BIOTECHNOLOGY INDUSTRY ORGANIZATION

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January 30, 2008

Ms. Diane Miller
Robert A. Taft Laboratories
National Institute for Occupational
Safety and Health
4676 Columbia Parkway
MS C-34
Cincinnati, OH 45226

Re: NIOSH Hazardous Drugs List Update; Federal Register 72 FR 33507; 18 June 2007
[Docket Number NIOSH 105]

Dear Ms. Miller:

The Biotechnology Industry Organization (BIO) wishes to thank the National Institute for Occupational Safety and Health (NIOSH) for the opportunity to submit comments on its revisions to Appendix A. Drugs Considered Hazardous of the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings (Hazardous Drug Alert), DHHS Publication No. 2004-165 (2004), and for its inclusion of BIO as a representative stakeholder. The safe handling of drugs and biologics is an important issue for healthcare workers and healthcare organizations, and BIO supports the efforts NIOSH has taken to update the Hazardous Drugs List.

BIO represents more than 1,150 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

technologies, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhance agriculture, and a cleaner and safer environment.

NIOSH's Federal Register Notice (72 FR 33507, June 18, 2007) also requested comments on the definition of "hazardous" drugs. The quality of certain aspects of healthcare worker occupational health and safety programs and, in particular, hazard communication, is based on the scientific accuracy and integrity of the industrial hygiene process (recognition, evaluation and control) or its counterpart four-step NAS risk assessment process (hazard identification, exposure assessment, dose-response assessment and risk characterization (NRC, 1983)), as well as the risk management mitigation measures that may be employed. BIO believes that it is critical that the information gleaned from these rigorous steps be used to identify only those drugs that are "hazardous" in the occupational context, to help inform the appropriate handling and exposure control precautions. Otherwise, limited health care resources will be used to protect against drugs that do not represent a hazard in the workplace. Moreover, any safe handling precautions should be harmonized with handling recommendations of the U.S. Food and Drug Administration (FDA) and risk assessment approaches defined by other expert groups (see further references described in our comments below). In our comments below, we also provide input on what constitutes "hazardous" with respect to biotechnology products, and on approaches to identifying which products are hazardous.

Specifically, BIO strongly supports the use of a risk-based classification system to identify those drugs and biologics that pose hazards in the workplace. However, it appears to us that the existing criteria used by NIOSH do not succeed in classifying drugs and biologics according to their risks. Therefore, we request the following recommendations be adopted and modifications made to 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**. In reviewing the list of drugs "Fitting" and "Not Fitting" the NIOSH Criteria we found that it was not apparent why some drugs have been included and others excluded. Drugs with

similar profiles appear on each list. It seems to us that either the published criteria have not been applied consistently, or that criteria beyond those published by NIOSH are being applied.

<u>Recommendation 1</u>: In order to promote the credibility of its lists of drugs "Fitting" and "Not Fitting" the NIOSH Criteria, BIO believes it is vital that NIOSH have a transparent process, in which the criteria, factors, and weights used to determine whether a drug is "fitting" or "not fitting" are clearly identified and the selection and evaluation process clearly explained.

In this regard, we recommend adoption of a weight-of-evidence approach that incorporates consideration of all scientifically relevant information (e.g., molecular weight, bioavailability by the routes of exposure traditionally considered in occupational health risk assessments (i.e., inhalation, oral, and dermal)) in making any final judgment of what constitutes a "hazardous" drug. BIO members are prepared to assist NIOSH in identifying other scientifically relevant data and developing a weight-of-evidence approach.

<u>Recommendation 2</u>: NIOSH should provide the specific basis for its weight-of-evidence judgment regarding each drug it identifies either as "Fitting" or "Not Fitting" its classification criteria. A narrative format should be used that summarizes the totality of the data reviewed, the evaluation process, and the rationale used to arrive at the decision whether to classify a drug as "hazardous" or not.

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

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

A. The Skin Is An Effective Barrier To Absorption

HMWPTs (molecular weights ~50-150 kDa) pose an extremely low likelihood of absorption following dermal or inhalation exposure in the workplace. Most biologics in this group are in an aqueous vehicle (as opposed to an organic solvent for small molecule drugs) and are hydrophilic (the epidermis is composed primarily of lipids, a property that inhibits the transfer of hydrophilic substances) and are therefore inherently less absorbable on dermal contact. In addition, such protein therapeutics 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. 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. Thus, the skin provides an effective barrier to penetration and systemic absorption of HMWPTs, and dermal exposure is not a significant concern.

