Dragon, Karen E. (CDC/NIOSH/EID)

From: Sara Radcliffe [sradcliffe@bio.org]
Sent: Tuesday, June 30, 2009 4:56 PM
To: NIOSH Docket Office (CDC)
Subject: Comments to 105-A: Biotechnology Industry Organization
Attachments: 2009 06 30 BIO Comments on NIOSH Hazardous Drugs List FINAL.doc

Dear Sir/Madam,

Please find attached our comments to NIOSH docket number 105-A "Updating the List of Hazardous Drugs for the NIOSH Alert: Additions and D

Regards,

Sara

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June 30, 2009

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Re: Updating the List of Hazardous Drugs for the NIOSH Alert: Additions and Deletions to the NIOSH Hazardous Drug List; Federal Register Volume 74, Number 81, Pages 19570-19571; 29 April 2009; Docket Number NIOSH-105-A

Dear Sir or Madam:

The Biotechnology Industry Organization (BIO) wishes to thank NIOSH for the opportunity to submit comments on the National Institute for Occupational Safety and Health's (NIOSH's) revisions to "Appendix A. Drugs Considered Hazardous, in the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings," DHHS Publication No. 2004-165 (2004). The safe handling of drugs and biologics is an important issue for healthcare workers and BIO supports the efforts NIOSH has taken to update the Hazardous Drugs List. We also strongly support NIOSH for incorporating well-accepted scientific principles in the decision-making process, such as consideration of mechanism, route of exposure, potency, and the principles of risk assessment.

BIO represents more than 1200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit mankind by providing better healthcare, enhance agriculture, and a cleaner and safer environment. We appreciate both the opportunity to submit general and specific comments on the Hazardous Drug Alert and your inclusion of BIO as a representative stakeholder.

We support the scientific rigor in NIOSH's process to identify those drugs "Fitting" the criteria described in "New FDA Drugs and Warnings Fitting NIOSH Criteria for Hazardous Drugs 2006" on the NIOSH web site. The inclusion of the National Academy of Sciences 4-step principles of risk assessment (hazard identification, exposure assessment, dose-response assessment and risk characterization) (NRC, 1983) is exemplified, and the risk-classification system identified only those drugs that are "hazardous" in the occupational context. This facilitates appropriate handling and exposure control precautions and properly directs limited health care resources. NIOSH has addressed the recommendations in our letter dated January 30, 2008 and we commend these changes to Appendix A of the Hazardous Drug Alert.

1. Need for Stakeholders to Understand the Process/Approach Used to Develop the Lists of Drugs "Fitting" and "Not Fitting" the NIOSH Criteria.

   Comment 1: The "Update of NIOSH Hazardous Drug List (Appendix A) for the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings (April 6, 2009)", on the NIOSH web site, explains why some drugs have been included and others excluded, and the selection and evaluation process. BIO supports this transparency and the adoption of the weight-of-evidence approach that incorporates consideration of all scientifically relevant information, e.g., molecular weight and bioavailability by the routes of exposure traditionally considered in occupational health risk assessments (i.e., inhalation, oral, and dermal).

2. Exclusion of High Molecular Weight Proteins (HMWPs) from the Hazardous Drugs List

   Comment 2: Occupational exposure traditionally focuses on three exposure pathways: dermal, oral and inhalation. For the reasons described below, and unlike for small molecular weight pharmaceuticals, none of these exposure pathways are likely to be of concern for high molecular weight protein (HMWPs) therapeutics.

