FOR FURTHER INFORMATION CONTACT: Broderick Yoerg, Division of Global Health Protection, Global Health Center, Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30329, email: *DGHPNOFOs@cdc.gov,* telephone: 404–234–0666.

SUPPLEMENTARY INFORMATION: The sole source award will target increased capacity at the national and subnational level to implement and achieve outbreak/epidemic/pandemic control in line with US Government (USG) and CDC strategy. This collaborative effort has led to significant progress in various areas under the Global Health Strategic Framework, including One Health workshops in multiple countries to prioritize zoonotic diseases and the development of a joint action plan for Central America.

SE–COMISCA is the only entity that can carry out this work, as it will improve outbreak control capacity, better integration between health systems, and increased equity in healthcare access for all populations, especially those historically marginalized.

Summary of the Award

Recipient: SE–COMISCA

Purpose of the Award: The purpose of this award is to support Global Health Security goals in Central America and the Dominican Republic by collaborating with MOH and other partners. Efforts will focus on reaching underserved populations, prioritizing equity to build resilient health systems that protect vulnerable groups.

Amount of Award: $5,000,000 in Federal Fiscal Year (FFY) 2025 funds, with a total estimated $25,000,000 for the 5-year period of performance, subject to availability of funds.

Authority: This program is authorized under section 307 of the Public Health Service Act [42 U.S.C. 24*l*) and Section 301(a)[42 U.S.C. 24*l*(a) of the Public Health Service Act.

Period of Performance: September 30, 2025 through September 29, 2030.

Dated: December 10, 2024.

Terrance Perry,

Acting Director, Office of Grants Services, Centers for Disease Control and Prevention.

[FR Doc. 2024–30223 Filed 12–19–24; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

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

Hazardous Drugs: NIOSH List of Hazardous Drugs in Healthcare Settings, 2024 and Final Reevaluation Determinations for Liraglutide and Pertuzumab

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 publication of the *NIOSH List of Hazardous Drugs in Healthcare Settings, 2024,* as well as final reevaluation determinations removing the drugs liraglutide and pertuzumab from the *NIOSH List of Hazardous Drugs in Healthcare Settings*.

DATES: The documents announced in this notice are available on December 20, 2024.

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/healthcare/hazardous-drugs/index.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 (notice) published on May 1, 2020 (85 FR 25439), NIOSH invited the public to participate in the development and reorganization 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.

The public was invited to submit written comments regarding the draft *List,* 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*. 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 *List* and two other documents discussed in the May 2020 notice are available in the docket for this activity.

NIOSH carefully considered all public comments and peer reviews concerning the draft *List* resulting from the 2020 notice and determined that some clarifications and changes should be made to the draft *List*. Public comments on the draft *List* and specific drugs are summarized and answered in section III. These changes are summarized in section V. of this notice and are reflected in the final document described in this notice.

In a January 16, 2024, **Federal Register** notice (89 FR 2614), NIOSH sought public comment and peer review on the reevaluation of two drugs requested to be removed from the *List* by their respective manufacturers: liraglutide and pertuzumab. Responses to public and peer review comments on the reevaluations of the placements of liraglutide and pertuzumab on the *List* are in section IV. These changes to the *List* are summarized in section V.

The *NIOSH List of Hazardous Drugs in Healthcare Settings, 2024* (2024 *List*) [1] is published on the NIOSH website and is also available in the docket for this activity.

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 hazardous to workers' health. NIOSH periodically updates this list, now named the *NIOSH List of Hazardous Drugs in Healthcare Settings (List),* to assist employers in providing safe and healthful workplaces by identifying drugs that meet the NIOSH definition of a hazardous drug. The *List* is informational in nature and confers no requirements or legal obligations on users.

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, 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

[1] NIOSH [2024]. *NIOSH List of Hazardous Drugs in Healthcare Settings, 2024.* By Ovesen JL, Sammons D, Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP, Whittaker C. 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 2025–103 (Supersedes 2016–161), *https://www.cdc.gov/niosh/docs/2025-103*. NB: NIOSH has periodically updated the *List* from 2010 through 2016; prior to the 2024 update to the *List,* it was named the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.*

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 Hazardous Drug Exposures: Information for Healthcare Settings* (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.

In April 2023, NIOSH published a notice in the **Federal Register** (88 FR 25642) that announced the publication of the final versions of the ''*Procedures*'' and ''*Managing Exposures*'' documents. The April 2023 notice summarized and responded to public input on the ''*Procedures*'' and ''*Managing Exposures*'' documents. Those changes were reflected in the finalized documents, *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings* [NIOSH 2023a] and *Managing Hazardous Drugs Exposures: Information for Healthcare Settings* [NIOSH 2023b], which are available on the NIOSH website at *https://www.cdc.gov/niosh/healthcare/hazardous-drugs/publications.html.*

In January 2024, pursuant to the *Procedures,* NIOSH conducted peer reviews and sought public comment on initial recommendations to change the status of the drugs liraglutide and pertuzumab, added to the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* in 2014 and 2016, respectively. NIOSH published its charge to peer reviewers and public commenters in a **Federal Register** notice on January 16, 2024 (89 FR 2614), requesting feedback on NIOSH's initial recommendations to remove the drugs liraglutide and pertuzumab from the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.* The two initial recommendations and summaries of evidence, *NIOSH Reevaluation of Liraglutide on the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* and *NIOSH Reevaluation of Pertuzumab on the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings,* were made available to peer reviewers and public commenters in the docket for this activity.

III. NIOSH Response to Public Comment in the May 2020 Federal Register Notice and Request for Comment

The public comments received in response to the draft *NIOSH List of Hazardous Drugs in Healthcare Settings,* proposed in the May 2020 notice and available in the docket, are summarized below, followed by NIOSH responses.

A. General Characteristics of the List

1. Timing of the List

Public comment: Several commenters mentioned that the NIOSH review has created a long gap between *List* updates and would like for NIOSH to have more frequent updates.

NIOSH response: NIOSH received a substantial response to its proposed revisions of the organization of the *List* in 2018 and has worked diligently to provide thorough and transparent responses to those comments. This notice is the finalization of that process. Moving forward, NIOSH intends to publish periodic updates to the *List* while maintaining the rigor of review by multiple scientists, outside experts, and public comment. Because the delay between the final date of drugs being approved to market and the publication of updates to the *List* is unavoidable, it is important for employers to review all relevant potential hazard information on the drugs being used in their facility, especially newly FDA-approved drugs that are new to the facility's formulary and which have not yet been publicly evaluated by NIOSH.

2. Drugs That Did Not Meet the NIOSH Hazardous Drug Criteria

Public comment: Two commenters requested that NIOSH publish a list of which drugs did not meet the NIOSH criteria of a hazardous drug, so that employers can avoid unnecessary reviews of drugs that do not appear on the NIOSH *List.*

NIOSH response: NIOSH does not identify the drugs that have been reviewed and have failed to meet the NIOSH criteria because doing so might be interpreted as indicating those drugs are free of potential hazards. In fact, even drugs that are not on the *List* may have some hazards associated with exposure. In addition, NIOSH repeatedly reviews drugs as new information and warnings are added to their package inserts, so publishing the names of reviewed drugs would be potentially confusing, as information changes. Moreover, some drugs do not meet the criteria due to a lack of data. Therefore, to be clear that NIOSH is not making an affirmative statement that drugs reviewed and not added to the *List* have no associated hazards, NIOSH does not publish such a list. No change to the 2024 *List* has been made in response to this comment.

B. General Drug Descriptors

1. Unique Identifiers

Public comment: In the May 2020 *notice,* NIOSH asked ''Which unique ingredient identifier is the most useful for users of the *List*?'' Among the six responses NIOSH received, there was broad agreement that the most useful identifier is the generic name of the drug. One reviewer suggested also including the brand name(s) of the drug, citing recognizability by staff unaccustomed to drug names.

NIOSH response: NIOSH agrees with the majority of commenters that generic drug names are preferred because of the potential volatility of brand names and the entry of generics once patents expire. No changes were made in response to these comments.

2. Use of AHFS Classifications

Public comment: Some commenters stated that the use of AHFS (formerly called the American Hospital Formulary Service) classifications on the *List* leads to imprecise or incorrect classification of drugs and should be discontinued.

NIOSH response: NIOSH does not use the AHFS classification to determine hazard, nor does the AHFS classification influence placement of a drug on a particular table. The AHFS classifications are provided only as information for users to aid in identifying the drugs and their potential therapeutic uses.

3. Use of AHFS Code for Hormone Drug Classification

Public comment: One commenter on the *List* noted that the use of AHFS classification for hormones led to some nomenclature concerns.

NIOSH response: The AHFS identifier is provided to give users some information on how the listed drugs are classified and utilized. Some drugs may be classified in more than one category, and AHFS may have used the same classification codes for drugs that have different mechanisms of actions or uses. Further information on the drugs may be found in their respective AHFS monograph.[2]

4. Monoclonal Antibodies as a Class of Drugs

Public comment: Several commenters suggested NIOSH reconsider listing the monoclonal antibodies as a class of

[2] *See www.ahfsdruginformation.com.*

drugs largely based on the high molecular weight of these compounds as an exclusionary factor or based on data from in vitro systems.

NIOSH response: NIOSH considers each drug based on the potential hazard each active pharmaceutical ingredient poses. Each is reviewed individually, and classes of drugs are not excluded *a priori.* Monoclonal antibodies may generally have lower systemic availability via inhalation, ingestion, and dermal absorption through intact skin, but that availability is not zero and not all workers have intact skin. NIOSH intends to continue reviewing each drug individually and considering the intrinsic hazard that each drug poses, including molecular properties, such as molecular weight, which may change the likelihood of occupational exposure.

NIOSH encourages employers to examine the potential hazards posed by all the therapies handled in their facility and evaluate the risk associated with occupational exposures. NIOSH encourages workplaces to take the appropriate risk management strategies for the risk related for their specific workplace handling of the hazardous drugs in their facility. The *List* is informational in nature and confers no legal obligations. How facilities implement risk management strategies should be reflective of the risk they identify in their handling scenarios. No change to the 2024 *List* was made in response to this comment.

5. Progestins

Public comment: One commenter suggested that the term ''progestins'' does not provide sufficient information about what exactly constitutes a progestin.

NIOSH response: Progestins are synthetic hormones that target the progesterone receptor. The AHFS identifier—AHFS classification code ''68:32: Progestins''—is provided in the 2024 *List* to give users some information on how the listed drugs are classified and utilized.

6. Additional Information Requested

Public comment: Some commenters requested that NIOSH include more specific information about the relevant hazards posed to healthcare workers in the *List* to provide healthcare workers access to more information and improve safety.

NIOSH response: The *List* identifies drugs that meet the criteria specified in the *Procedures.* It is not intended to be a comprehensive review of every hazard potentially posed by a drug. Drugs are repeatedly reviewed as new information and warnings are added to their package inserts, and some drugs do not meet the criteria due to a current lack of data. NIOSH suggests that workplaces review the potentially hazardous drugs handled in their facilities to identify specific details on the hazard of those drugs.

C. General Reorganization of the List

1. Content of Tables

Public comment: More than a dozen commenters voiced opinions on the reorganization of Table 1. Table 1 was formerly focused on antineoplastic drugs. NIOSH has dropped this nomenclature and reorganized Table 1 in the 2024 *List* to include only ''[d]rugs with MSHI [manufacturer's special handling information] in the package insert and/or those that meet the NIOSH definition of a hazardous drug and one or more of the following criteria: are classified by NTP (National Toxicology Program) as *known to be a human carcinogen* or are classified by IARC (International Agency for Research on Cancer) as Group 1 *carcinogenic to humans* or Group 2A *probably carcinogenic to humans.*'' Eight commenters suggested that the reorganization of Table 1 was appropriate, but some commenters were concerned that the change would confuse some users and that some drugs with shared mechanism of action ended up on different tables. In summary, commenters expressed agreement with the proposal to remove the AHFS therapeutic descriptor ''antineoplastic'' as a criterion for placement in Table 1 and base drug placement in Table 1 on drugs with manufacturer's special handling information (MSHI) and/or those that are carcinogenic to humans or probably carcinogenic to humans. Other commenters were less supportive of the changes, citing potential end-user confusion, and perceived conflict with United States Pharmacopeia (USP) <800> requirements.

