UPDATE OF NIOSH HAZARDOUS DRUG LIST (APPENDIX A) FOR THE NIOSH ALERT: PREVENTING OCCUPATIONAL EXPOSURES TO ANTINEOPLASTIC AND OTHER HAZARDOUS DRUGS IN HEALTH CARE SETTINGS (April 6, 2009)

On June 18, 2007 NIOSH published a Notice of Request for Public to Submit Comments and Attend Public Meeting regarding the draft document, "NIOSH Hazardous Drugs List Update." This document is a summary of the comments received through NIOSH Docket Number 105 with NIOSH responses.

NIOSH should clearly articulate the scientific evidence or basis for evaluating whether a drug fits the definition of a hazardous drug.

NIOSH used the NIOSH definition of a Hazardous Drug as outlined in the Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings (see NIOSH Definition of Hazardous Drugs below). We assessed the evidence found in the Prescribing Information for organ toxicity, reproductive toxicity, genotoxicity, carcinogenicity, teratogenicity, and potency. We assessed each drug individually, not classes of drugs.

All information came from the drug package inserts:

1. Carcinogenicity: If information was available on cancer in patients treated with a drug, this was compelling evidence to classify it as carcinogenic. For newer drugs, this was often a few cases so the evidence was not as solid as it would be for an epidemiological study. If there were supporting animal studies, it would help to strengthen the human data.

If the only information came from animal studies, the number of species, the effect in more than one gender and more than one organ was weighed. If the tumors were species-specific, this was considered in the evaluation.

2. Teratogenicity: The extent and the severity of the effects were evaluated. Similar to carcinogenicity, the number of species and the effect in more than one organ was weighed. If effects were seen at doses well above the therapeutic dose, this was taken into consideration.

3. Reproductive toxicity: If information was available on cancer in patients treated with a drug, this was compelling evidence to classify it as a reproductive toxin. The FDA reproductive category was also evaluated. A drug in Category X was considered a reproductive toxin. Most drugs in Category D were also considered a reproductive toxin, but other factors such as dose were evaluated. If effects were seen at doses well above the therapeutic dose, this was taken into consideration.

4. Organ toxicity at low doses: If serious organ toxicity was evident at low doses (a therapeutic dose of 10 mg/day or a laboratory dose of 1mg/kg/day), the drug was usually considered toxic.

5. Genotoxicity: Often results from a battery of genetox studies were reported in the package insert and the results were usually mixed. In vivo data usually outweighed in vitro data. However, if several in vitro studies gave positive results, the drug was usually considered genotoxic.

6. Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria: This was seldom used because it was superseded by one of the above criteria. (Example: a new Thalidomide analog that has been approved could be included based on its structure, but it would already be considered for the list due to its reproductive Category X classification)

NIOSH Definition of Hazardous Drugs

The 1990 ASHP definition of hazardous drugs ** was revised by the NIOSH Working Group on Hazardous Drugs for this Alert. Drugs considered hazardous include those that exhibit one or more of the following six characteristics in humans or animals:

1. Carcinogenicity
2. Teratogenicity or other developmental toxicity ††
3. Reproductive toxicity ††
4. Organ toxicity at low doses ††
5. Genotoxicity ‡‡
6. Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria.

**ASHP [1990] definition of hazardous drugs:

1. Genotoxicity (i.e., mutagenicity and clastogenicity in short-term test systems)
2. Carcinogenicity in animal models, in the patient population, or both, as reported by the International Agency for Research on Cancer (IARC)
3. Teratogenicity or fertility impairment in animal studies or in treated patients
4. Evidence of serious organ or other toxicity at low doses in animal models or treated patients.

†† All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less). For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg per day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 µg/m3 after applying appropriate uncertainty factors [Sargent and Kirk 1988; Naumann and Sargent 1997; Sargent et al. 2002]. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. Under all circumstances, an evaluation of all available data should be conducted to protect health care workers.

‡‡In evaluating mutagenicity for potentially hazardous drugs, responses from multiple test systems are needed before precautions can be required for handling such agents. The EPA evaluations include the type of cells affected and in vitro versus in vivo testing [51 Fed. Reg. 34006–34012 (1986)].

