' Because the list of drugs proposed for placement on the *List* has been updated based on the draft *Procedures,* the monoclonal antibodies bevacizumab and trastuzumab are no longer proposed for placement on the *List.* Blinatumomab continues to be proposed for placement and other monoclonal antibodies that have properties meeting the NIOSH definition of a hazardous drug will remain on the *List.*

Periodicity

Three commenters offered opinions on the timeliness of the *List,* which NIOSH has attempted to publish every 2 years since 2010.

Comment: The *List* seems to be heavily weighted toward older drugs.

[4] *See* USP, *FAQs: <800≤ Hazardous Drugs—Handling in Healthcare Settings, https://www.usp.org/frequently-asked-questions/hazardous-drugs-handling-healthcare-settings.*

[5] *See* draft *Procedures* footnote 18, ''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), distribution, metabolism, and/or elimination *e.g.,* chemical structure, molecular weight or mass.''

NIOSH response: The *List* is about 4 years behind the introduction of new drugs when it is periodically updated because there are several steps in the review process. NIOSH appreciates that a timelier *List* might be helpful and is working toward that end. The current *List* created by NIOSH requires an extensive review process that does not readily allow more frequent publication. That said, when NIOSH becomes aware of new drugs with MSHI, NIOSH identifies such drugs on the web page for the current *List* to immediately alert stakeholders. The inclusion of MSHI makes such drugs automatically hazardous under the NIOSH definition and thus, the extensive review process is not required.

Comment: FDA-approved drugs should be reviewed in real time or NIOSH should provide ''off-cycle'' updates to the *List.*

NIOSH response: The *List* is updated any time NIOSH is aware that a drug manufacturer has added special handling information to the patient information for a specific drug. For example, three drugs were added to the 2016 *List* after it was initially published; they are identified on the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016* web page, *https://www.cdc.gov/niosh/docs/2016–161/default.html.* NIOSH's extensive review process only allows for periodic updates of hazardous drugs that do not have MSHI.

Methodology/Process

Seven commenters asked questions and offered suggestions about the procedures themselves.

Comment: The methodology used to develop the list of drugs proposed for placement on the *List* was not the same as the methodology used in previous years.

NIOSH response: In 2004, NIOSH used lists from several organizations as examples of hazardous drugs. In 2010, NIOSH first updated the *List* based on the NIOSH definition of a hazardous drug. The draft *Policy and Procedures* used to develop the drugs proposed for placement on the *List* in the February 2018 FRN described the methodology used by NIOSH since 2010. The draft *Procedures* reflects peer review and public comment; the list of drugs proposed for placement on the *List* has been updated based on the revised draft *Procedures.*

Comment: NIOSH should conduct or commission a meta-analysis or systematic review, ''[i]n the absence of published literature synthesizing the body of clinical knowledge'' about a specific drug.

NIOSH response: A systematic review is a significant undertaking requiring the prior publication or dissemination of multiple studies relating to a specific drug. In very few cases, if any, would sufficient studies be available to conduct a formal meta-analysis relating to a specific drug. NIOSH will consider conducting a systematic review if such studies become available relating to the hazard that a specific drug may pose in healthcare settings.

Comment: What is the mechanism for evaluating investigational new drugs (*i.e.,* drugs used in preclinical and clinical research but not yet FDA-approved)?

NIOSH response: Drugs still under investigation are not included on the *List* because no scientific information, including information normally provided in package inserts, is available for NIOSH review. Accordingly, the *List* is derived only from drugs approved by FDA's Center for Drug Evaluation and Research. NIOSH does not review drugs that are not yet approved for use in humans. NIOSH does not review biologics reviewed by the FDA Center for Biologics Evaluation and Research.

Comment: Peer reviews should be conducted before the close of the public comment period to allow public commenters time to review them. Not allowing public commenters to review peer reviews before submitting their own comments to the docket is ''in conflict with the principle of transparency'' established in the OMB *Final Information Quality Bulletin for Peer Review* (70 FR 2664, Jan. 14, 2005).

NIOSH response: NIOSH views peer review and public comment as two distinct, often complementary, tools in ensuring both quality and transparency in influential scientific information products. As stated in the OMB *Final Information Quality Bulletin for Peer Review* (Bulletin), ''[p]eer reviewers shall be charged with reviewing scientific and technical matters. . .'' whereas public comment, including stakeholder review, often provides NIOSH with crucial feedback on how a project or publication may impact the interests of employees, stakeholder organizations, or other parties. While the Bulletin recognizes the benefit of both forms of input to agencies, it provides agencies with broad discretion in determining how to implement peer review, including timing as it relates to public comment, if applicable. NIOSH does not offer peer reviews for public comment for any scientific publications because the technical and scientific review conducted by independent peer reviewers are not NIOSH products.

Comment: The draft *Policy and Procedures* should provide the drug manufacturer with ''transparent documentation as to the basis of adding a drug to the *List.*'' Without a thorough understanding of the basis for adding a drug, the drug manufacturer may not be able to formulate a request for reconsideration of the drug.

NIOSH response: The rationale for proposing the placement of each drug to the *List* is provided in the **Federal Register** notice preceding the final *List* publication. The manufacturer or any other stakeholder is invited to comment on the sufficiency of the explanation of the basis for adding a drug to the *List.*

Comment: Providing sufficient information to rebut a NIOSH determination to add or not add a drug to the *List* is difficult for healthcare organizations.