NIOSH response: NIOSH has reorganized the tables with an understanding that all antineoplastic drugs do not carry the same hazard. As discussed above, the new organization creates a Table 1 in the 2024 *List* that includes ''[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.*'' Table 1 does not contain all drugs that are used in the treatment of cancer, which may carry different types of potential occupational hazards because of their mechanism of action. This aligns more with the NIOSH goal of providing a list that helps identify potential workplace hazards. To alleviate some confusion, NIOSH has maintained the AHFS classification of drugs so that antineoplastic drugs on both tables can be identified. In June 2020, USP revised Chapter <800> to clarify that the chapter's requirements for antineoplastic drugs apply only to those antineoplastic drugs found in Table 1 of the *List.*[3] Questions concerning the language of USP Chapter <800> should be directed to USP.

Public comment: Several commenters noted concerns about combining Tables 2 and 3 into one table. Table 3, included in previous iterations of the *List* but removed in the 2020 draft, addressed only those non-antineoplastic drugs that have adverse reproductive effects. Concerned commenters thought that not enough was done to identify drugs that were only reproductive or developmental hazards, citing challenges for healthcare workers in adequately identifying drugs with reproductive and/or developmental risks. In addition, a commenter expressed concern that the information on reproductive and developmental hazards was not clearly identified in Table 2.

NIOSH response: NIOSH has reorganized Table 2 in the 2024 List to include ''[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.)''

NIOSH recognizes that there is an important interest in identifying drugs that pose a developmental and reproductive hazard so that risk management strategies can be tailored to the situation and has revised Table 2 in the 2024 *List* to include a new column to allow readers to find those drugs more easily on the *List.* In addition, NIOSH worked with its visual information specialists to ensure that the information is clear and easy to find.

With regard to the concern that some Table 2 drugs are more toxic than Table 1 drugs, it is important to note that placement of a drug on Table 1 or Table 2 does not indicate relative potency or relative hazard of the drugs. All drugs

[3] U.S. Pharmacopeia [June 2020], Revision Bulletin, *https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/gc-800-rb-notice-20200626.pdf.*

on the *List* have been determined by NIOSH to meet the definition of a hazardous drug. 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. The drugs are separated into two tables based on type of hazard. The word ''only'' in the notation regarding reproductive and developmental toxicity allows for identification of drugs that met just one or both of these NIOSH toxicity criteria for inclusion on the *List.* Pointing out that a drug met just one or both of these criterion helps management tailor strategies to the hazard. However, this designation does not indicate the severity of the hazard.

2. DailyMed and DrugBank Links

Public comment: Two commenters requested that NIOSH keep the links to DailyMed and DrugBank on the NIOSH *List.*

NIOSH response: Because internet links change frequently and links in the PDF of the *List* cannot be updated once published, NIOSH has removed the DailyMed and DrugBank links. However, users are encouraged to access these databases to find more information about drugs of interest.

D. Drugs Not on the Draft 2020 List

1. Drugs Proposed in February 2018 and Not Added to the Draft 2020 List

Public comment: One commenter noted some drugs proposed for placement on the *List* in February 2018 were no longer proposed for placement in the May 2020 draft *List.*

NIOSH response: In response to public and interested party comments to the proposals published in the February 2018 *notice,* NIOSH clarified the *Procedures* for developing the *List* and reevaluated specific drugs in drafts published for public comment in the May 2020 *notice.* After consideration of the revised draft *Procedures* and the public comments, NIOSH ultimately determined that several drugs proposed to be placed on the *List* in the February 2018 *notice* either did not meet the NIOSH criteria or were identified as needing additional review to be considered for future *List* updates. Accordingly, the following drugs proposed in 2018 were not included on the draft 2020 *List:* bevacizumab, botulinum toxins, darbepoetin alfa, interferon beta-1b, osimertinib, trastuzumab, and triazolam.

2. Bacillus Calmette-Guerin (BCG)

Public comment: Several commenters requested that NIOSH relist BCG and suggested NIOSH broaden its definition of a hazardous drug to include drugs approved by FDA Center for Biologics Evaluation and Research (CBER). The major issue was that by excluding drugs approved by CBER, healthcare workers would not be apprised of occupational hazards that may occur from exposure to those drugs.

NIOSH response: BCG is an infectious agent approved for use by the FDA CBER. It was included in the 2004 *Alert* as part of the compiled list of drugs sourced from other external hazardous drug lists. It was maintained on the *List* from that time. While BCG is an infectious agent and should be handled appropriately, it does not fall under the NIOSH definition of a hazardous drug for evaluation for placement on the *List* and has thus been removed. Healthcare workplaces should review the potential hazards of all treatments utilized in their facilities, including potentially infectious agents, gene therapy treatments, radiological treatments, and experimental treatments that may not be evaluated by NIOSH and identify the proper strategies to reduce the risk of worker exposure to those hazards.

3. Botulinum Toxins

Public comment: NIOSH received four comments in response to its request for information on botulinum toxins. Comments included requests for clarification of the criteria to place drugs on the *List* and a request for additional information about how NIOSH considers balancing the hazard with other considerations.

NIOSH response: In response to comments, NIOSH determined that additional review of the issues raised by commenters on the toxicity data on botulinum toxins would be beneficial. Therefore, as stated in the May 2020 *notice,* NIOSH is not adding botulinum toxins to the 2024 *List* at this time. One of the issues with botulinum toxins is whether the molecular weight of the molecule precludes consideration of the drugs as an occupational hazard. NIOSH intends to apply those concepts as described in the *Procedures* to the botulinum toxins in a future reevaluation of the drugs.

As to the issue of whether NIOSH considers balancing the hazard with other considerations, NIOSH reminds readers that the *List* is a hazard identification tool. It should be used to identify drugs that may pose an occupational hazard in healthcare settings. However, NIOSH does not conduct risk assessment for these drugs. NIOSH recommends that employers familiarize themselves with the toxicity of the drugs in their formularies, considering factors such as use, dosage form, engineering controls, work practices, and personal protective equipment (PPE) in developing risk mitigation strategies for their workplace.

E. Requests for Specific Drugs To Be Removed From the List

1. Blinatumomab

Public comment: Some commenters suggested that NIOSH remove the recombinant therapeutic protein-based drug blinatumomab from the *List.* This was primarily based on molecular size and related bioavailability. With regard to the observed neurological effects of blinatumomab, one commenter suggested that these effects may be caused by a response of lymphoma cells present in the brain and may not be relevant in healthy people exposed to blinatumomab.

Alternatively, one commenter noted that the manufacturer of blinatumomab has provided the statements ''[e]nsure that personnel are appropriately trained in aseptic manipulations and admixing of oncology drugs'' and ''[e]nsure that personnel wear appropriate protective clothing and gloves.'' The commenter indicated that such warnings are similar to MSHI and therefore the drug warrants inclusion in Table 1.

NIOSH response: Blinatumomab has been found to have neurological effects at low doses. NIOSH intends to review the information available on the role of lymphoma cells present in the brain and is considering reevaluating blinatumomab in a future update of the *List.* For now, no change to the 2024 *List* was made in response to these comments.

Regarding the issue of large molecules, NIOSH considers each drug based on the potential hazard posed intrinsically. Each is reviewed individually. NIOSH recognizes that large molecules may have lower systemic availability via inhalation, ingestion, and dermal absorption through intact skin, and takes that into account in its assessment. However, the systemic availability of these drugs, though low, is not zero, and not all workers have intact skin. In response to comments, NIOSH has added a column to both tables in the 2024 *List* that allows for identification of drugs that have been approved by CDER under a biologics license application (BLA). These drugs are often large protein/peptide-based drugs. Identifying drugs that are approved by CDER under BLAs will make it easier for users to identify drugs that are large peptides and make the appropriate risk management strategies.

With regard to the statements from the manufacturer that appear similar to MSHI, NIOSH has thus far used manufacturers' identification of cytotoxic/genotoxic hazards and suggestions that special care be taken with these drugs as MSHI. NIOSH continues to review how it considers MSHI with each *List* update to ensure these criteria are applied consistently and appropriately. In any case, NIOSH recommends that employers familiarize themselves with the potential hazards posed by the drugs in their formularies and prepare the appropriate strategies to reduce the risks of occupational exposure.

2. Carfilzomib

Public comment: One commenter suggested that carfilzomib should be removed from the *List* based on recent studies that suggest less than 1 percent bioavailability of the drug via oral and inhalation bioavailability.

NIOSH response: This comment appears to be based on proprietary data that is not currently available to NIOSH, but NIOSH will consider evaluating carfilzomib again in a future update of the *List.*

3. Eslicarbazepine, Lomitapide, Mifepristone

Public comment: A commenter suggested NIOSH remove eslicarbazepine from the *List* because of insufficient human data on the reproductive and developmental effects and no data about occupational exposure and risk. Two commenters suggested that lomitapide be removed from the *List* due to a lack of data on risk associated with occupational exposure. One commenter suggested NIOSH remove mifepristone due to a lack of data identifying a risk associated with occupational exposure.

NIOSH response: Developmental effects were observed in experimental animals exposed to eslicarbazepine at concentrations lower than the maximum recommended human dose (MRHD). Results in humans are inconclusive to rule out the potential for occupational hazard. Therefore, NIOSH is maintaining eslicarbazepine on the 2024 *List.* Lomitapide was observed to be teratogenic in several animal species. Mifepristone has been shown to cause termination of pregnancy and is listed due to potential reproductive and developmental effects. Some reproductive effects are seen in humans and teratogenicity has been observed in rabbits.

NIOSH also notes that sufficient data on health effects related to occupational exposure to individual drugs are very rarely available. The *List* is intended to identify potential hazards to aid employers in assessing risks to workers, therefore, no change to the 2024 *List* was made in response to these comments.

4. Hazardous Drugs Listed for Reproductive and Developmental Effects: Cabergoline, Clonazepam, Fluconazole, Plerixafor, Riociguat, and Ziprasidone

Public comment: One commenter suggested that NIOSH remove cabergoline from the *List.* They cited data suggesting in humans it does not cause reproductive or developmental harm. They suggested that effects in some tested species are secondary to maternal toxicity and that the effects seen in a rat study on embryo survival were species specific.

Another commenter suggested that clonazepam should be removed from the *List.* The commenter noted that the manufacturer's safety data sheet states that it is neither teratogenic nor embryotoxic. They noted, however, that exposure during late stages of pregnancy can lead to post-natal dependence and withdrawal, while exposures immediately prior to childbirth may lead to adverse outcomes. They also noted some, though inconsistent, evidence of adverse developmental effects in animals and stated that there are no studies of occupational exposures to clonazepam.

Two commenters suggested that fluconazole should be removed from the NIOSH *List.* One commenter noted that teratogenic risk had only been associated with exposures in excess of 400 mg/day. The commenter also noted that data suggested that lower doses were not associated with potential hazard to reproduction or the developing offspring in pregnancy or through breastfeeding. Finally, the commenter noted that no data were available on the health effects of occupational exposures.

One commenter suggested NIOSH remove the drug plerixafor from the NIOSH *List* because no data were identified on occupational exposures leading to reproductive hazards. They also noted that reproductive effects in animals occurred mainly at a dose 10 times the MRHD.

One commenter suggested NIOSH remove riociguat. The commenter noted that the observed developmental and reproductive effects seen in rats and rabbits only occurred at doses that correlated with doses greater than twice the MRHD.