NIOSH should ensure that the information in the Alert is consistent with other recommendations to avoid confusion for both employers and employees, including the regulations covering the use of radiopharmaceuticals.

NIOSH agrees that it is important for the Alert to be consistent with existing government regulations and recommendations. NIOSH is working with representatives from the Food and Drug Administration, Occupational Safety and Health Administration, American Society of Health-System Pharmacists, Oncology Nursing Society, as well as other stakeholders to ensure compatibility in the final updated Alert. Additionally, NIOSH believes that radiopharmaceuticals are sufficiently regulated and will not consider them as part of the final list.

NIOSH should consider the consequences of misclassifying a drug as hazardous, such as increased administrative burden, increased cost associated with staff time, training, drug transportation and disposal, decreased credibility of the hazardous drug designation and difficulty with risk communication.

NIOSH appreciates the concerns regarding the consequences of misclassifying drugs as hazardous and is following a rigorous process in order to ensure the validity of the final list. This process has included working closely with government agencies and stakeholders, utilizing expert peer review and actively engaging the public through notice and comment.

NIOSH should consider the likelihood of exposure when developing the final list of hazardous drugs. It was felt that dosage form, route of exposure, and standard drug preparation practices all mitigate the risk of occupational exposure.

NIOSH acknowledges that some drugs defined as hazardous may not pose a significant risk of direct occupational exposure because of their dosage formulation (for example, coated tablets or capsules - solid, intact medications that are administered to patients without modifying the formulation). However, they may pose a risk if solid drug formulations are altered, such as by crushing tablets or making solutions from them outside a ventilated cabinet. This is stated directly in the Alert.

With regard to route of exposure, NIOSH considered expert reviewer comments and balanced the inherent hazard with potential exposures. The management of hazardous drugs should take into consideration the potential for exposure, among other factors with the resultant recommendations tailored to the risk of exposures.

NIOSH should consider dose, dose-response, pharmacokinetics, potency, mechanism of action and margin of safety between the exposure levels that may be encountered in the healthcare environment and the doses known to cause adverse genotoxic, reproductive, developmental, or systemic effects in animals or patients.

The initial proposed list was refined based on comments from the public, stakeholders and external experts.

Dose, dose-response, potency and margin of safety were considered when assessing the weight of the evidence available from the Package Insert. In general, drugs with a therapeutic dose that was similar to the dose causing adverse health effects were considered to represent a greater potential for hazard.

NIOSH recognizes that the mechanisms of action of drugs can be an important determinant of whether the drug may be hazardous to a worker (e.g. targeted therapies that bind exclusively to receptors expressed in disease states). Consequently, the mechanism of action was considered when compiling the revised draft list.

NIOSH recognizes that pharmacokinetics may be an important determinant of whether the drug can be hazardous to a worker (e.g. some drugs may not be readily absorbed dermally or by inhalation). Consequently, the pharmacokinetics of the drugs was considered when compiling the revised draft list.

NIOSH must also consider the possibilities of accidental exposures and low dose occupational exposures, possibly over many years. The goal of NIOSH is to develop a concise list that includes well-defined hazardous drugs and will be useful to the end users without imposing an undo burden.

NIOSH should consider the characteristics of the health care practitioner as another important factor in determining toxicity. For example, immunocompromised individuals and women of child-bearing age may have special drug handling considerations. The list of medications that may be harmful to specific populations extends beyond those found on the NIOSH list. It may be more appropriate to advise use of universal precautions to those groups rather than enforcing restrictions more broadly.

NIOSH is aware of the issues related to special populations. In the NIOSH Alert on Hazardous Drugs, NIOSH recommends the use of a universal precautions approach.

NIOSH should be aware that reclassification of an existing drug into the hazardous category may result in practitioners and patients recognizing the drugs as "newly" hazardous.