NIOSH response: For reevaluation of a listed drug, NIOSH does not require requestors to provide a complete analysis of the available evidence. The requestor need only provide some new information that is relevant to the issue of whether the drug does or does not meet the NIOSH definition of a hazardous drug or the decision to place a drug on a particular table in the *List.* NIOSH will begin the reevaluation process for any request to add or remove a drug that provides some new supporting evidence by searching for additional hazard identification (toxicity) and hazard characterization information about the drug that is relevant to the criteria set out in the NIOSH definition of a hazardous drug.

Criteria Clarification

Six commenters were critical of the methodology NIOSH described for adding drugs to the *List* and asked that NIOSH clarify the language in certain sections of the draft *Policy and Procedures.*

Comment: NIOSH should include the professional qualifications of the NIOSH staff who perform these evaluations.

NIOSH response: NIOSH relies on a range of knowledge, experience, and skills to evaluate drugs for placement on the *List,* including but not limited to pharmacology, toxicology, medicine, and risk evaluation. The specific backgrounds of the professional staff engaged in the evaluation process may change over time, but NIOSH is committed to a high-quality process conducted by a team of professionals with the needed knowledge and experience. Additionally, peer reviews provide the Agency with a review of its science; peer reviewers and their credentials are identified in the NIOSH Peer Review Agenda.

Commenters: NIOSH should identify the criteria used to evaluate study quality and strength, and describe how they are used to critically appraise the quality and risk of bias and other limitations of individual studies; arbitrate conflicting information; and synthesize the totality of animal and human studies data in support of, or opposition to, the listing of a drug as ''hazardous.''

NIOSH response: The majority of these evaluations are based on the information provided in the drug package insert; thus, NIOSH relies on the quality of science generated by a drug manufacturer, subsequently reviewed by FDA during the drug approval process, and then published in the drug package insert. When studies are available for review of a drug being considered for placement on the *List* or for the reevaluation of a drug already on the *List,* quality may be evaluated by NIOSH scientists and independent peer reviewers on a case-by-case basis. In the case of a drug being reevaluated, conclusions about study quality would be discussed in a **Federal Register** notice.

Comment: While NIOSH describes several Bradford Hill criteria [6] used to evaluate information from human studies in footnote 44 of the draft *Policy and Procedures,* no rationale is offered to explain why many of the original nine Bradford Hill criteria are not used. Moreover, caution should be taken when making determinations about potentially hazardous drugs because causality is not necessarily demonstrated by a strong association just as absence of causality is not necessarily demonstrated by weak associations; associations that demonstrate a monotonic trend in health outcome frequency (steadily increasing or decreasing without ever changing direction) are not necessarily causal if a confounding factor demonstrates a dose-response relationship with the health outcome; and prior beliefs should not be allowed to cloud judgment with regard to plausibility. NIOSH should clarify the criteria described in the footnote and explain how evidence against these various criteria is evaluated, how each independent line of evidence is systematically and critically appraised, how the quality and risk of bias of individual studies is evaluated, how conflicting information is arbitrated, and how the totality of the data is synthesized.

NIOSH response: NIOSH uses the subset of Bradford Hill criteria which are most useful for evaluating human study results on hazardous drugs. The most important criteria for the review of human studies are strength of association, temporality, plausibility, and biological gradient.

Comment: In the draft *Policy and Procedures* footnote 45, NIOSH lists criteria used to evaluate information from animal studies. It is unclear if NIOSH will conduct meta-analyses to test for consistency of results; how NIOSH will interpret evidence for, or absence of, concordance across species or between structural analogs of the drug; whether NIOSH will conduct categorical regression analyses to evaluate dose-response data; and how NIOSH evaluates routes of exposures. Furthermore, animal studies must be evaluated for the recovery/reversibility of effects and the pharmacological relevance of the species studied. NIOSH must add criteria for animal studies to include the recovery/reversibility of adverse effects and the pharmacological relevance of the test species.

NIOSH response: NIOSH has not conducted a formal meta-analysis or systematic review for any drug currently on the *List.* In very few cases, if any, would sufficient studies be available to conduct a formal meta-analysis relating to a specific drug. Accordingly, NIOSH primarily uses information available in the package inserts to make determinations about whether to place a drug on the *List.* NIOSH may conduct a meta-analysis or systematic review when reevaluating the placement of a drug already on the *List,* if the available evidence warrants such a review. In that case, important criteria for animal studies include strength of association; consistency between studies; relevance of the model system and routes of exposure; the duration, reversibility, and recoverability of the observed effects; and concordance of those effects with effects in humans. If a meta-analysis or systematic review is warranted for a reevaluation, NIOSH would consider these criteria on a case-by-case basis. Under the draft *Procedures,* NIOSH's rationale, including a description of any meta-analysis or systematic review if performed, and final determination would be described in a notice published in the **Federal Register**.

Comment: It is unclear how NIOSH interprets evidence of increasing progression or severity with increased dose, and how the value for ''low dose'' was derived. Specifically, whether NIOSH conducts categorical regression analyses to evaluate dose-response data for severity. The value for ''low dose'' should be drug-specific and a function of several factors such as normal therapeutic doses, body weight, and length of exposure.

NIOSH response: The daily therapeutic dose at which serious organ toxicity, developmental toxicity, or reproductive toxicity occurs (10 mg/day in human adults and 1 mg/kg per day in laboratory animals) has long been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 $\mu g/m^3$ after applying appropriate uncertainty factors.[7] OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. NIOSH is adding text in footnote 16 of the draft *Procedures* to clarify and emphasize the derivation.