One commenter suggested that NIOSH remove ziprasidone from the *List* because occupational exposures via dermal or inhalation routes have not been shown to cause teratogenicity. However, animal studies have demonstrated potential embryofetal toxicities without a no-observed-adverse-effect level (NOAEL) as low as 0.2 times the MRHD. The commenter also described two case studies of in utero exposure, one with no adverse outcome and one with cleft palate attributed to ziprasidone exposure.

NIOSH response: In reviewing the totality of the evidence, NIOSH believes the evidence supports listing cabergoline, clonazepam, fluconazole, plerixafor, riociguat, and ziprasidone. In the case of fluconazole, the teratogenic effects observed are consistent with effects seen in animals at similar species at equivalent doses, and in rats at lower doses. In the case of ziprasidone, embryofetal toxicity was observed with a NOAEL as low as 0.2 times the MRHD and at least one case study resulted in a cleft palate in the offspring of an individual exposed to ziprasidone. NIOSH notes that it is not unusual that there are no studies of occupational exposure to these drugs, as there are few occupational studies of hazardous drugs exposure. However, NIOSH intends to reevaluate the evidence on reproductive and developmental hazards for these drugs, along with other potential reproductive and developmental hazards, in a future update of the *List* to assure consistency of application of the criteria. No changes to the 2024 *List* were made in response to these comments.

5. Icatibant

Public comment: One commenter suggested that NIOSH remove icatibant from the NIOSH *List* because the limited case studies and reports have not shown signs of adverse effects in humans.

NIOSH response: The data indicate that in rats, at doses lower than human doses, there is fetal death, preimplantation loss, and delayed parturition. In addition, in rabbits, increased abortion rate, increased fetal death, increased preimplantation loss, and increased preterm births were observed at doses lower than MRHD. Reproductive effects were also seen in dog studies that affected both males and females, though these effects were reversible 4 weeks after exposure ceased. In an occupational setting, where a drug is being used on a regular basis, repeated exposure to the drug or to contaminated surfaces are not unexpected. Therefore, NIOSH has retained icatibant on the 2024 *List.* No change to the 2024 *List* was made in response to this comment.

6. Leuprolide

Public comment: One commenter noted that leuprolide requires continuous systemic exposure for 2–3 weeks to cause the decrease in sex hormones that would lead to either fetal toxicity or reproductive harm. They suggested that occupational exposures would not lead to continuous systemic exposure, and relevant levels of exposure can only occur following injection of the extended-release formulation. They acknowledged that initial exposure may cause a spike in gonadotropin release and sex hormones levels rather than a decrease.

Another commenter suggested that leuprolide should be removed from the *List* because it can be obtained in a kit that decreases the risk of exposure to healthcare workers.

NIOSH response: With regard to occupational exposures not being equivalent to a sustained systemic exposure, NIOSH notes that working in areas with contaminated surfaces or working regularly with hazardous materials may lead to chronic or repeated exposures. However, as with some of the other drugs identified as reproductive or developmental hazards, NIOSH intends to consider reevaluating leuprolide during a future update to the *List* to ensure consistent application of the NIOSH criteria.

Regarding the distribution of leuprolide in a kit that may lower occupational exposure, NIOSH notes that the *List* contains active pharmaceutical ingredients based on the hazards they pose. The *List* does not differentiate based on dosage form. Many things may affect the risk associated with handling hazardous drugs, including drug formulation, proper handling technique, and PPE utilization. In addition, formulations may change, and packaging and delivery mechanisms can be damaged. Therefore, NIOSH identifies the intrinsic hazards of drugs and not the scenario-based risks associated with handling each drug in a specific way. Healthcare workplaces should further consider what risk management strategies are appropriate for their specific needs, given their specific exposure scenarios.

7. Olaparib and Teriflunomide

Public comment: One commenter suggested that NIOSH remove olaparib because the risk of direct occupational exposure is likely low when handling intact olaparib capsules. One commenter noted that while the hazards posed by teriflunomide exposure exist, the risk of exposure due to formulation and packaging means it should not be on the NIOSH *List.*

NIOSH response: The *List* is intended as a hazard identification tool. The *List* does not differentiate based on dosage form. Many things may affect the risk associated with handling hazardous drugs, including drug formulation, proper handling technique, and PPE utilization. In addition, formulations may change, and packaging and delivery mechanisms can be damaged. Therefore, NIOSH identifies the hazards of drugs and not the scenario-based risks associated with handling each drug in a specific way. Healthcare workplaces should further consider what risk management strategies are appropriate for their specific needs, given their specific exposure scenarios. No change to the 2024 *List* was made in response to these comments.

8. Oxytocin and Other Oxytocic Drugs

Public comment: Many commenters asked NIOSH to remove oxytocin and the other oxytocic drugs ergonovine and methylergonovine from the *List.* Most commenters stated that there are no documented cases where routine handling has resulted in occupational hazard. In addition, some noted that because the mechanism of action of ergonovine, methylergonovine, and oxytocin differs, they should not be treated similarly.

NIOSH response: NIOSH has recognized that the oxytocic drugs were added to the *List* as part of the initial compilation in 2004. They have been maintained as a class on the *List* since that time. In response to comments on the mechanism of action, NIOSH agrees that ergonovine, methylergonovine, and oxytocin do not appear to have the same mechanism of action. Oxytocin and methylergonovine have been observed to pose a hazard to fetuses in the third trimester of pregnancy. Therefore, they are retained on the 2024 *List.* However, NIOSH intends to evaluate oxytocin and methylergonovine in a future *List* update. Ergonovine has never been approved for use in humans by the FDA and therefore does not meet NIOSH's definition as a drug. Therefore, ergonovine has been removed from the 2024 *List.*

9. Paroxetine

Public comment: One commenter suggested NIOSH remove paroxetine from the *List,* stating that the studies are currently inconclusive. The commenter also noted that there are no data on occupational exposures.

NIOSH response: Studies indicate that therapeutic doses are suspected of damaging fertility in males and increasing congenital malformations in developing fetuses. These effects suggest a potential hazard to workers who are pregnant, trying to conceive, or males who are trying to have children. There are also data suggesting that there are negative adverse effects on neonates exposed during the third trimester of pregnancy. These data clearly support maintaining paroxetine on the 2024 *List.* With regard to the lack of data from occupational exposures, NIOSH notes that this is not uncommon, as there are few studies of occupational exposure to hazardous drugs. However, the totality of the evidence supports maintaining paroxetine on the 2024 *List.* No change to the 2024 *List* was made in response to this comment.

10. Spironolactone

Public comment: Two commenters suggested spironolactone be removed from the NIOSH *List* because the health effects were only observed after long-term relatively high exposures.

NIOSH response: Studies have shown that long-term (18-month) exposures in rats led to significant increases in hepatocellular adenomas. There were also increases in adenoma of the testes in males and proliferative changes in the liver in that study. Doses ranged from 50 to 200 mg/kg/day. In another study, significant increases in hepatocellular adenomas and testicular interstitial cell tumors were observed in rats exposed to 10 mg/kg/day to 100 mg/kg/day; 100 mg/kg/day represents a dose five times the human dose of 200 mg/day.

NIOSH also notes that evidence of changes in estrous cycles, retardation of follicular development, decreased numbers of implanted embryos, and increases in stillborn pups were also observed in some studies. NIOSH has determined that the totality of the evidence supports maintaining spironolactone on the 2024 *List.* However, as with some of the other drugs identified as reproductive and/or developmental hazards, NIOSH intends to consider evaluating spironolactone again in a future *List* update to ensure consistent application of the NIOSH criteria. No change to the 2024 *List* was made in response to these comments.

11. Topiramate

Public comment: One commenter recommended that topiramate be removed from the *List* and noted that no data were identified describing reproductive risk of associated with occupational exposure to topiramate.

NIOSH response: The lack of occupational exposure studies is not unusual. In evaluating the totality of the

available evidence, NIOSH notes that studies have shown limb malformations and reduced fetal body weights in rats exposed to doses half the recommended human dose. In addition, the NOAEL for rats in that study was less than the MRHD. In rabbits, embryofetal effects were seen only at doses greater than human recommended doses.

In a different rat developmental study with administration through the later part of gestation and throughout lactation, it was observed that doses as low as 2 mg/kg/day led to decreased pre- and/or post-weaning body weights. The NOAEL for these studies, 0.2 mg/kg/day, was also below the MRHD. In mice, when topiramate was administered during organogenesis fetal malformations, primarily craniofacial were seen at all tested doses (0, 20, 100, or 500 mg/kg/day) with no NOAEL. The lowest dose tested in this study was lower than the MRHD. Human data from the pregnancy registries suggest that infants exposed in utero are at increased risk for cleft palate and being small at gestational age, the latter seen at all tested doses and appearing to be dose dependent. From this evidence, NIOSH determined that topiramate poses a potential hazard to the development of offspring of workers exposed while pregnant and has maintained it on the 2024 *List.* No change to the 2024 *List* was made in response to these comments.

12. Ulipristal

Public comment: One commenter suggested NIOSH remove ulipristal from the *List.* The commenter noted that the effects after pregnancy are established are insufficient to determine if ulipristal poses a teratogenic/developmental hazard at that time.

NIOSH response: Ulipristal is a progesterone agonist/antagonist indicated for pregnancy prevention within 5 days of unprotected intercourse or contraception failure. Workers may be trying to become pregnant or be pregnant potentially at any time, and the data indicate that there may be a hazard that affects reproductive ability within the first 5 days of attempted conception. Therefore, NIOSH has maintained ulipristal on the 2024 *List.*

13. Vigabatrin

Public comment: One commenter suggested that vigabatrin should be removed from the NIOSH *List* because no adverse effects on fertility have been reported in rats up to a dose of ½ the MRHD. They also stated that the manufacturer notes that changes in post-natal development and male fertility in rats may be related to the drug-related effects on food intake and weight. When exposed to vigabatrin during development, there was an increase in cleft palate and embryofetal deaths for rabbits but not for rats. In rabbits, the no effect level for development was approximately ½ of the MRHD, and the effects in rabbits were repeated in two studies.

NIOSH response: The manufacturer's package insert notes that exposure throughout organogenesis in rats led to decreased fetal weights and increased fetal anatomical variations with an embryo-fetal NOAEL approximately equivalent to ⅕ of the MRHD. Additionally, when rats were exposed through the later part of pregnancy throughout lactation, long-term neuro-histopathological changes and neurobehavioral effects were observed. These effects had no NOAEL and a lowest-observed effect level of ⅕ of the MRHD. Exposure during early post-natal period in rats, a period that is generally thought to correspond with late pregnancy in humans, also resulted in neurobehavioral and neuro-histopathological with a NOAEL that was 1/30 of the measured plasma exposures in pediatric patients receiving a 50 mg/kg dose. Therefore, NIOSH determined that vigabatrin may pose a potential hazard to the development of unborn offspring when the mother is exposed during pregnancy and has maintained it on the 2024 *List.*

F. Placement of Specific Drugs Within the List

1. Carfilzomib

Public comment: Some commenters noted that carfilzomib is on Table 2 while a similar proteosome inhibitor bortezomib appears on Table 1. One noted that while the manufacturers of bortezomib provide ample identification of bortezomib as a cytotoxic agent and suggest appropriate handling for the protection of healthcare workers, the manufacturers of carfilzomib do not.

NIOSH response: Table 1 of the 2024 *List* includes ''[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.*'' The manufacturers of carfilzomib did not provide MSHI. Nor was carfilzomib evaluated by NTP or IARC. Therefore, it was not included on Table 1.

Table 2 of the 2024 *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.)'' However, NIOSH notes that the tables in the *List* are not hierarchical; Table 1 does not contain inherently more hazardous drugs than Table 2. It is expected that in some cases, drugs in the same class with similar activity could be on different tables because of the information available.

2. Dasatinib and Imatinib

Public comment: One commenter suggested dasatinib and imatinib should be moved to Table 2. They noted similar kinase inhibitors, bosutinib, nilotinib, and ponatinib, are on Table 2.