   - The skin, pulmonary system, and gastrointestinal system are effective barriers to absorption of HMWP therapeutics (molecular weights ~50-150 kDa). There is an extremely low likelihood of absorption. Biotherapeutics are IgG-based and "immunoglobulins have restricted access across diffusional barriers unless transport is facilitated by specific mechanisms" (Roskos, 2004); this is the reason these drugs are administered only by injection. In addition, it has been suggested that a compound must be < 500 daltons (0.5 kDa) to penetrate the stratum corneum (the outermost layer of the epidermis) (Bos and Meinardi, 2000). Monoclonal antibodies (mAbs), for example, are 300 times larger than this maximum size. HMWP therapeutics are intricately folded proteins that are easily susceptible to denaturation (unfolding and subsequent aggregation) from environmental conditions (Vermeer and Norde, 2000), and loss of biological activity would occur in the acidic environment in the stomach. Due to the large particle size of HMWP therapeutics (approximately μ10), the pulmonary system provides an effective barrier to absorption.

- The risks of genotoxicity are non-existent or very low for biotherapeutics because they are not designed to interact directly with DNA or other chromosomal material (ICH S6, 1997).

BIO supports NIOSH's approach to evaluating each drug on an individual basis and not on its classification. With few exceptions, HMWP therapeutics will not meet the criteria for a "hazardous drug" using this approach, after consideration of the available toxicological and clinical data scientific for each one. We encourage NIOSH to continue to apply this case-by-case, scientific approach. For example, we encourage NIOSH to carefully examine biologics proposed for addition to the list and consider the removal of those for which the only concern is potential mutagenicity at therapeutic doses that require parenteral administration over prolonged periods of time.

3. Harmonization with Other Handling Recommendations

Comment 3: BIO agrees that the current approach described in the "Update of NIOSH Hazardous Drug List (Appendix A) for the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings (April 6, 2009)", on the NIOSH web site, is harmonized with handling recommendations of other expert groups. Specifically, the current approach is harmonized with that of U.S. Food and Drug Administration (FDA) (referring to the reliance on Pregnancy Categories), and the British Centralized Intravenous Additives Group (CIVAS) and British Oncology Pharmacy Association (BOPA) CIVAS and BOPA (CIVAS/BOPA, 2001). By identifying only those drugs that are "hazardous" in the occupational context, appropriate handling and exposure control precautions will be taken and limited health care resources will be wisely used to protect against drugs that do represent a hazard in the workplace.

Conclusion

The scientific accuracy of the NIOSH Alert is essential in contributing to the use of best practices for worker occupational health and safety programs and hazard communication. BIO supports NIOSH's transparency in the decision-making process, and use of a public comment process to solicit input on the proposed update to the Hazardous Drug Alert. We commend NIOSH in their use of well-accepted scientific principles to identify drugs that meet the Hazardous Drug Alert criteria, including relating low-dose effects of hazardous drugs to the hazard categories of organ, developmental, and reproductive toxicity.

For HMWP therapeutics, the use of hazard characterization vs. hazard identification allows consideration of the potential for many factors, such as absorption, bioavailability, potency, dose-response of drugs, and margin of safety between the exposure levels that a healthcare worker may be exposed to and the exposure levels known to cause adverse effects. To assure scientifically sound guidelines on the potential risk to healthcare workers handling hazardous drugs, we agree it is critical that these be taken into account. BIO supports NIOSH's approach to evaluating each drug on an individual basis and not on its classification; with few exceptions, HMWP therapeutics will not meet the criteria for a "hazardous drug" based on the scientific evidence. The scientific

approach used to update the Hazardous Drug Alert is consistent with those of other expert groups, and further strengthens its importance in providing guidance on risk assessment and exposure controls to employees and employers in healthcare settings.

We appreciate your consideration of these comments. We would be pleased to discuss them with members of the NIOSH staff at your convenience.

Respectfully submitted,

/s/

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Biotechnology Industry Organization

cc: Debora Van der Sluis, Senior Manager, Product Stewardship Programs, Environment, Health and Safety, Genentech (BIO's representative to the Hazardous Drugs Update panel)

References

Bos, J.D., and Meinardi, M.M. (2000) The 500 dalton rule for the skin penetration of chemical compounds and drugs. Experimental Dermatology, 9 (3): 165-169.
CIVAS/BOPA (2001) Monoclonal Antibodies. Hospital Pharmacist, 8:153, June.

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