The term "hazardous drug," as it used in this Alert, applies to occupational exposures only and does not include the intentional administration of drugs to patients. Given that the available information regarding existing drugs continues to evolve, periodic evaluation will be necessary in order to continue to protect healthcare workers from occupational exposures. NIOSH is following a rigorous process in order to ensure that the final list of drugs is consistent with the hazardous drug definition as established in the Alert.

Several comments addressed whether a specific drug met the NIOSH definition of a hazardous drug.

Development of the proposed list of drugs was based on new FDA drug approvals since September 2004 and FDA warnings on existing drugs. For the preliminary list of drugs that fit the NIOSH definition of hazardous drugs, over 60 drugs were identified and published for comment in NIOSH Docket Number 105.

After expert panel review, public review and comment, input from stakeholders and review of the scientific literature NIOSH has proposed a second, draft list of hazardous drugs. A number of drugs were removed from the initial proposed list based on comments from the various groups and organizations. The second, draft list identifies 26 drugs that fit the NIOSH definition of hazardous drugs and provides the rationale for inclusion.

NIOSH should carefully re-evaluate the inclusion of monoclonal antibodies as appropriate additions to the roster of hazardous drugs. Some of these materials might represent appreciable health risks upon intravenous or subcutaneous dosing; however, there is little or no evidence to suggest monoclonal antibodies as relevant occupational hazards given the low likelihood of substantial systemic exposure in healthcare settings where dermal and possibly respiratory exposure predominate.

NIOSH has taken the approach to evaluate each drug on an individual basis and not based on its classification. Individual monoclonal antibodies may possess unique characteristics that would warrant them being included on the list of hazardous drugs.

NIOSH should further stratify the list of hazardous drugs according the likelihood of harmful effects. Surrogates suggested include route of absorption, dosage form, drug mechanism, inherent toxicity, route of administration and overall anticipated extent of exposure.

NIOSH is of the opinion that a tiered approach would not be a practical solution and that a single, precise list generated with input from as many stakeholders as possible is the best approach. To this end, NIOSH has solicited the assistance of the public, interested stakeholders, drug manufacturers and a group of 10 expert reviewers.

There is an ongoing need to increase awareness about risks associated with other hazardous drugs and the use of antineoplastic drugs for nontraditional uses, such as rheumatoid arthritis, lupus, nephritis, and multiple sclerosis. Additional educational efforts should be directed to housekeeping, patient transport, and nonclinical staff who may be exposed to hazardous drug products or wastes. Education that instructs on the proper use, and limitations, of personal protective equipment should also be enhanced.

NIOSH is in agreement with these comments and would welcome the opportunity to partner with interested stakeholders on educational outreach programs. NIOSH is currently addressing some of these issues through the publication of future NIOSH

documents, many of which will made be available for public comment on the NIOSH web site.

NIOSH received contrasting comments regarding the utilization of occupational exposure limits (OEL) for determining handling of hazardous drugs. Some comments supported the use of occupational exposure limits, whereas others challenged their utility based on the current variability in models, lack of standards and lack of regulations utilized to calculate OELs.

The use of OELs in the healthcare setting would require an immense amount of work to perform risk assessments on the approximately 120 current hazardous drugs identified by NIOSH. In many cases, the information required to conduct this process may not be available. The utility of OELs given the large number of drugs in use would be limited at best.

The table format used in the new proposed "new FDA Drugs and warnings Fitting NIOSH Criteria for Hazardous Drugs 2006 is a clearer format than the original "Appendix A" list with respect to understanding the rationale for listing because of the five hazard criteria columns. In addition, the "how supplied" information would be helpful for workplaces in developing handling guidance. NIOSH should change the original Appendix A to the new format.

The NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings was published in September 2004. Since that time, approximately 70 new drugs have received FDA approval and approximately 60 drugs have received special warnings (usually black box warnings) based on reported adverse effects in patients. An additional 18 drugs were included from the updated NIH Hazardous Drug List.

In order to continue to provide healthcare workers and their employers with the best information possible, it is important to update the 2004 list in a timely manner. Consequently, NIOSH is not considering a change in format at this time. Consideration of revisions to the format will be reserved for future updates.