NIOSH response: In reviewing the package insert, some data suggest that dasatinib and imatinib may be carcinogenic, clastogenic, or genotoxic. The manufacturers of dasatinib and imatinib include MSHI, which provides guidance on appropriately handling these clastogenic and/or genotoxic compounds to protect healthcare workers. At this time, all evaluated drugs with this information are included on Table 1 of the 2024 *List.* However, NIOSH notes that the tables in the *List* are not hierarchical; Table 1 does not contain inherently more hazardous drugs than Table 2. It is expected that in some cases, drugs in the same class with similar activity could be on different tables because of the information available. No change to the 2024 *List* was made in response to this comment.

3. Eribulin

Public comment: One commenter suggested that NIOSH include eribulin on Table 1 because the mechanism of action, mitotic inhibition by suppression of microtubule growth, is similar to those of several other cytotoxic drugs such as vinblastine and paclitaxel, which are located on Table 1.

NIOSH response: Table 1 of the 2024 *List* includes ''[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 by IARC as Group 1 *carcinogenic to humans* or Group 2A *probably carcinogenic to humans.*'' NIOSH agrees that manufacturers of other genotoxic/cytotoxic drugs that inhibit mitosis via microtubule inhibition have included

MSHI for healthcare workers to handle them appropriately. In 2021 the manufacturers of eribulin updated the eribulin prescribing information noting that it is a cytotoxic drug with the instructions that special handling and disposal procedures should be followed. Because the manufacturer of eribulin suggests special handling it has been placed on Table 1 in the *NIOSH List of Hazardous Drugs, 2024.*

4. Exenatide

Public comment: One commenter suggested that exenatide should be listed on Table 1 because it meets NIOSH criteria as carcinogenic.

NIOSH response: Table 1 of the 2024 *List* includes ''[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.*'' However, NIOSH notes that the tables in the *List* are not hierarchical; Table 1 does not contain inherently more hazardous drugs than Table 2. It is expected that in some cases, drugs in the same class with similar activity could be on different tables because of the information available. In the 2024 *List,* Table 2 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.)''

5. Ganciclovir and Valganciclovir

Public comment: One commenter suggested NIOSH move these antiviral drugs to Table 2 from Table 1 because of confusion regarding the application of USP <800>.

NIOSH response: Ganciclovir and valganciclovir are listed on Table 1 because these nucleoside drugs have been identified by the manufacturers to pose a hazard to workers handling them and they both have MSHI. According to NIOSH criteria, this warrants placement on Table 1. Table 1 of the 2024 *List* includes ''[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.*'' This means some drugs listed on Table 1 may not be antineoplastic drugs. The tables comprising the *List* are not intended to stratify levels of hazard, and neither are the inclusion of AHFS classification. The AHFS classifications are included as helpful information for users. NIOSH suggests that concerns with USP <800> standard be addressed with USP. No change to the 2024 *List* was made in response to this comment.

6. Hormonal Agents: Goserelin, Degarelix, Leuprolide, Estrogens, and Progesterone

Public comment: One commenter suggested NIOSH moving the hormonal agents goserelin, degarelix, and leuprolide to Table 3 as they were previously listed under Table 1—Antineoplastic Drugs. Two commenters asked NIOSH to move the estrogens and progesterone drugs from Table 1 to Table 2.

NIOSH response: In the current *List,* leuprolide, goserelin, and degarelix are listed on Table 2. There is no longer a Table 3, and all of these drugs on Table 2 are now described as only having met NIOSH criteria as a developmental or reproductive hazard.

For the estrogens and progesterone, Table 1 of the 2024 *List* includes ''[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.*'' This means some drugs that are potential carcinogens via different mechanisms may be listed on Table 1 because they met one of the criteria for placement on Table 1. The tables comprising the *List* are not intended to stratify risk and NIOSH recommends that facilities evaluate the potential hazards of the drugs in their formulary so they can make the appropriate exposure control management strategies. Specifically, for the estrogens and progesterone, IARC classifies the estrogen/progesterone combination drugs as *carcinogenic to humans* (Group 1) with sufficient evidence that they cause cancer of the breast and endometrium. . While as one commenter noted, the increased risk for estrogen-related endometrial cancer is decreased depending on the number of days that progesterone is included in the treatment, the drugs are still classified as IARC Group 1 and are therefore the appropriate placement according to the NIOSH criteria is on Table 1. No change to the 2024 *List* was made in response to these comments.

7. Mycophenolate Mofetil and Mycophenolic Acid

Public comment: Two commenters requested NIOSH move mycophenolate mofetil and mycophenolic acid to Table 1 because of the potential carcinogenic hazard and because most facilities currently treat them as hazardous antineoplastic drugs.

NIOSH response: Table 1 in the 2024 *List* includes ''[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.*'' This means some drugs that are potential carcinogens and are potential genotoxic/cytotoxic compounds may be on Table 2 because they had not yet been evaluated by IARC or NTP or because the manufacturer has not identified the need for safe handling to protect healthcare workers who may handle the drug. The tables comprising the *List* are not intended to stratify hazard. Some drugs on Table 2 may be more hazardous than those on Table 1. In general, NIOSH recommends that facilities evaluate the potential hazards of the drugs in their formulary so they can make the appropriate exposure control management strategies. Mycophenolate mofetil, while not an antineoplastic, had MSHI added to the prescribing information in 2019 and has been moved to Table 1 in response to this comment.

8. Sirolimus and Other Related mTOR Targeting Drugs

Public comment: One commenter requested NIOSH move sirolimus to Table 1 because of the potential carcinogenic hazard and because the similar drug, tacrolimus, is on Table 1. Another reviewer asked that everolimus and temsirolimus be moved to Table 2 because they are a similar class as sirolimus, which is on Table 2.

NIOSH response: Table 1 in the 2024 *List* includes ''[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.*'' This means some drugs that are in the same class and may carry similar hazards may be listed on different tables because of differences in MSHI and evaluation of the drugs by IARC or NTP. The tables

comprising the *List* are not intended to stratify hazard and NIOSH recommends that facilities evaluate the potential hazards of the drugs in their formulary so they can make the appropriate exposure control management strategies. No change to the 2024 *List* was made in response to these comments.

9. Thalidomide, Lenalidomide, and Pomalidomide

Public comment: One commenter suggested thalidomide and the related analogs lenalidomide and pomalidomide should not be listed on Table 1 because they have only reproductive and developmental effects and have not demonstrated genotoxicity or carcinogenicity.

NIOSH response: Table 1 in the 2024 *List* includes ''[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 the 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.*'' Thalidomide, lenalidomide, and pomalidomide include MSHI with guidance on handling these drugs in a way that protects workers. In the 2024 *List,* not all drugs on Table 1 are genotoxic or carcinogenic. Additionally, drugs that are carcinogenic on Table 1 may not be genotoxic but act through a different mechanism of carcinogenicity. It is important that workplaces identify what the specific hazards are related to the drugs in their facility's formulary and use the appropriate exposure management strategies for those hazards. No change to the *2024 List* was made in response to these comments.

10. Vandetanib

Public comment: One commenter suggested that vandetanib should be placed in Table 2 similar to other EGFR tyrosine kinase inhibitors.

NIOSH response: The vandetanib package insert includes MSHI indicating that it be handled and disposed of in a way that protects the healthcare workers. All evaluated drugs with this information are included on Table 1 of 2024 *List.* However, NIOSH notes that the tables in the *List* are not hierarchical; Table 1 does not contain inherently more hazardous drugs than Table 2. It is expected that in some cases, drugs in the same class with similar activity could be on different tables because of the information available. No change to the 2024 *List* was made in response to this comment.

G. Specific Drug Classification/ Identification

1. Triptorelin

Public comment: One commenter suggested that noting the antineoplastic designation for the drug triptorelin will confuse some healthcare professionals and lead them to deny patients needed therapy due to special handling of neoplastic agents.

NIOSH response: Triptorelin is identified on the *List* in Table 2 as having both AHFS classifications ''68:18:08 Gonadotropin Agonist/ Antagonist'' and ''10:00 Antineoplastic.'' These are offered as information to aid the user. NIOSH suggests that facilities evaluate all the hazards that may be present in their formulary. A designation of antineoplastic by AHFS does not identify some special hazard. Cancer treatments have changed over time and not all drugs utilized in the treatment of cancer have the same hazards. Because of this, NIOSH no longer groups all antineoplastic drugs together on a single table. The tables comprising the *List* are not intended to rank levels of hazard, and neither are the identification of AHFS classifications. These are only intended as potentially useful information for users. No change to the 2024 *List* was made in response to this comment.

2. Ziv-Aflibercept, Ado-Trastuzumab Emtansine, Fam-Trastuzumab Deruxtecan

Public comment: In the draft *List* published in the docket for the May 2020 *notice,* NIOSH removed the prefixes that are part of several generic drug names in an attempt to focus on identifying the active pharmaceutical ingredient. NIOSH was alerted by several commenters that in doing so NIOSH had listed names that were not actual products or were different products than originally intended.

NIOSH response: NIOSH appreciates the commenters who brought up this issue and regrets the confusion that this caused. NIOSH has revised the 2024 *List* to include the FDA assigned prefixes (*i.e.,* ziv-, ado-, and fam-) in the appropriate generic drugs names (ziv-aflibercept, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan) to correct the issue and refer to the appropriate pharmaceutical products.

H. Suggested Copyedits

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

NIOSH response: NIOSH accepted all editorial, spelling, and correction comments in the 2024 *List,* as appropriate.

IV. NIOSH Response to Public Comment and Peer Review in the January 2024 Federal Register Notice and Request for Comment on Proposed Removal of Liraglutide and Pertuzumab From the List

As described above, on January 16, 2024, NIOSH published a request for public comment in the **Federal Register**, charging peer reviewers and public commenters with considering five questions about the liraglutide initial recommendation and summary of evidence:

1. Are the evaluated health effects the appropriate health effects to evaluate? If not, what other health effect(s) should be evaluated and why?

2. Are the assumptions about the potential exposures to liraglutide in a healthcare setting reasonable? Please explain.

3. Is the determination that the amount of exposure to liraglutide in a healthcare setting does not constitute a hazard for healthcare workers reasonably supported by the available scientific information? Please explain.

4. What alternative approaches could be considered to characterize the potential hazard to workers from peptide-based drugs?

5. Is there any additional information that NIOSH should consider in its reevaluation of liraglutide?

Peer reviewers and public commenters were also charged with considering six questions about the pertuzumab initial recommendation and summary of evidence:

1. Is this an appropriate method for evaluating the potential for exposure to pertuzumab?

2. Is oligohydramnios the best health effect to evaluate? If not, what other health effect(s) should be evaluated and why?

3. Is a needlestick injury the only reasonable route of exposure for healthcare workers? Please explain.

4. Are the assumptions about the amount of exposure to pertuzumab in a healthcare setting reasonable? Please explain.

5. Is the determination that the amount of exposure to pertuzumab in a healthcare setting does not constitute a hazard for healthcare workers reasonably supported by the available scientific information? Please explain.

6. What alternatives could be considered to this approach for monoclonal antibodies to characterize the potential hazard to workers?

NIOSH received comments from three public commenters on the January 2024

notice, including a trade association, a pharmaceutical manufacturer, and a private individual. One commenter addressed liraglutide and pertuzumab, as well as the process NIOSH used to reevaluate placing liraglutide and pertuzumab on the *List.* Two commenters addressed just pertuzumab. NIOSH received two peer reviews of the proposal to remove liraglutide from the *List* and three peer reviews of the proposal to remove pertuzumab from the *List.*

Following review and consideration of the peer reviews and public comments, and as discussed below, NIOSH has agreed to clarify some points in the initial recommendations and summaries of evidence, *NIOSH Reevaluation of Liraglutide on the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* and *NIOSH Reevaluation of Pertuzumab on the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.* Those changes are reflected in the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* and *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings,* available in the docket for this activity. Based on the evaluations described in the initial recommendations and on peer reviews and public comments discussed below, NIOSH has made final determinations to remove both liraglutide and pertuzumab from the *List.*

A. Public Comment

1. General Comments

Public comment: The commenter ''expresses concern that the methods used to reevaluate liraglutide and pertuzumab for inclusion in the *List* represent risk assessment, not hazard identification. The physical properties of a drug molecule are not among the six characteristics considered for hazard determination. The purpose of the NIOSH *List* should be to identify hazards so that healthcare settings can assess and mitigate risk. If NIOSH removes these drugs based on risk assessment, healthcare settings may incorrectly think that a hazard does not exist.