Comment: NIOSH should clarify how close chemical analogs are identified, and whether NIOSH establishes site concordance across analogs and how evidence for and against the absence of concordance is interpreted. Similar questions were raised about animal studies.

NIOSH response: NIOSH examines chemical analogs based on similarities in a drug's structure and toxicity profile compared with other drugs on the *List.* Often the mechanism of action for the drug being assessed is known and can be compared to other drugs of a similar structure/activity. This criterion is typically only used when toxicity information specific to the drug under evaluation is insufficient or unavailable but is available for the chemical analog.

Comment: Hazardous drugs should also be identified by UNII code (the unique ingredient identifier used by FDA and USP) on the *List.*

NIOSH response: There are several methods for identifying active pharmaceutical ingredient compounds, including Chemical Abstract Service Registry number (CAS) and UNII. At this time, NIOSH has chosen not to list any of the identification numbers but is considering doing so in the future. NIOSH encourages public input on the question of which ingredient identifier may be the most useful for the *List.*

Editorial Suggestions

Two commenters offered editorial suggestions for clarifying language in the draft; although the comments are not summarized here, changes were made to the revised draft *Procedures* as appropriate.

[6] Aschengrau A, Seage GR [2018], *Essentials of Epidemiology in Public Health. 4th Edition,* (Burlington, MA: Jones & Bartlett).

[7] *See supra* note 3.

C. Draft Procedures: Summary of Changes

NIOSH considered peer review and public comment received in response to the February 2018 FRN, and significantly revised the draft *Policy and Procedures;* that document is now called *Procedures.* These changes now reflected in the draft *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings* (draft *Procedures*) include the clarification of some language and streamlining the procedures NIOSH uses to determine the hazard potential of a specific drug. Most importantly, the definition of the term ''hazardous drug'' would now acknowledge that ''hazard characterization'' is an important factor for drugs under consideration. Section C of the draft *Procedures,* which includes the evaluation criteria, would be expanded to include new clauses 4 and 5 to allow NIOSH to consider additional factors beyond the intrinsic toxicity of the drug molecule in determining whether to place the drug on the *List.* The draft *Procedures* is in the docket for this activity.

III. The NIOSH List of Hazardous Drugs in Healthcare Settings, 2020

A. Public Comment Summaries and NIOSH Responses

As discussed extensively in the notice published February 14, 2018, NIOSH identified 275 potentially hazardous drugs between January 2014 and December 2015 (83 FR 6563). Of the 275 drugs identified during that timeframe, two had special handling information specified by the manufacturer (MSHI) and were automatically placed on the *List.* The other 273 were screened and the information available for 44 drugs suggested one or more toxic effects; those drugs were evaluated by NIOSH and shared with peer reviewers and stakeholders. After considering the peer and stakeholder reviews, NIOSH determined that 20 drugs and one class of drugs exhibit toxicity that meets the NIOSH definition of a hazardous drug and proposed them for placement on the *List.* The two drugs with MSHI that were placed on the *List* and the 20 drugs and one drug class proposed for placement on the *List* were identified in the February 14, 2018 notice, along with NIOSH's rationale for each proposed addition. A new peer review was not conducted. Public comments on the drugs and drug class proposed for placement on the *List* in 2018 are summarized and answered below.

Do Not Place Drug on the *List*

Comment: Botulinum toxins, including abobotulinumtoxinA and onabotulinumtoxinA, should not be placed on the *List.* Botulinum toxins do not meet the criteria for placement on the *List;* abotulinumtoxinA and rimabotulinumtoxinB did not have labeling changes during the search period January 2014 through December 2015, and changes to the labels for onabotulinumtoxinA and incobotulinumtoxinA do not meet the criteria for organ toxicity at low doses or teratogenicity or other developmental toxicity. Moreover, NIOSH is not properly weighing the low therapeutic index of the drug against the relatively low risk of handling the drug by healthcare workers who are knowledgeable about safe handling. According to the safety data sheets for botulinum toxins, no engineering controls or respiratory protective devices are required for safe handling.

NIOSH response: NIOSH reviews the relevant data on a drug when a label change is made, not just the data relating to the label change. However, after consideration of input from the public and stakeholders, NIOSH has decided to review the toxicity and the hazards related to occupational exposure to botulinum toxins. Therefore, at this time NIOSH is no longer proposing to place the class of botulinum toxins on the 2020 *List.* Any additional information from any interested party that will assist with further reviews of the botulinum toxins will be reviewed for potential placement on the *List* in the future.

Comment. Darbepoetin alfa should not be placed on the *List.* This drug poses no risk to healthcare workers; the evidence supporting its addition is not based on occupational exposure. The large molecular size limits dermal absorption and aerosolization. The drug's mechanism of action does not indicate DNA damage.

NIOSH response: NIOSH concurs with commenters that the evidence of carcinogenicity for darbepoetin alfa in patients who did not already have cancer was insufficient to support a NIOSH finding of carcinogenicity. In addition, darbepoetin alfa did not meet the NIOSH criteria for a hazardous drug based on any other toxicity endpoint. Accordingly, darbepoetin alfa is no longer proposed for placement on the 2020 *List.*

Comment: Dihydroergotamine should not be placed on the *List.* The safety data sheet for this drug indicates that it does not pose a heightened risk to healthcare workers.