B. The Gastrointestinal System Is An Effective Barrier To Absorption

HMWPTs obtain their biological activity to cause pharmacologic effects because of their complex structure, which consists of their:

- primary structure (i.e., the sequence of amino acids);
- secondary structure (i.e., local folding influenced by hydrogen bond pairings);
- tertiary structure (additional three-dimensional folding maintained by more distant interactions); and in some biologics
- quaternary structure (i.e., combination of two or more chains to form a complete unit) (Roger, 2006)

Unlike most small molecule weight pharmaceuticals, HMWPTs are intricately folded proteins that are easily susceptible to denaturation (unfolding and subsequent aggregation) from environmental conditions (Vermeer and Norde, 2000). That is why HMWPTs are shipped and stored within a tightly controlled temperature range (typically refrigerated at between 2° to 8°C (36° to 46°F)). Loss of biological activity

may occur from protein unfolding and aggregation following the loss of either the secondary, tertiary, or quaternary structure in ambient temperatures, lighting, adverse pH conditions, or desiccation, or destruction of their primary structure of amino acids through biological or chemical degradation. For instance, the acidic environment that food encounters in the stomach speeds digestion by denaturing and breaking down proteins. Denaturing or degradation of protein biologics (HMWPTs as well as relatively small proteins like insulin (MW ~5.8 kDa)) would be expected to be rapid under most environmental conditions. Thus, the gastrointestinal system provides an effective barrier to HMWPTs, and oral exposure is not a significant concern.

C. The Pulmonary System Is An Effective Barrier To Absorption

Inhalation is the primary route of occupational exposure to materials. The most critical factor that determines the deposition of particles or aerosols in the respiratory tract is the aerodynamic size of the particle. The respiratory tract consists of the conducting airway (nose, pharynx, larynx, trachea, bronchus and bronchiole) through which air is transported, and respiratory exchange occurs in the alveoli. Particles larger than about 5 μm of aerodynamic diameter, such as mAb molecules at approximately 10 μm, settle in the oropharynx (area of the throat at the back of the mouth). For a compound to be inhaled to the level of the bronchiolar region, it must be 2.5-5 μm in diameter, and to reach the alveoli must be able to pass through 16-17 airway branches and be <2.5 μm (Hext, 1999)(Newman *et. al., 1994, 1995)*. In addition, for absorption of an inhaled HMWPT particle from the lung into the blood it must first escape mucociliary clearance then pass through a number of dynamic barriers in the lung. Again, for the reasons stated above these drugs are administered by injection. Thus, the pulmonary system provides an effective barrier to HMWPTs, and inhalation exposure is not a significant concern.

In summary, we believe that incidental dermal, oral, and inhalation exposure to HMWPTs in the workplace will not result in adverse health effects. Non-injection routes of delivery (including oral, buccal, transdermal, and nasal) have been shown to

be virtually impenetrable to macromolecules unless penetration enhancers were used (Patton and Byron, 2007).

D. Risks of Genotoxicity Are Non-Existent or Very Low For Biologics

Furthermore, genotoxicity is minimally or never an issue with biologics. The British Centralized Intravenous Additives Group (CIVAS) and the British Oncology Pharmacy Association (BOPA) have made a joint statement regarding the handling of monoclonal antibody therapeutics that are non-conjugated and non-radiolabeled (CIVAS/BOPA, 2001), excerpted below.

> "Although genetic engineering techniques are used to produce humanized antibodies, those in current use are not designed to interact directly with the recipient's genetic material."

This is consistent with the ICH S6 guideline (1997), which states, in part,

> "The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. Moreover, the administration of large quantities of peptides/proteins may yield uninterpretable results. It is not expected that these substances would interact directly with DNA or other chromosomal material."

3. **Harmonization with Other Handling Recommendations.** We are concerned that if NIOSH's designation of a hazardous drug is not supported by strong scientific evidence, and is not harmonized with handling recommendations of the U.S. Food and Drug Administration (FDA) (referring to the reliance on Pregnancy Categories) and other expert groups such as CIVAS and BOPA, then risk decisions and hazard control measures by employers and employees in health care settings will not reflect the hazards that exist.

<u>Recommendation 4</u>: NIOSH should ensure that the information in the Hazardous Drug Alert reflects the hazards that exist to employees and is

consistent with other recommendations to avoid confusion for both employers and employees.

Conclusion

BIO believes it is critically important that the revised NIOSH Hazardous Drug Alert process be science-based and as transparent as possible, so that healthcare workers, their employers, and the healthcare community, in general, can wisely allocate resources and make appropriate decisions about controlling exposures to drugs that pose significant risk in the workplace. The risk of health effects from a pharmacologic agent is a function of its inherent toxicity (or potency) and exposure. As described above, the three primary routes of occupational exposure are not relevant for HMWPTs as only direct injection can effectively circumvent the body's natural barriers. Consequently, we urge NIOSH to amend its classification process to exclude high molecular weight proteins from the Hazardous Drugs List. Moreover, we urge NIOSH to consider our recommendations for amending its classification process to harmonize its judgments with other key organizations' warnings, precautions, controls and recommendations for safe handling of drugs in the occupational setting. We believe that making these changes will greatly improve the credibility and acceptance of the listings in the Hazardous Drug Alert.

Thank you for your consideration of our comments. If there are questions on the content of our comments please contact me, or contact BIO's representative on the Hazardous Drugs Update Panel, Debora Van der Sluis (Senior Manager, Product Stewardship Programs, Environment, Health and Safety, Genentech) at 650-225-8232 or vandersluis.debora@gene.com.

Respectfully submitted,

/s/

Sara Radcliffe
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