While [we] agree[ ] that a drug's physical properties may reduce the risk of absorption through common methods of occupational exposure, NIOSH should not assume that all healthcare staff and healthcare environments are the same. Exposure through mucous membranes or other routes may be rare, but they are still important considerations that healthcare settings should evaluate when performing a risk assessment specific to their environment and to their employees.''

NIOSH response: NIOSH evaluates the hazard to healthcare workers posed by exposure to FDA Center for Drug Evaluation and Research (CDER) approved drugs. NIOSH considers hazards at maximum human recommended dose via all relevant routes of exposure. NIOSH considers the molecular properties as they relate to the specific adverse effects posed by the drug via all relevant routes of exposure. The NIOSH hazardous drugs definition [4] clarifies that NIOSH considers molecular properties when characterizing the hazard a drug actually poses to healthcare worker after exposure. It recognizes that although a drug may meet the definition of a hazardous drug, the drug may be excluded from the *List* if NIOSH determines that occupational hazards are limited due to the molecular properties of the drug. The purpose of this exclusion is to focus the *List* on drugs that have a potential for toxicity due to occupational exposure, so that workers' attention is focused on drugs that are likely to be hazardous in occupational settings. This is a way for NIOSH to more specifically characterize the hazard posed by the pharmaceutical ingredients; it is important to note that this is not an automatic exclusion. NIOSH has not established specific molecular properties for which drugs are automatically excluded from the *List.* Instead, NIOSH reviewers look at the totality of the evidence and evaluate whether there is a hazard to healthcare workers. NIOSH considers molecular properties as they relate to the specific adverse effects to characterize those hazards posed by the drug being evaluated.

Public comment: The commenter ''also urges caution when making assumptions about occupational exposure based on commercially available dosage forms of a drug. NIOSH should not base hazard identification on a specific route of exposure, such as needlestick injuries. Splashes, leaks, and spills all occur in healthcare settings. While a currently available dosage form (*e.g.,* prefilled syringe or pen) may limit the risk of a splash, leak, or spill, dosage forms available at some time in the future may not offer the same protection.

Pharmacy employees may handle bulk active pharmaceutical ingredients when compounding various preparations. In the case of 503B registered outsourcing facilities [FDA 2022], workers may handle a hazardous drug in bulk powder form in higher quantities and with more frequency than a typical healthcare worker might handle a commercial preparation. Duration and intensity of exposure are important factors to consider when assessing and mitigating exposure risk. Individual healthcare settings can evaluate exposure duration and intensity when assessing risk, but that evaluation is unlikely to occur if the hazard has not been recognized.''

NIOSH response: NIOSH agrees that evaluating the hazards of potentially hazardous drugs should not be limited to currently commercially available formulations. NIOSH evaluates how the molecular properties influence hazard potential at occupational exposures to doses equivalent to therapeutic human recommended doses via occupationally relevant routes of exposure. This is true even if a route of exposure is unlikely given currently available formulations. NIOSH understands that formulations may change, and handling needs may be different across facilities. For liraglutide and pertuzumab, NIOSH evaluated how the molecular properties influence bioavailability after exposures via needlesticks, dermal exposure, ingestion, and inhalation. A large peptide molecule, currently only available in liquid formulations, may not lead to exposure equal to a human recommended dose via inhalation of dust or droplets, but NIOSH still considered that potential exposure route in its reevaluations. NIOSH noted in both reevaluations that inhalation of a full therapeutic dose is unlikely to result in systemic exposures that would cause the relevant adverse effects. This is not based on any formulation, but rather on intrinsic molecular properties of the reevaluated pharmaceutical ingredients. The formulations and marketed products that include the pharmaceutical ingredients may decrease the risk of exposure, but they were not part of NIOSH's characterization of the hazard posed by the active pharmaceutical ingredients, pertuzumab and liraglutide.

NIOSH uses a recommended human dose as a benchmark to indicate the high end of doses of concern. NIOSH would be typically concerned with toxic effects that occurred below this level. NIOSH considers exposures at the human recommended doses to be greater than the expected dose for healthcare workers. In situations where

[4] The NIOSH definition of a hazardous drug is established in sec. IV of the *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings* [2023].

healthcare workers may be exposed to therapeutic agents at levels greater than what patients are exposed to, then pharmacological effects may occur. Based on this comment, NIOSH made changes in the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* and *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings.*

2. Liraglutide

Public comment: The commenter ''agrees that repeated exposure and absorption to peptide-based drugs is not likely in many clinical settings. However, we again stress concern about using physical properties for hazard identification for reasons already mentioned. Since carcinogenic effects and fetal abnormalities cannot be ruled out in humans, liraglutide meets the existing criteria for hazard identification. The duration, intensity, and routes of exposure should be part of a healthcare setting's risk assessment. [We] disagree[ ] with removal of liraglutide from the NIOSH *List*.''

NIOSH response: Consideration of intrinsic molecular properties of potentially hazardous drugs is important to characterizing if they pose a hazard to healthcare workers in the workplace. The NIOSH hazardous drugs definition [NIOSH 2023] considers the molecular properties of hazardous drugs because although a drug may meet some criteria as a hazardous drug, those occupational hazards may not be significant due to intrinsic molecular properties of the drug and therefore that drug may be excluded from the *List.* The purpose of this exclusion is to focus the *List* on drugs that have a potential for toxicity due to occupational exposure, so that workers' attention is focused on drugs that are likely to be hazardous in occupational settings. This is a way for NIOSH to more specifically characterize the hazard posed by the pharmaceutical ingredients; it is important to note that this is not an automatic exclusion. Occupational exposure to liraglutide is unlikely to reach systemic exposure levels that pose a hazard to workers. No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* and *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* as a result of this comment.

3. Pertuzumab

Public comment: While the commenter ''agrees that repeated exposure and absorption of a monoclonal antibody is not likely in many clinical scenarios, we again express concern about assumptions made about healthcare workers and environments when defining a hazard. [We] also [have] concerns with consideration about whether a condition is reversible or not when performing hazard identification. While oligohydramnios may be reversible, the condition can lead to fetal complications [Keilman and Shanks 2022]. [We] question[ ] whether NIOSH will begin considering whether an *adverse* effect is reversible when determining other hazard assessments. [We] disagree[ ] with removal of pertuzumab from the NIOSH list.''

Public comment: ''I think the biggest issue is whatever is the most fatal or can cause the most damage or permanent damage. While this sounds reversible, I still would not want to risk my fetus through the possibility of exposure.''

NIOSH response: NIOSH agrees that whether a hazard is reversible alone is not enough to determine if a drug is hazardous to healthcare workers. In the case of pertuzumab, data for the related drug trastuzumab show that continuous exposures at therapeutic levels causes delayed-genitourinary development-related oligohydramnios.[5] If systemic exposure is continuous, that will lead to further fetal complications. However, if treatment is ceased, and oligohydramnios is resolved in the first trimester, further fetal complications are avoided. Oligohydramnios requires continuous systemic exposure to pertuzumab, and continued HER2 inhibition, to occur. As noted in the reevaluation, for the related HER2 inhibitor monoclonal antibody trastuzumab, use during pregnancy showed that patients who had exposure during just the first trimester had babies born with no complications, deaths, or oligohydramnios. There was a trend of increased incidence in oligohydramnios with increased exposure to trastuzumab. In the available studies, it appears that trastuzumab-related oligohydramnios was reversible following cessation of treatment with generally good outcomes for the fetus, as seen in the Watson [2005] case.

Healthcare workers are unlikely to experience prolonged and consistent exposure to pertuzumab in the workplace that would lead to high levels of systemic exposure. This is due to various factors, such as limited availability of systemic exposure and the rarity of incidental needlestick injuries with significant volumes, which are necessary for sustained high systemic exposures. As a result, the development of oligohydramnios that goes unresolved beyond the first trimester is not expected in healthcare workers. No changes were made in the document based on these comments.

a. Is this an appropriate method for evaluating the potential for exposure to pertuzumab?

Public comment: This commenter ''agrees it is appropriate to consider the physicochemical properties of pertuzumab that minimize the potential for adverse health effects from inhalation, dermal, or oral exposure. With regard to potential exposures via inhalation, [We] agree[ ] there is no scenario in which substantial air concentrations of pertuzumab could be generated while preparing or administering Perjeta® in a healthcare setting. In addition, [We] agree[ ] it is appropriate to consider the minimal volume that could be delivered to a healthcare worker when evaluating the potential exposure to pertuzumab in a needlestick scenario.

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on these comments.

b. Is oligohydramnios the best health effect to evaluate? If not, what other health effect(s) should be evaluated and why?

Public comment: ''The notable potential health effects in patients treated with Perjeta® (*i.e.,* those described in the Warnings and Precautions section of the prescribing information) include embryo-fetal toxicity, left ventricular dysfunction, infusion-related reactions, and hypersensitivity reactions/anaphylaxis.

Embryo-fetal toxicity and left ventricular dysfunction are recognized as pharmacologically mediated class effects of therapies that target HER–2. In addition to being over-expressed in some tumors, HER2 is expressed in normal renal epithelium and cardiomyocytes. The embryo-fetal effects of HER2 inhibitors are secondary

[5] HER2 inhibition refers to the inhibition of the activation of the Human Epidermal growth factor Receptor 2. Oligohydramnios is the disorder during pregnancy of having a low level of amniotic fluid for gestational age. HER2 inhibitory monoclonal antibodies cause oligohydramnios by causing a delayed development of the urinary tract development of the embryo, leading to decreased amniotic fluid production.

to delayed fetal kidney development that can result in oligohydramnios and related effects (oligohydramnios sequence). In cardiomyocytes, HER2 activation results in a protective effect that may be inhibited in patients treated with HER2 antagonists [Perez et al. 2008]. In contrast to anthracycline-induced cardiac toxicity, HER2-related cardiac dysfunction does not appear to increase with cumulative dose or to be associated with ultrastructural changes in the myocardium; it is also generally reversible. Both oligohydramnios and left ventricular dysfunction are non-acute effects that would require sustained, biologically significant inhibition of HER2 to manifest. Such exposures can only be reasonably expected to occur via intentional intravenous administration of pertuzumab in a therapeutic context. Consequently, Genentech does not consider oligohydramnios or left ventricular dysfunction to be relevant health effects for the purpose of evaluating potential risks to healthcare workers.

Other notable adverse reactions observed in patients receiving pertuzumab include infusion-related reactions and hypersensitivity reactions/anaphylaxis. Both are common risks of intravenous monoclonal antibody therapies and are not specific to pertuzumab. In addition, the risk of infusion-related reactions is only relevant to patients being treated with pertuzumab via intravenous infusion. Neither of these endpoints would therefore be appropriate to evaluate for the purposes of the *List.*

Because none of the notable adverse reactions associated with therapeutic uses of pertuzumab are considered relevant to healthcare exposure scenarios, it would not be meaningful to consider any of these hazards to be better suited for evaluation for the purpose of the *List.*''

NIOSH response: NIOSH agrees that none of these effects posed a hazard to healthcare workers. No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on these comments.

Public comment: ''We might however, want to think about allergic reactions from exposure? Utilizing less measures than chemo with tubing, gear, and gloving exposes nursing and pharmacy teams to the drugs more because of less need for precautions.''

NIOSH response: Sensitization and allergic reaction are not criteria under the *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings.* No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

c. Is a needlestick injury the only reasonable route of exposure for healthcare workers? Please explain.