NIOSH response: NIOSH has determined that dihydroergotamine has demonstrated reproductive toxicity in experimental animals. In embryo-fetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses approximately 0.4–1.2 times the exposures in humans receiving the maximum recommended daily dose of 4 mg or greater. Accordingly, NIOSH proposes to place dihydroergotamine on the *List.*

Comment: Exenatide should not be placed on the *List.* NIOSH did not take into account the real risk of occupational exposure or the mechanism of action of this relatively large molecule. The size of the molecule limits dermal absorption and aerosolization.

NIOSH response: While some drugs may have low bioavailability by relevant routes of exposure due to molecular weight, other factors in the characterization of the hazard are considered as well. NIOSH has determined that exenatide extended-release caused a dose-related and treatment-duration–dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats. In mice, doses near the maximum recommended human dose lead to increased neonatal death. In rats, exenatide administered during the period of organogenesis reduced fetal growth and produced skeletal ossification deficits at doses that approximate the maximum recommended human dose. Accordingly, NIOSH proposes to place exenatide on the *List.* Polypeptides of this size and larger have been shown to have bioavailability through relevant routes of exposure. Because dosage forms can change and new dosage forms may be approved, dosage form is not considered in making *List* placement determinations.

Comment: Interferon beta-1b should not be placed on the *List,* or, in the alternative, it should only be placed on Table 3. The rationale for placing interferon beta-1b on the *List* is that information from the package insert indicated reproductive toxicity: spontaneous abortion in human clinical trials. Data evaluation submitted to the docket by the manufacturer demonstrates that interferon beta-1b is not causally associated with spontaneous abortion or with any ''patterns or signals suggesting pregnancy outcomes.'' Research on

populations who have received interferon beta-1b throughout pregnancy have demonstrated no difference in spontaneous abortions or birth weight compared to population comparators.

NIOSH response: The manufacturer provided information indicating that multiple evaluations of pregnancy registries did not provide any signals suggesting negative pregnancy outcomes associated with interferon beta-1b. Accordingly, NIOSH has determined that interferon beta-1b does not meet the criteria for a hazardous drug and is no longer proposing to place it on the *List.*

Comment: Ivabradine should not be placed on the *List.* This drug is administered as a coated tablet, self-administered by the patient at home; as such, ivabradine poses no risk to healthcare workers.

NIOSH response: NIOSH has determined that reproductive effects were observed in pregnant rats at doses near the equivalent maximum recommended human dose. Drugs are placed on the *List* based on their intrinsic properties. Because dosage forms can change and new dosage forms may be approved, dosage form is not considered in making *List* placement determinations. Accordingly, NIOSH continues to propose placing ivabradine on the *List.*

Comment: Olaparib should not be placed on the *List* because the risk to direct occupational healthcare worker exposure is anticipated to be minimal when handling intact olaparib capsules.

NIOSH response: NIOSH has determined that teratogenicity occurred in rats at doses approximately 0.3 percent of therapeutic doses in humans. Accordingly, NIOSH proposes to place olaparib on the *List.* Because dosage forms can change and new dosage forms may be approved, dosage form is not considered in making *List* placement determinations.

Comment: Osimertinib should not be placed on the *List.* Embryo-fetal toxicity is shown to happen at dose exposure 1.5 times the recommended ingested human dose of 80 mg; it is unlikely that a healthcare worker would accidentally be exposed to osimertinib during handling at levels found to cause embryo-fetal harm. In addition, there are no reports of teratogenicity, developmental toxicity, embryo-fetal toxicity, lethality, or reduced growth in clinical trials conducted in humans, or in real world use since FDA approval in 2015.

NIOSH response: NIOSH has determined that teratogenicity or other developmental toxicity after exposure to osimertinib were observed at doses higher than the maximum recommended human dose and reproductive effects at doses lower than the maximum recommended human doses were equivocal. Therefore, NIOSH no longer proposes to place osimertinib on the *List.*

Comment: Triazolam should not be placed on the *List.*

NIOSH response: NIOSH's rationale for proposing the placement of triazolam on the *List* was that it mimics the benzodiazepines which are included on the *List* because they are teratogenic or cause other developmental effects. However, NIOSH did not independently evaluate triazolam. After review, NIOSH now finds that the information in the package insert for this drug does not support a determination that it presents a hazard to healthcare workers and is no longer proposing to place it on the *List.*

Place Drug on the *List*

Comment: NIOSH indicated that two drugs—daratumumab and dinutuximab—demonstrated insufficient toxicity information available to meet the NIOSH definition of a hazardous drug. Both drugs should be placed on the *List* because information available in the respective package inserts indicates that both drugs may cause teratogenic effects. NIOSH should provide the rationale for not proposing their placement on the *List.*

NIOSH response: As presented in the 2018 FRN, daratumumab and dinutuximab were reviewed and did not meet the NIOSH criteria for a hazardous drug because the available information about each drug's toxicity was insufficient to support placement on the *List.* There are no human studies relating to the developmental effects of daratumumab or dinutuximab. No animal studies have been performed regarding developmental effects of daratumumab or dinutuximab. Accordingly, NIOSH is not proposing to place these two drugs on the *List.*

Comment: NIOSH indicated that 10 drugs—cetuximab, ibrutinib, ipilmumab, necitumumab, nintedanib, nivolumab, palbociclib, panitumumab, ramucirumab, and ruxolitinib—demonstrated available information that shows a toxic effect that does not meet the NIOSH definition of a hazardous drug. These drugs should be placed on the *List* because of their teratogenic and/or reproductive effects or the rationale for not proposing their placement on the *List* should be further explained.