Public comment: ''There is no scenario in which inhalation, dermal, or oral exposure could be expected to result in a pharmacologically active dose of pertuzumab. [We] therefore agree[ ] that a needlestick injury is the only relevant route of exposure for Perjeta® for healthcare providers.''

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

d. Are the assumptions about the amount of exposure to pertuzumab in a healthcare setting reasonable? Please explain.

One commenter stated their agreement with the general approach and conclusions described for each route.

i. Inhalation

Public comment: ''The peer-reviewed publications support the statement that the inhalation bioavailability of monoclonal antibodies such as pertuzumab is minimal. The 5% value utilized in the review is considered to be a conservative, upper-limit estimate for the inhalation bioavailability of an IgG antibody, and the systemically available fraction is more likely <1% [Gould et al. 2018; Pfister et al. 2014]; Perjeta® is supplied as a liquid in vial, is prepared using aseptic techniques, and is not administered as a powder or aerosol. [We] agree[ ] there is no mechanism by which volumes of pertuzumab dusts or aerosols sufficient to achieve systemic exposures associated with adverse effects could be generated in a healthcare setting.''

NIOSH response: When evaluating the potential hazard to healthcare workers, NIOSH does not limit evaluation to just the currently produced commercially available formulations and therefore also considers powders or aerosol exposures. NIOSH based the evaluation on assumptions for exposures that are unlikely in commercially available formulations and on intrinsic properties of the active pharmaceutical ingredients, not on any particular formulation or treatment product. No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

Public comment: ''[P]harmacy compounds the medication and moving drugs to the nonhazardous list means we use more needles than safety features. Hazardous medications we use items such as chemolock to protect us from needle sticks, we do not with the nonhazardous medications. My concern with medications like this is we can compound these for prolonged times and over days, months, and years. We could expose technicians to the amount listed and harm them and if they were to not know they were pregnant yet or whatever the case this could be an issue.''

NIOSH response: NIOSH evaluated how the molecular properties affected bioavailability after exposures via needlesticks, dermal exposure, ingestion, and inhalation. A large molecule currently only available in liquid formulations may not lead to exposure equal to a human recommended dose via inhalation of dust or droplets, but that potential route of exposure was considered.

NIOSH has used the recommended human dose as a benchmark to indicate the high end of doses of concern. NIOSH is typically only concerned with toxic effects that occurred below this level. NIOSH considers exposures at the human recommended doses to be greater than the expected dose for healthcare workers. In situations where healthcare workers may be exposed to therapeutic agents at levels greater than the levels that patients are exposed to, then the pharmacological effects may occur. Some changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* to clarify.

ii. Percutaneous Exposure

Public comment: ''The published literature on needlestick injuries supports the statement that the volume of Perjeta® delivered from an inadvertent percutaneous exposure is expected to be minimal (*e.g.,* <1 microliter) and would be insufficient to deliver a toxicologically relevant dose. However, the 670 microliter 'human dose,' because needlestick exposures are expected to occur infrequently, it would be more appropriate to compare the <1 microliter needlestick volume to the volume of Perjeta® that would be required to deliver a therapeutic dose (30 mL).''

NIOSH response: NIOSH agrees that the use of a relevant human dose is

highly protective, and an incidental percutaneous exposure is unlikely to result in such a high exposure; however, NIOSH evaluated what was certainly a worst-case scenario. No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* in response to this comment.

iii. Oral Exposure

Public comment: ''The peer-reviewed publications support the statement that the oral bioavailability of monoclonal antibodies such as pertuzumab is negligible. In addition, the sterile preparation and administration procedures used to administer pertuzumab further reduce any potential for oral exposure.''

NIOSH response: When evaluating the potential hazard to healthcare workers, NIOSH does not limit its evaluation to just the currently produced commercially available formulations, therefore it also considers powders or aerosol exposures. NIOSH based the evaluation on assuming unlikely exposures in commercially available formulations and considering intrinsic properties of the active pharmaceutical ingredients, rather than focusing on any particular formulation or treatment product. No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* in response to this comment.

e. What alternatives could be considered to this approach for monoclonal antibodies to characterize the potential hazard to workers?

Public comment: ''Monoclonal antibodies have been approved for use to treat humans for more than 25 years and have been safely prepared and administered using routine aseptic procedures. Although they were still relatively novel when the *List* was first developed, monoclonal antibody-based products are now mainstream therapies for cancer and other conditions in humans, and their molecular and physiological properties are well characterized. The properties of monoclonal antibodies and other high molecular weight molecules result in occupational risk profiles that are clearly distinct from that of traditional, small molecule 'chemotherapies' that drove the original 2004 *NIOSH Alert* [2004] and subsequent publication of the *List.*

The current process for evaluating monoclonal antibodies for potential inclusion on the *List* is initially based on hazard (*i.e.,* any potential effect associated with a molecule). The various exposure-related factors that determine that the potential risk to a healthcare worker are secondary considerations.

An alternative approach to characterizing the potential hazard that a monoclonal antibody-based product poses to healthcare workers would be a risk-based paradigm that initially considers exposure potential. Based on the properties of monoclonal antibodies that minimize the potential for systemic exposure, nearly all monoclonal antibody-based pharmaceuticals could be excluded from consideration without the need for a comprehensive review of all hazards that are considered to be relevant to patients in a therapeutic context. Eliminating products with little potential to cause health effects in workers would greatly streamline the nomination and review process for the *List.*

Potential exceptions to this approach may include immunoglobulin-based products with usually high potency (*e.g.,* a monoclonal antibody with a therapeutic maintenance dose <1 mg) or immunoglobulin-based products that are conjugated to a low-molecular weight component that may meet the criteria for the *List* (*e.g.,* a product consisting of a monoclonal antibody conjugated to a small molecule anti-mitotic agent). However, such examples are relatively rare and can be readily identified based on the description in the prescribing information (Section 11).''

NIOSH response: NIOSH considers each drug based on the potential hazard posed intrinsically. Each is reviewed individually, and classes of drugs are not excluded. Monoclonal antibodies may generally have lower systemic availability via inhalation, ingestion, and dermal absorption through intact skin, but that availability is not zero and not all workers have intact skin. NIOSH intends to continue reviewing each drug individually and will consider the intrinsic hazard that each drug poses, including molecular properties, such as molecular weight, which may change the likelihood of occupational exposure. The process of excluding a whole class of drugs proposed by the commenter may miss some hazards for some healthcare workplaces. The *NIOSH List of Hazardous Drugs in Healthcare Settings* is a hazard identification tool, and using a risk-based paradigm that considers exposure potential first may not be sufficient to identify hazards that many drugs may potentially pose in a wide variety of healthcare settings.

Public comment: ''For compounding, could there possibly be the consideration of an adapter that goes with it? This would prevent a needle from technically being used at all as we often use a bag spike to inject the medications in the bags on either side.''

NIOSH response: The *List* does not take into consideration the specific practices used when handling different formulations of the potentially hazardous drugs used by each facility. No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

f. Additional Pertuzumab Comments

Public comment: The commenter ''requests clarification of the statement that 'No oral, inhalation, or dermal exposure studies of therapeutic monoclonal antibodies have been conducted' (on Page 4 of the reevaluation). This statement suggests that there is a large degree of uncertainty related to these key presumptions related to the evaluation of the risk posed by pertuzumab to healthcare workers.''

NIOSH response: NIOSH agrees and has clarified *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* that these studies were not performed because those therapies are not typically delivered via these routes.

Public comment: The commenter ''requests clarification of the statement that 'The toxicity profile of pertuzumab shows it is a potent developmental hazard.' There is no regulatory or other consensus definition for a 'potent' hazard in a pharmaceutical context. The use of this term in policy or regulatory documents is therefore likely to cause confusion and/or an unwarranted degree of concern among the intended audiences. The doses of pertuzumab that have been associated with adverse developmental outcomes in a therapeutic context are relatively high when compared with many other pharmaceuticals or chemicals, so its characterization as a potent developmental hazard is potentially misleading. In addition, the available data from nonclinical studies and human experience provide evidence of a dose-responsive effect that is unlikely to occur at far sub-therapeutic exposures. The description of pertuzumab as a potent developmental hazard therefore overstates the risk of Perjeta® to healthcare workers.''

NIOSH response: NIOSH agrees and has rephrased this sentence in *NIOSH*

Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings to note that pertuzumab caused oligohydramnios which is a clear developmental hazard. The word ''potent'' has been removed.

Public comment: In relation to the results of a study included in the reevaluation, in the table form on Page 7, the commenter states, ''[t]he findings from the embryo-fetal development toxicity study support the expectation that the adverse developmental effects of pertuzumab are dose-related and are not expected to occur at the far sub-therapeutic exposure scenarios relevant to healthcare workers. The evidence of a dose-responsive relationship between maternal pertuzumab doses and adverse outcomes can be leveraged to support many of the presumptions in the external review.''

NIOSH response: The evidence in this study does not provide a dose at which developmental effects are not seen. The commenter is correct that it does support a dose-response relationship between pertuzumab and developmental effects, supporting the conclusion that lower systemic doses resulting from occupational exposures are less likely to cause developmental effects. No changes were made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

B. Peer Review

1. Liraglutide Peer Review

Two external peer reviewers submitted responses to NIOSH, which are marked as ''Reviewer comment'' below. In general, both peer reviewers agreed with the approach NIOSH used to determine if liraglutide posed a hazard to workers in healthcare settings. Both peer reviewers also agreed with NIOSH that thyroid tumors and adverse developmental effects were appropriate health outcomes to consider. Lastly, both peer reviewers agreed that the systemic and occupational exposure assumptions NIOSH used in the evaluation were appropriate, and the resulting determination that liraglutide does not constitute a hazard for healthcare workers is correct.

a. Are the evaluated health effects the appropriate health effects to consider? If not, what other health effect(s) should be evaluated and why?

Reviewer 1 comment: ''Yes, the evaluated health effects are the appropriate health effects to consider.''

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

Reviewer 2 comment: ''Yes. Thyroid tumors as indicated in the black box warning and developmental effects, as indicated by the Pregnancy Category C determination, and are the most relevant adverse health effects to be considered. The assertions made concerning a causal association between incretin-based drugs like liraglutide and pancreatitis or pancreatic tumors, as expressed currently in the scientific literature and in the media, are inconsistent with the current data. In the NIOSH review, concerns about the potential effects, including thyroid cancer and developmental effects, should be reduced in light of more recent data. There are no other potential health effects to be considered that are supported by current data. Other nonspecific effects noted in the package insert, such as nausea, injection site pain, and low blood sugar, are manageable and not serious.''

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

b. Are the assumptions about the potential occupational exposures to liraglutide in a healthcare setting reasonable? Please explain.

Reviewer 1 comment: ''The assumptions about the potential occupational exposures to liraglutide in a healthcare setting are reasonable. Given the formulation and packaging of liraglutide, it would be expected that occupational exposure may occur if a vial leaks or breaks, which would lead to inhalation or dermal exposure, neither of which produce significant systemic bioavailability; or if a needlestick injury occurs, in which the quantity of drug actually injected would also be insignificant in the majority of cases.''

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

Reviewer 2 comment: ''Yes. This is a peptide with approximately 3750 molecular weight. Substances with molecular weights greater than 1000 Daltons show nil to poor absorption (less than 0.1%). Thus, dermal absorption in a healthcare workplace exposure would be nil, as the skin is a barrier for substances of this molecular weight. Normally (in clinical use) this substance is injected. The substance would also be expected to be degraded in oral exposure scenarios. Inhalation exposure scenarios can also be ruled out as this substance is in aqueous form in prefilled syringes and thus aerosolization is not expected. Absorption through this route would also be expected to be nil to poor. Needlestick exposures do occur in healthcare situations, but the mechanism of action for a chronic carcinogenic mechanism of action would not be triggered by needlestick exposures because of the toxicokinetics of peptides. A sufficient peak concentration would not be sustained for a sufficient duration to produce chronic effects. In short, exposures to this drug in the occupational exposure scenarios are exceedingly low . . . de minimis, in my opinion.''

NIOSH response: While inhalation of liraglutide in current formulations can be ruled out, NIOSH still evaluated inhalation routes of exposure. NIOSH does not limit the evaluation to current formulations. NIOSH determined that liraglutide would not pose a hazard to workers even via the inhalation route. No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

c. Is the determination that the amount of exposure to liraglutide in a healthcare setting does not constitute a hazard for healthcare workers reasonably supported by the available scientific information? Please explain.

Reviewer 1 comment: ''Yes, the determination that the amount of exposure to liraglutide in a healthcare setting does not constitute a hazard for healthcare workers is reasonably supported by the available scientific information. Given the mechanisms of action of liraglutide, sustained exposure is required for significant effect, which would not likely be encountered in the occupational setting if medication is prepared, transported and administered as indicated (*i.e.,* in sealed vials).''

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

Reviewer 2 comment: ''Yes. In my review of the literature, the hazard to humans due to the ''black box'' warning about thyroid tumors is low. In the study, at least some of the cases of thyroid tumors occurred in subjects with existing thyroid disease, and

should have been excluded. Secondly, a mitogenic mode of action is suggested, which would require continuous exposures, which are unlikely. Evidence suggests species-specific effects due to elevated GLP–1R receptor levels and downstream signaling. The knockout mouse study seems compelling in suggesting that the effects observed in rodents should not be directly extrapolated to humans. Thus, in addition to having a de minimis exposure, the potential of adverse effects is less than previously recognized. While the developmental effects in rats/rabbits cannot be ruled out, the statistical significance/magnitude of these hazards was not identified. For example, while it was stated that doses in the same range as human caused developmental effects, it was not clear that this was a 'human equivalent dose' . . . some sort of body weight ¾ calculation. That lack of significance/magnitude of these potential hazards also raise concerns about the potential over-interpretation of these developmental effects. Thus, de minimis exposures coupled with lower than previously recognized hazards combine to lower the risks to healthcare workers in clinical settings. NIOSH has evaluated data and estimated exposures and has come to the correct conclusion. I fully agree.''

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

d. What alternative approaches could be considered to characterize the potential hazard to workers from peptide-based drugs?

Reviewer 1 comment: ''The alternative approaches that could be considered to characterize the potential hazard to workers from peptide-based drugs include surveillance regarding OSHA reportable injuries or illness related to occupational exposure to liraglutide and periodic review of the Medullary Thyroid Carcinoma (MTC) Surveillance Study [Hale et al. 2020].''

NIOSH response: The Medullary Thyroid Carcinoma (MTC) registry could provide data that could affect future evaluations of liraglutide. NIOSH evaluates drugs when a safety related labeling change is posted regarding the drugs [NIOSH 2023]. Further, if new data related to the MTC surveillance study were brought to NIOSH's attention, NIOSH could further evaluate the potential hazards of liraglutide exposures to healthcare workers as indicated in the NIOSH *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings* [NIOSH 2023].

Reviewer 2 comment: ''It might be possible to do a literature search on studies for adverse effects in occupational exposures to insulin. This is a common peptide hormone with 100 years of clinical experience. I'd imagine that the exposures to healthcare workers to insulin (by all routes) would be similar to liraglutide. As liraglutide had a molecular weight about 7-fold higher than that of insulin, it would be more poorly absorbed and less of a risk. The incidence of adverse effects in worker exposures in health care settings for insulin could be used as a 'worst-case' analogue to estimate of the incidence of liraglutide exposures and potential risk.''

NIOSH response: Due to the rapid acute effects of insulin, NIOSH agrees it would likely serve as a worst-case scenario and overestimate the effects of exposure to liraglutide. Also, as the reviewer notes, any use of insulin as a surrogate would involve consideration of many caveats, including absorption, effect intensity/duration, and different specific mechanisms of action. These uncertainties would make the resulting evaluation less useful for the purpose of NIOSH's hazard identification for placement on the *List.* Therefore, NIOSH would not use insulin as a surrogate for evaluation of the hazard of liraglutide or other GLP–1 agonist drugs since only hazard identification is the basis for placement on the List. No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

e. Is there any additional information that NIOSH should consider in its reevaluation of liraglutide?

Reviewer 1 comment: ''There is no additional information that NIOSH should consider in its reevaluation of liraglutide at this time.''

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

Reviewer 2 comment: ''As with all things, decisions are based on the best available data. As the availability of data will change with time, a further reevaluation in the decades that come will be appropriate should new data become available about any of the potential health effects or new ones that emerge.''

NIOSH response: No changes were made to the *NIOSH Final Reevaluation Determination of Liraglutide on the NIOSH List of Hazardous Drugs in Healthcare Settings* based on this comment.

2. Pertuzumab Peer Review

Three external peer reviewers submitted responses to NIOSH. Overall, all agreed with the general approach NIOSH used to determine if the molecular properties, molecular size in this case, of pertuzumab would limit the hazard it poses in healthcare settings. Two of the reviewers agreed with the conclusion that NIOSH proposed, which was that pertuzumab would not be able to pose a developmental hazard in healthcare settings. They did however believe that the NIOSH inhalation exposure scenario overestimated the potential systemic exposure and that an incidental needlestick would pose the most relevant exposure. Both expressed an interest in other potential hazards. One expressed an interest in cardiac hazards and one in sensitization.

The third reviewer, while agreeing that the approach was sound and the assumptions reasonable, disagreed with NIOSH on some points and felt that pertuzumab should remain on the *List.* This reviewer stated that there was not enough quantitative data to rule out potentially relevant levels of exposures via the dermal and oral routes. They stated that without quantitative data to support the assumptions made that the lack of a NOAEL and the severity of effects in the animal study in the FDA review supported leaving pertuzumab on the *List.* This reviewer expressed a concern that while the observed effect, oligohydramnios, was reversible that did not rule out that there are no adverse effects to the fetus, including potential upstream and downstream effects. They also expressed concerns that using trastuzumab as a model for pertuzumab effects might not be appropriate. There may be some differences in their effects, as some differences in molecular signaling have been identified in a cell system model.

a. Reviewer 1

Reviewer 1 comment 1: ''More quantitative information is needed, quantitative gaps need to be addressed, and justification in the face of the gaps need to be outlined. The examination of routes of exposure seems to be limited to the molecular properties of the drug. Workplace exposure scenarios are not described (*e.g.,* opportunities of splashing, use of PPE such as gloves, potential for hand to mouth activity, etc.). Inclusion of these exposure scenarios would be informative, but if they are not described the rationale for

not providing a set of exposure scenarios, should be explained.''

NIOSH response: Evaluation of workplace exposure scenarios are outside of the scope of the *List.* Because the large variety of scenarios that may take place in healthcare workplaces and the different properties of hazardous drugs, NIOSH does not take into account all of the possible workplace exposure scenarios. Therefore, for pertuzumab, NIOSH considered maximum occupational systematic exposure via all available routes to be less than a full therapeutic dose. In this case, NIOSH considered if the properties of the drug might limit the systemic availability via worst-case relevant routes of occupational exposure. Individual scenario analysis would not add significantly to these findings, as the resultant exposures would likely be much less than the worst-case scenarios. This is why the examination is limited to molecular properties of the drug and an evaluation of worst-case workplace exposures.

Reviewer 1 comment 2: ''The assumptions are reasonable, but the evidence to support them is very limited. Research gaps should be identified and described. An example is the lack of quantitative data on the absorption of pertuzumab following oral exposure. The statement that bioavailability as 'low' lacks clarity. The studies cited to back up the qualitative statement do not present quantitative data or reference other studies to support the claims regarding oral bioavailability.''

NIOSH response: No quantitative data on the oral bioavailability of pertuzumab exist. The bioavailability of monoclonal antibodies and proteins are low because they are degraded in the gastrointestinal tract and are poorly absorbed through the gastrointestinal epithelium [Keizer et al. 2010; Wang et al. 2008]. This severely limits the bioavailability of intact proteins passing through the GI tract. Because of this, systemic exposure via the oral route is likely much lower when compared with the inhalation worst-case scenario NIOSH considered. The same is true for dermal exposures. The worst-case scenario NIOSH addressed in the inhalation scenario is likely the worst-case scenario overall. Some clarifying language has been added to the appropriate sections of the document.

Reviewer 1 comment 3: ''Oligohydramnios being reversible does not necessarily indicate no adverse effect on the fetus. Downstream and upstream effects should be considered.''

NIOSH response: Only one case study of exposure to pertuzumab during pregnancy in a human was identified and that exposure included co-exposure with trastuzumab. Information was available on exposure to trastuzumab, the similar monoclonal antibody targeting the same HER2 mechanism. No long-term follow-up on the exposed children was identified, but the Zagouri et al. [2013] review noted that all children with only first trimester exposure, when treatment was ceased, had good outcomes, and all babies born healthy were still healthy at nine months after birth. However, this is the only follow-up identified.

Reviewer 1 comment 4: ''Given the severity of the renal effects seen in cynomolgus monkey offspring, removal of pertuzumab from the *List* based on its molecular properties related to exposure should be based on a strong evidence base (*e.g.,* direct evidence in humans that a single low exposure dose does not carry risk of renal effects in the fetus).''

NIOSH response: Only one case study identifying human pregnancy exposure to pertuzumab was identified and that patient was also receiving trastuzumab. In the cynomolgus monkey study, the effects did appear to be dose-related and treatment was continued throughout gestation. Data in humans with in utero exposure to the monoclonal antibody trastuzumab, which targets the same mechanism, suggest that the effects are reversible, and when exposure is ceased, outcomes improve with healthy babies being born. Lambertini et al. [2019] found 12 cases of potential in utero exposure to trastuzumab and/or the HER2 targeting small molecule drug lapatinib, seven had elective abortions and five continued the pregnancy. In all cases where the child was born, exposure was only during the first trimester. Outcomes at birth were normal for four. In the fifth, the baby was delivered via caesarian at 34 weeks due to growth retardation. In that case, the mother had received radiation therapy for brain metastasis and died 17 days following delivery. The mechanism of action of pertuzumab appears to lead to reversible effects when exposure is not continuous.

Reviewer 1 comment 5: ''The use of another drug, trastuzumab, as a model for pertuzumab, may provide some insights, but this evidence must be interpreted with caution because small differences between substances with similar structures or mechanisms of action can significantly impact their biological activity, as exemplified by (but not limited to) the ability of pertuzumab, but not trastuzumab to induce activation of the PI3K cell survival pathway [FDA 2012].''

NIOSH response: In cell lines, pertuzumab does block activation of the PI3K survival pathway as indicated by decreased phosphorylation of AKT in a cancer cell line.[6] Physiological effects appear similar between the two monoclonal antibodies. There are no available reports of fetal effects of pertuzumab without concurrent trastuzumab exposure in humans during pregnancy. Trastuzumab was used as a model of human exposure during pregnancy because the primary target pathway for the two molecules is the same, and the effect in humans and the cynomolgus monkeys are the same. This indicates that the mechanism of action is related to the similar HER2 inhibition of the two molecules.

Reviewer 1 comment 6: ''The lack of a NOAEL suggests that a strong case is needed for this drug to be exempt based on the 'molecular properties' argument.''

NIOSH response: While there is no identified NOAEL stated in the available monkey studies, the effects do appear to increase in severity with dose. For trastuzumab, which targets the same molecular mechanism, it also appears that continued exposure in the later trimesters of pregnancy is required to initiate the effects that lead to oligohydramnios. The molecular properties of monoclonal antibodies mean the bioavailability to a single exposure is lower. Repeated exposure to a level that might lead to systemic exposures that could lead to continued reversible effects are also unlikely.

Reviewer 1 comment 7: ''Would this section [the section called Hazard Characterization] be more appropriately named something related to exposure rather than hazard?''