NIOSH response: As presented in the 2018 FRN, NIOSH reviewed cetuximab, ibrutinib, ipilimumab, necitumumab, nintedanib, nivolumab, palbociclib, panitumumab, ramucirumab, and ruxolitinib for placement on the *List* and, for each, the available information showed a toxic effect that does not meet the NIOSH definition of a hazardous drug. For some of these drugs, no drug-specific data were available in the package inserts to support warnings in the inserts regarding developmental or reproductive effects; for other drugs, the toxic effects occurred at doses higher than human recommended doses. For example, NIOSH found that ibrutinib had developmental effects in animals but only at doses twice the maximum recommended human dose of 560 mg/day. If new information becomes available about any of these drugs, NIOSH will reevaluate them in a future update to the *List.*

Comment: Eight drugs were approved by FDA prior to December 2015, but do not appear on the 2016 *List* and were not proposed for placement on the *List* in the February 2018 FRN. The drugs and rationales for each of them include the following:

Fosamprenavir	Carcinogenicity: Cited studies demonstrated an increased incidence of various oncologic presentations (hepatocellular adenoma/carcinoma, interstitial cell hyperplasia, and uterine endometrial adenocarcinoma), in multiple animal species (rat and mice) at exposure lower than human doses (0.7–1.4 fold in rats and 0.3–0.7 fold in mice compared to a human dosing).
Gefitinib	Carcinogenicity/teratogenicity: Cited studies demonstrated an increased incidence of hepatocellular adenomas in mice. The package insert also cites gefitinib as exhibiting teratogenicity.
Idelalisib	Genotoxicity: Cited studies demonstrated genotoxicity in male rats at high doses (2 grams/kilogram).
Lapatinib	Reproductive toxicity/teratogenicity: The FDA classifies lapatinib as pregnancy category D indicating positive evidence of human fetal risk. Cited studies in the package insert also demonstrate impaired fertility in rats.
Midostaurin	Reproductive toxicity: Cited studies in the package insert demonstrated reproductive toxicity in male and female rates.
Nicotine	Carcinogenicity/genotoxicity: Cited studies in the package insert demonstrated an increased incidence of tumors in hamsters and rats. Genotoxicity has been noted in Chinese hamster ovary cells.

Pembrolizumab	Teratogenicity: The package insert contains a warning of embryofetal toxicity when administered to pregnant women. Manufacturer recommendation: that females of reproduction potential use effective contraception during and for four months after completing therapy.
Talimogene laherparepvec	Reproductive toxicity: The package insert contains MSHI stating, ''Healthcare providers who are immunocompromised or pregnant should not prepare or administer IMLYGIC and should not come into direct contact with the IMLYGIC injection sites, dressings, or body fluids of treated patients'' due to the risk of transmission of talimogene laherparepvec and herpetic infection.

NIOSH response: Each of these drugs has either been previously reviewed and found not to meet the NIOSH definition of a hazardous drug, falls outside the scope of the *List,* or is slated for review in the future. NIOSH's findings about each drug are as follows:

Fosamprenavir	This drug was reviewed by NIOSH for a previous update to the *List* and it did not meet the criteria for a hazardous drug. The available information showed this drug has a toxic effect that does not meet the NIOSH definition of hazardous drug. No new information has been reported that would meet the NIOSH criteria for a hazardous drug. If new information becomes available, NIOSH will reevaluate it in a future update to the *List.*
Gefitinib	This drug was reviewed by NIOSH for a previous update to the *List* and it did not meet the criteria for a hazardous drug. However, because new safety information was recently added to the package insert, this drug is scheduled to be reviewed for the update after the 2020 *List* update.
Idelalisib	This drug was reviewed by NIOSH and presented in the 2018 FRN; it did not meet the criteria for a hazardous drug. The available information does not demonstrate or support a determination that the drug meets the NIOSH definition of hazardous drug. No new information has been reported that would meet the NIOSH criteria for a hazardous drug. If new information becomes available, NIOSH will reevaluate it in a future update to the *List.*
Lapatinib	This drug was reviewed by NIOSH for a previous update to the *List.* The available information showed this drug has a toxic effect that does not meet the NIOSH definition of hazardous drug. No new information has been reported that would meet the NIOSH criteria for a hazardous drug. If new information becomes available, NIOSH will reevaluate it in a future update to the *List.*
Midostaurin	This drug was approved by FDA in 2017. This drug is scheduled to be reviewed for the next *List* update.
Nicotine	Because drugs sold over the counter are not contemplated in this activity, this drug has not been and will not be reviewed for placement on the *List.*
Pembrolizumab	This drug was reviewed by NIOSH and presented in the 2018 FRN; the available information shows a toxic effect that does not meet the NIOSH definition of hazardous drug. It is scheduled to be re-reviewed for the next update to the *List,* because new information has been added to the package insert.
Talimogene laherparepvec	This oncolytic viral therapy product is outside the scope of NIOSH's definition of a hazardous drug because it is approved by FDA's Center for Biologics Evaluation and Research. NIOSH's definition of a hazardous drug only covers drugs approved by FDA's Center for Drug Evaluation and Research and is not considered for inclusion on the *List.*

Move From One Table on the *List* to Another

Comment: The hormonal agents in Table 1 of the 2016 *List* that are exclusively reproductive risks, including estrogens (estrogen agonist-antagonists such as tamoxifen and antiestrogens such as anastrozole, exemestane, and letrozole), gonadotropins (leuprolide and triptorelin), antigonadotrophins (degarelix), and progestins (megestrol) should be moved to Table 2 or 3.

Comment: Monoclonal antibodies do not have a cytotoxic mechanism of action and, as such, do not pose the same level of occupational risk or toxicity as conventional antineoplastic drugs. Those monoclonal antibodies that are not directly cytotoxic or conjugated with a cytotoxic agent should be moved from Table 1 to another place on the *List.*

Similarly, small-molecule kinase inhibitors, such as afatinib, crizotinib, dabrafenib, and imatinib, act through a targeted mechanism of action and are not directly cytotoxic; they primarily pose a reproductive and teratogenic risk. As such, they should be moved from Table 1 to another place on the *List.*

NIOSH response: After scientific review and consideration of input from peer reviewers and public commenters, NIOSH is proposing a reorganization of the *List.* As cancer therapy has changed from primarily cytotoxic drugs to non-cytotoxic and targeted therapies, there is sometimes a mismatch in general recommendations for safe handling and the hazardous nature of the drugs. In light of these changes, NIOSH proposes a new *List* structure, described in the preamble to the *List,* which is available for review in the docket for this activity. In accordance with the new structure, many of the hormonal agents on the 2016 *List* have been moved to Table 2. Hormonal agents that are classified by NTP as ''known to be a human carcinogen'' or by IARC as ''carcinogenic'' or ''probably carcinogenic'' will be identified in Table 1.

Remove Drug From *List*

Comment: Bacillus Calmette-Guerin (BCG) should be removed from the *List.*

NIOSH response: BCG, a vaccine approved by the FDA Center for Biologics Evaluation and Research, was included in the original 2004 Alert and 'grandfathered' into the *List.* However, because NIOSH has reaffirmed in the draft *Procedures* that only those drugs approved by the FDA Center for Drug Evaluation and Research are included in the *List,* BCG is no longer included in the *List.*

Drugs Handled Inconsistently

Comment: The drugs ibrutinib and blinatumomab, both antineoplastic monoclonal antibodies, are treated inconsistently in the February 2018 FRN. Ibrutinib was identified as a drug for which the available information shows a toxic effect that does not meet the NIOSH definition of a hazardous drug; blinatumomab was proposed for placement on the *List* on the basis of evidence which shows the drug is a neurotoxin at low doses. NIOSH should consider whether reliance on the AHFS Class 10:00 (antineoplastic agents) alone ''is enough to necessitate Table 1

inclusion even if a drug does need to be on the NIOSH list.''

NIOSH response: In response to input from peer reviewers and external comments and following scientific review, NIOSH proposes a reorganization of the tables in the draft 2020 *List* in a manner that may address at least some of the concerns expressed. Because the way cancer is treated therapeutically has changed, and the types of drugs used to fight cancer have changed, antineoplastic drugs are no longer all cytotoxic, genotoxic, and highly hazardous chemicals. Furthermore, some drugs carry multiple AHFS code classifications and are not just antineoplastic drugs. Therefore, when antineoplastic drugs are grouped, as they were in earlier versions of Table 1, drugs that required different levels of protection were grouped together (non-cytotoxic drugs with cytotoxic drugs). NIOSH determined that grouping all antineoplastic drugs together in one table is no longer the most useful or informative for the user. In light of these changes, NIOSH proposes a new *List* structure, described in the preamble to the draft *List,* which is available for review in the docket for this activity.

Comment: Azole antifungal drugs are being treated inconsistently. Fluconazole is included in the *List* on Table 3, but for two newer azole antifungals, the available information showed a toxic effect that does not meet the NIOSH definition of a hazardous drug (ketoconazole) and information does not demonstrate or support that the drug meets the NIOSH definition (itraconazole) in the FRN. Thus, neither was proposed for placement on the *List* in the February 2018 FRN.

NIOSH response: NIOSH has evaluated each drug individually and not by class of drug. Two very similar drugs may have substantially different toxicities and at different doses. Fluconazole meets the NIOSH criteria for a hazardous drug while the other two, ketoconazol and itraconazole, do not. Animal data on the developmental effects of fluconazole suggest developmental changes in rats at doses less than the equivalent maximum human recommended dose of 400 mg/day. In humans receiving 400 mg/day or higher developmental effects consistent with animal data have been observed and epidemiological data suggest a risk of spontaneous abortions and congenital abnormalities in infants whose mothers were treated with 150 mg/day fluconazole. Data on the developmental effects of itraconazole and ketoconazole suggest developmental toxicity has only been observed in doses greater than the maximum human recommended dose.

Add New Category of Drugs

Comment: Add a new category for drugs that sublime and offer information about proper handling, including the conditions under which sublimation (transition of a solid substance to a gas) happens as well as the need to filter and exhaust the work area where such drugs are used. The *List* should also indicate that hazardous drugs that do not sublime may be exhausted through a HEPA filter back into the work area.

NIOSH response: Sublimation depends on the drug form and is not an inherent toxicity property of the drug. Accordingly, drugs that sublime should be handled using risk management strategies relevant to the conditions of use. Although assessing specific controls for specific exposure situations is beyond the scope of the *List,* information about the use of respiratory protection in the handling of hazardous drugs is found in the draft risk management document, *Managing Hazardous Drug Exposures: Information for Healthcare Settings,* which is available in the docket for this activity.

Comment: The *List* should identify those hazardous drugs that are both cytotoxic and cytostatic as well as volatile. The drugs pose the greatest risk to healthcare workers, ''based on a combination of volatility and dose-related toxic potential of those vapors.''

NIOSH response: Only a few of the drugs on the *List* are known to have an appreciable vapor pressure; reliable information concerning the vapor pressure of most drugs can be difficult to identify. Because this issue is a matter of delivery form, rather than inherent toxicity, it is currently beyond the scope of the *List.* NIOSH will consider identifying hazardous drugs that are known to be volatile in future updates to the *List.*

B. Draft NIOSH List of Hazardous Drugs in Healthcare Settings, 2020: Summary of Changes

In February 2018, NIOSH proposed adding 21 drugs (including one class of drugs) to the *List.* After evaluating public comments, NIOSH made the following determination:

- 13 drugs are proposed for placement on the *List*
- 3 drugs are automatically added to the *List* because they have MSHI in the package insert (2 drugs identified in the 2018 FRN and another recently-approved by FDA)
- 7 drugs proposed for placement on the *List* in the 2018 FRN are no longer considered in this action

The 13 drugs proposed for placement on the *List* are presented for public comment in the table below, along with the rationale for their placement on the *List.*

Two drugs included in the 2018 FRN, inotuzumab ozogamicin and trabectedin, have MSHI and are automatically added to the 2016 *List.* One additional drug, polatuzumab vedotin, was approved by FDA's Center for Drug Evaluation and Research in July/August 2019 and its package insert includes MSHI provided by the drug's manufacturer. Because drugs with MSHI are automatically placed on the *List* and are not subject to public or peer review, polatuzumab vedotin was added to the 2016 *List* in September 2019 and will appear in the 2020 *List.*[8] These three drugs do not appear below because they are not subject to public comment.

The following seven drugs that were proposed for placement on the *List* in the February 2018 FRN are no longer proposed for placement on the *List,* for the reasons discussed above in Sections II.B. and III.B: bevacizumab, botulinum toxins, darbepoetin alfa, interferon beta-1b, osimertinib, trastuzumab, and triazolam.

DRUGS PROPOSED FOR PLACEMENT ON THE NIOSH LIST OF HAZARDOUS DRUGS IN HEALTHCARE SETTINGS, 2020

Generic drug name[a] and AHFS class[b]	Rationale[c] and proposed location[d] on the ***List***
Blinatumomab AHFS Class: Antineoplastic	Rationale *Organ toxicity at low doses:* neurotoxicity at low doses in patients in clinical studies. Proposed Location *Table 2:* No MSHI, not classified as known or probable carcinogen by NTP or IARC.

[8] *See https://www.cdc.gov/niosh/docs/2016-161/default.html* for all drugs with special handling information added to the 2016 *List.*

DRUGS PROPOSED FOR PLACEMENT ON THE NIOSH LIST OF HAZARDOUS DRUGS IN HEALTHCARE SETTINGS, 2020—Continued

Generic drug name [a] and AHFS class [b]	Rationale [c] and proposed location [d] on the ***List***
Ceritinib	Rationale
AHFS Class: Antineoplastic	*Developmental toxicity:* embryo-fetal toxicity at low doses in rats and rabbits.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Clobazam	Rationale
AHFS Class: Antiepileptic	*Reproductive toxicity and Developmental toxicity:* embryo-fetal mortality and other harm at low doses in rats and rabbits, present in human breast milk.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Cobimetinib	Rationale
AHFS Class: Antineoplastic	*Reproductive toxicity and Developmental toxicity:* increased post-implantation loss, including total litter loss in rats at low doses; post-implantation loss and fetal malformations in humans.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Dihydroergotamine	Rationale
AHFS Class: 5-hydroxytryptamine (HT) receptor binder.	*Reproductive toxicity:* oxytocic properties at low doses in humans.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Exenatide	Rationale
AHFS Class: Antidiabetic	*Carcinogenicity and Developmental toxicity:* thyroid C-cell tumors in rat studies; adverse fetal effects in rats and mice.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Isotretinoin	Rationale
AHFS Class: Retinoid	*Developmental toxicity:* severe fetal malformations at any dose in humans.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Ivabradine	Rationale
AHFS Class: Hyperpolarization-activated cyclic nucleotide-gated (HCN) blocker.	*Developmental toxicity:* embryo-fetal toxicity and teratogenicity at low doses in rats.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Lenvatinib	Rationale
AHFS Class: Antineoplastic	*Developmental toxicity:* embryo-fetal toxicity at low doses in rats and rabbits; abortifacient in rabbits at low doses.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Miltefosine	Rationale
AHFS Class: Antibiotic	*Developmental toxicity:* fetal death and teratogenicity at low doses in rats and rabbits.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Olaparib	Rationale
AHFS Class: Antineoplastic	*Carcinogenicity and Developmental toxicity:* myelodysplastic syndrome/acute myeloid leukemia in patients in clinical studies; embryo-fetal toxicity, post implantation loss, malformations at low doses in rats.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Sonidegib	Rationale
AHFS Class: Antineoplastic	*Reproductive toxicity and Developmental toxicity:* embryo-fetal toxicity, teratogenesis, and spontaneous abortions at low doses in rabbits.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.
Urofollitropin	Rationale
AHFS Class: Ovulation stimulator	*Developmental toxicity:* drug is known to cause fetal harm in patients.
	Proposed Location
	Table 2: No MSHI, not classified as known or probable carcinogen by NTP or IARC.

[a] FDA-approved drug (January 2014–December 2015).
[b] AHFS (American Hospital Formulary Service) Pharmacologic-Therapeutic Classification system.
[c] *See Procedures* section IV.
[d] NIOSH proposes that the *List* include only two tables. Table 1 includes only those drugs that contain MSHI in the package insert; and/or meet the NIOSH definition of a hazardous drug and are classified by the NTP as ''known to be a human carcinogen,'' or classified by the IARC as ''carcinogenic'' or ''probably carcinogenic.'' Table 2 includes those drugs that meet the NIOSH definition of a hazardous drug but are not drugs that have MSHI or are classified by the NTP as ''known to be a human carcinogen,'' or classified by the IARC as ''carcinogenic'' or ''probably carcinogenic.''

C. NIOSH List of Hazardous Drugs in Healthcare Settings, 2020—Title, Reorganization, and Removals

NIOSH has retitled and reorganized the *List* in response to comments received. Many of the drugs currently used to fight cancer function differently than those previously used. Antineoplastic drugs are no longer all cytotoxic, genotoxic, and highly hazardous chemicals. Therefore, when drugs are grouped by their function (*i.e.,* antineoplastic), as they were in earlier versions of Table 1, drugs that required different protective measures were grouped together (non-cytotoxic drugs with cytotoxic drugs). NIOSH has determined that grouping all antineoplastic drugs together in one table is no longer the most useful or informative for users. Therefore, NIOSH has regrouped the tables by hazard. The *List* now comprises only two tables:

Table 1: Drugs that contain MSHI in the package insert and/or meet the NIOSH definition of a hazardous drug and are classified by NTP as ''known to be a human carcinogen,'' or classified by IARC as ''carcinogenic'' or ''probably carcinogenic.''

Table 2: Drugs that meet the NIOSH definition of a hazardous drug, but do not have MSHI and are not classified by NTP as ''known to be a human carcinogen,'' or classified by IARC as ''carcinogenic'' or ''probably carcinogenic.''

Additional changes to the *List,* including those drugs proposed for removal from the *List,* are described in detail in the draft *NIOSH List of Hazardous Drugs in Healthcare Settings, 2020,* which is available for review in the docket for this activity.

IV. Risk Management for Hazardous Drugs in Healthcare Settings

In the 2016 *List,* Table 5 provided information on recommended exposure controls for hazardous drugs based on formulations. In order to clarify that the *List* is a hazard identification tool, NIOSH has removed this table from the document. In its place, NIOSH has developed a new, comprehensive document on risk management strategies entitled, *Managing Hazardous Drug Exposures: Information for Healthcare Settings,* which includes a revision of this table on control approaches to safe handling of hazardous drugs. The new risk management document is available for review in the docket for this activity.

NIOSH is seeking input from the public on the draft risk management strategies document and table to ensure that they contain accurate and helpful information. Independent peer reviewers are being consulted as well; their charge is available on the NIOSH website [9] and includes the following questions. NIOSH encourages public comment on these questions.

1. Please provide feedback on the overall document:

a. What additional information would improve its usefulness and why?

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

c. What information is redundant, incorrect, missing, or not needed? Please explain.

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.

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.

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.

5. NIOSH has provided its proposed recommendations and related information about controlling hazardous drugs in the Table of Control Approaches in Chapter 8.

a. What additional information would improve the usefulness of this table and why?

b. What structural or format changes could be made to improve the utility of this table?

c. What information is redundant, incorrect, missing, or not needed? Please explain.

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.

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.

8. Please provide any additional studies or scientific information related to the use of a medical surveillance program as an additional approach to protect workers in healthcare settings. Information of particular interest includes considerations for design and implementation of a medical surveillance program, data analysis, and communication of results to participants.

[9] NIOSH Peer Review Agenda, *https://www.cdc.gov/niosh/review/peer/isi/healthsafetyrisks.html.*

John J. Howard,

Director,National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

[FR Doc. 2020–09332 Filed 4–30–20; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Mine Safety and Health Research Advisory Committee (MSHRAC)

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

ACTION: Notice of meeting.

SUMMARY: In accordance with the Federal Advisory Committee Act, the CDC announces the following meeting for the Mine Safety and Health Research Advisory Committee (MSHRAC). This is a virtual meeting. It is open to the public, limited only by web conference lines (500 web conference lines are available). If you wish to attend, please contact Marie Chovanec by email at *MChovanec@cdc.gov* or by telephone at 412–386–5302 at least 5 business days in advance of the meeting. She will provide you the Zoom web conference access.

DATES: The meeting will be held on June 2, 2020, 10:00 a.m.–2:30 p.m., EDT.

ADDRESSES: The Zoom web conference access can be obtained via email at *MChovanec@cdc.gov* or by telephone at 412–386–5302.

FOR FURTHER INFORMATION CONTACT: Jeffrey H. Welsh, Designated Federal Officer, MSHRAC, NIOSH, CDC, 626 Cochrans Mill Road, Pittsburgh, PA 15236, telephone 412–386–4040; email *jwelsh@cdc.gov.*

SUPPLEMENTARY INFORMATION:

Purpose: This committee is charged with providing advice to the Secretary, Department of Health and Human Services; the Director, CDC; and the Director, NIOSH, on priorities in mine safety and health research, including grants and contracts for such research, 30 U.S.C. 812(b)(2), Section 102(b)(2).

Matters to be Considered: The agenda will include discussions on mining safety and health research projects and outcomes, including updates from one MSHRAC Workgroup, the Health Advisory in the Mining Program