NIOSH response: Under the heading Integrated Toxicity and Molecular Property Hazard Characterization of the *NIOSH Reevaluation of Pertuzumab on the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings,* NIOSH discussed how the relevant molecular properties, in this case, molecular weight, affect the hazard of the drug. In this case, consideration of relevant potential exposures influence how the potential hazard is characterized. This information is about hazard characterization rather than exposure. No change was made to the *NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings* in response to this comment.

[6] Pertuzumab, but not trastuzumab, blocks the activation of a cell survival pathway in cultured cell lines in an *in vitro* assay.

b. Reviewer 2

Reviewer 2 comment 1: ''An accidental needle stick is the only reasonable route of exposure for healthcare workers. The skin serves as an effective barrier to penetration of most environmental sources of chemicals, including large molecules such as pertuzumab. Orally, pertuzumab will be degraded by intestinal proteases. Since pertuzumab is provided as a solution in a single use vial to be mixed with saline prior to infusion, inhalation of droplets will not provide sufficient exposure to result in risks to the fetus of a healthcare worker.''

NIOSH response: NIOSH does not limit the consideration to the currently available formulation. Formulations may change over time, so inhalation was considered.

Reviewer 2 comment 2: ''The estimate for inhalation exposure of 5% was developed for workers in a manufacturing setting to derive occupational exposure limits but is likely an overestimate of potential exposure of pertuzumab in a healthcare setting. According to the data and discussion in Pfister et al. [2014], the 5% value represents a maximum bioavailability for proteins >40 kDa; 1.7% was the median. According to the package insert, pertuzumab has an approximate molecular weight of 148 kDa. Proteins >40 kDa were applied by intratracheal instillation (Table 1). This is not a likely route of exposure for pertuzumab in a healthcare setting.''

NIOSH response: While intratracheal instillation is not a likely route of exposure for a drug in a healthcare setting, it provided the only data to consider bioavailability through the respiratory tract tissues. The studies reviewed by Pfister et al. [2014] did include studies that looked at intratracheal instillation of monoclonal antibodies like pertuzumab.

Reviewer 2 comment 3: ''Another sensitive endpoint could be assessing respiratory sensitization in workers though workplace monitoring, but this should be applied only if there is a hazard identified in a clinical trial or post marketing setting. According to Pfister et al., respiratory sensitization has not been observed in a manufacturing setting to date.''

NIOSH response: The NIOSH *List* does not consider respiratory sensitization as a criterion for identifying potential drug hazards.

c. Reviewer 3

Reviewer 3 comment 1: ''[A]nother potential health effect could be heart problems associated with Perjeta treatment [Shrim et al. 2007; Swain et al. 2014]. The decreased left ventricular ejection fraction resulting in cardiac failure and congestive heart failure has been listed as possible side effects of the treatment and should be reversible when the treatment is stopped. To the best of my knowledge, there were no reported heart related issues with the offsprings from the in vivo studies. Whether the occupational exposure concentrations would be high enough to cause the potential heart problems or not, this should be considered as a probable hazard to healthcare workers in occupational exposure settings.''

NIOSH response: Cardiac effects may occur at treatment levels, but these do not meet NIOSH criteria. Even in the worst-case scenario, systemic exposures in healthcare workplaces are unlikely to reach levels near treatment levels. The cardiac effects are unlikely to be of relevance in occupational exposures in healthcare settings because they are associated with exposures only at treatment levels.

Reviewer 3 comment 2: ''Based on the highest concentration provided (30 mg/mL), an accidental needle stick delivery based on the different needle properties [Foster et al. 2010; Gaughwin et al. 1991; Krikorian et al. 2007; Mast et al. 1993; Napoli and McGowan 1987] would be negligible (<1 µL) to achieve the human dose. Since pertuzumab is not volatile, an inhalation route would pose negligible hazard. As mentioned above, the accidental needle stick delivery would be extremely low to achieve the human dose.''

NIOSH response: NIOSH evaluated a scenario for needlestick that went beyond the worst case. NIOSH agrees that an incidental needlestick would not deliver a human dose, but even if it did, multiple needle sticks providing the relevant exposures are not considered to be likely. The effect of concern is reversible and requires repeated exposure to maintain the systemic exposure levels that would cause oligohydramnios, which would not happen even in the NIOSH evaluated worst-case scenario.

V. Summary of Updates and Changes to NIOSH List of Hazardous Drugs in Healthcare Settings

In this update, 25 drugs have been added to the *List* since the publication of the *NIOSH List of Antineoplastics and Other Hazardous Drugs, 2016.* Twelve of those newly added drugs have special handling information from the manufacturers. Seven drugs have been removed from the *List,* including liraglutide and pertuzumab. These additions and removals, as well as the reorganization discussed below, are now reflected in the *NIOSH List of Hazardous Drugs in Healthcare Settings, 2024,* available on the NIOSH website (*see https://www.cdc.gov/niosh/healthcare/hazardous-drugs/index.html*) and in the docket for this activity.

Drugs reviewed for this update were either new drug approvals or those drugs that received new safety-related warnings from FDA in the period between January 2014 and December 2015. In addition to these updates, the tables categorizing hazardous drugs have been reorganized.

Table 1 now includes 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 and/or by IARC as carcinogenic to humans (Group 1) or probably carcinogenic to humans (Group 2A).

In the 2016 *List,* Table 1 focused on antineoplastic drugs. However, in the 2024 *List,* NIOSH has removed the identifier ''antineoplastic'' because of advances in cancer treatment, the therapeutic designation ''antineoplastic'' no longer indicates drugs of high toxicity. Therefore, Table 1 focuses on the toxicity and carcinogenicity of drugs, regardless of their therapeutic use.

Table 2 now contains drugs that:

- Meet one or more of the NIOSH definitions of a hazardous drug, and
- Are not drugs with MSHI, and
- Are not classified by NTP as known to be a human carcinogen or by IARC as carcinogenic to humans (Group 1) or probably carcinogenic to humans (Group 2A).

Some of the drugs in Table 2 have adverse reproductive effects for populations at risk.

This table includes those drugs that only meet the NIOSH criteria as a developmental (including teratogenicity) and/or reproductive hazard. In the 2016 update of the *List,* such drugs were included in a separate table (Table 3), which has been combined with Table 2. Drugs that only meet the NIOSH criteria as a reproductive and/or developmental hazard are identified in a column labeled ''Only Developmental and/or Reproductive Hazard'' in the 2024 *List.*

Changes to the placement of drugs on the *List,* including drugs that are no longer considered hazardous and those that have been moved from one table to another, are described in a new section in the 2024 *List* and not called out in a

separate table as in the 2016 update (former Table 4).

In the 2016 update, Table 5 provided information on recommended exposure controls for hazardous drugs based on formulations. NIOSH moved and expanded the risk management information formerly provided in Table 5 and developed a new document, *Managing Exposures.* This document includes information on engineering controls, administrative controls, and PPE for working with hazardous drugs in healthcare settings. It is available on the NIOSH Hazardous Drug Exposures in Healthcare website.[7]

In previous updates, NIOSH included a supplemental information column that contained additional information about individual drugs, including pregnancy categories. However, as of 2015, FDA no longer uses the pregnancy categories for drugs and this information was not necessarily related to the NIOSH decision to place the drug on the *List.* Therefore, NIOSH has removed the supplemental information column from the 2024 *List.*

Finally, in the 2024 *List,* NIOSH has added a column to identify drugs that were approved by CDER under a BLA. These drugs tend to be large, protein-based molecules. The properties of these drugs may affect the strategies used to address the hazards they pose. Identifying them would aid in hazard identification for risk management in healthcare settings. NIOSH notes that some of the drugs that were approved under a BLA may include conjugates with their own separate hazards, which should also be taken into account.

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John Howard,

Director, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Centers for Disease Control and Prevention (CDC)/Health Resources and Services Administration (HRSA) Advisory Committee on HIV, Viral Hepatitis and STD Prevention and Treatment; Notice of Charter Renewal

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

ACTION: Notice of charter renewal.

SUMMARY: The Centers for Disease Control and Prevention (CDC), within the Department of Health and Human Services (HHS), announces the renewal of the charter of the Centers for Disease Control and Prevention (CDC)/Health Resources and Services Administration (HRSA) Advisory Committee on HIV, Viral Hepatitis and STD Prevention and Treatment (CHAC).

FOR FURTHER INFORMATION CONTACT: Jonathan Mermin, M.D., M.P.H., Designated Federal Officer, CDC/HRSA Advisory Committee on HIV, Viral Hepatitis and STD Prevention and Treatment, Centers for Disease Control and Prevention, Department of Health and Human Services, 1600 Clifton Road NE, Mailstop H24–6, Atlanta, Georgia 30329–4027. Telephone: (404) 639–8000; email: *JMermin@cdc.gov.*

SUPPLEMENTARY INFORMATION: CDC is providing notice under 5 U.S.C. 1001–1014 of the renewal of the charter of the Centers for Disease Control and Prevention (CDC)/Health Resources and Services Administration (HRSA) Advisory Committee on HIV, Viral Hepatitis and STD Prevention and Treatment, Centers for Disease Control and Prevention, Department of Health and Human Services. This charter has been renewed for a two-year period through November 25, 2026.

The Director, Office of Strategic Business Initiatives, Office of the Chief Operating Officer, Centers for Disease Control and Prevention, has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities, for both the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry.

Kalwant Smagh,

Director, Office of Strategic Business Initiatives, Office of the Chief Operating Officer, Centers for Disease Control and Prevention.

[FR Doc. 2024–30414 Filed 12–19–24; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Mine Safety and Health Research Advisory Committee; Notice of Charter Renewal

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

ACTION: Notice of charter renewal.

SUMMARY: The Centers for Disease Control and Prevention (CDC), within the Department of Health and Human Services (HHS), announces the renewal of the charter of the Mine Safety and Health Research Advisory Committee (MSHRAC).

FOR FURTHER INFORMATION CONTACT: Robert Randolph, M.S., Designated Federal Officer, Mine Safety and Health Research Advisory Committee, Centers for Disease Control and Prevention, Department of Health and Human Services, 626 Cochrans Mill Road, Pittsburgh, Pennsylvania 15236. Telephone: (412) 386–4660; email: *RRandolph@cdc.gov.*

SUPPLEMENTARY INFORMATION: CDC is providing notice under 5 U.S.C. 1001–1014 of the renewal of the charter of the Mine Safety and Health Research Advisory Committee, Centers for Disease Control and Prevention, Department of Health and Human Services. This charter has been renewed for a two-year period through November 30, 2026.

The Director, Office of Strategic Business Initiatives, Office of the Chief Operating Officer, Centers for Disease Control and Prevention, has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities, for both the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry.

Kalwant Smagh,

Director, Office of Strategic Business Initiatives, Office of the Chief Operating Officer, Centers for Disease Control and Prevention.

[FR Doc. 2024–30408 Filed 12–19–24; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

[Document Identifier: CMS–R–65 and CMS–10142]

Agency Information Collection Activities: Submission for OMB Review; Comment Request

AGENCY: Centers for Medicare & Medicaid Services, Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: The Centers for Medicare & Medicaid Services (CMS) is announcing an opportunity for the public to comment on CMS' intention to collect information from the public. Under the Paperwork Reduction Act of 1995 (PRA), federal agencies are required to publish notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension or reinstatement of an existing collection of information, and to allow a second opportunity for public comment on the notice. Interested persons are invited to send comments regarding the burden estimate or any other aspect of this collection of information, including the necessity and utility of the proposed information collection for the proper performance of the agency's functions, the accuracy of the estimated burden, ways to enhance the quality, utility, and clarity of the information to be collected, and the use of automated collection techniques or other forms of information technology to minimize the information collection burden.

DATES: Comments on the collection(s) of information must be received by the OMB desk officer by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE **FEDERAL REGISTER**].

ADDRESSES: Written comments and recommendations for the proposed information collection should be sent within 30 days of publication of this notice to *www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting