Miller, Diane M. (CDC/NIOSH/EID)

From: Elizabeth A. Treanor [etreanor@phylmar.com]
Sent: Thursday, September 20, 2007 12:45 AM
To: NIOSH Docket Office (CDC)
Subject: Comments on NIOSH Hazardous Drug Notice
Importance: High
Attachments: NIOSH Haz Drugs Sept 07 final.doc

Dear Ms. Miller:

Attached are the comments of the BioPharma EHS Forum on the 18 June 2007 Federal Register notice.

Please let me know that you received them.

Many thanks.

I hope someone does something nice for you today.

sincerely,

Elizabeth

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Phylmar Group® Environmental Health & Safety Social Responsibility

20 September 2007

Diane Miller
Robert A. Taft Laboratories
National Institute for Occupational
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4676 Columbia Parkway
MS C-34
Docket 105
Cincinnati, OH 45226

Re: NIOSH Hazardous Drugs List Update; Federal Register 72 FR 33507; 18 June 2007

Dear Ms. Miller:

Thank you for the opportunity to submit comments on the NIOSH approach to updating its Hazardous Drugs List. We note that although the Federal Register notice solicits comments on a draft document entitled "NIOSH Hazardous Drugs List Update," we were not able to locate a document with that specific title on the website provided in the notice. However, we understand that NIOSH is in the process of updating the document entitled "NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings," DHHS Publication No. 2004-165 (2004), and we are very interested in this Alert. These comments are divided into Introduction, General Comments, and Specific Comments.

The BioPharma EHS Forum is an informal group comprised of 25 companies that has met since 2004 to provide an opportunity for environmental, health and safety professionals within BioPharma companies to exchange ideas, share best practices, network, and benchmark with other companies. The goal of the BioPharma EHS Forum is to improve worker and environmental protection. Some of the BioPharma EHS Forum companies are submitting comments on their own behalf.

Obviously, the safe handling of hazardous drugs is an important issue for healthcare workers. We support NIOSH's efforts to revise the Alert to keep it current, and the inclusion of representative stakeholders, including manufacturers of biotherapeutic agents, in its Review Committee as this project goes forward.

Introduction

We believe that since NIOSH is a highly respected Agency, known for its scientific rigor, it is essential that the information developed be as accurate as possible. Healthcare workers and employers rely on information provided by NIOSH for incorporation into training programs and

to assure that proper precautions are taken in the workplace. These people will be especially interested in the revised Alert to understand the nature of the hazards and appropriate protective measures.

We apologize in advance for our confusion, and our inability to correctly follow the Federal Register Notice and the website. We are confused as to the scope of the comments sought by NIOSH. On its website, NIOSH notes that it "has assessed the scientific literature and found no reason to change the definition of hazardous drugs at this time." On the other hand, the Federal Register Notice seems to be requesting comments on the definition of hazardous drugs, as the Notice requested comments on the following topics:

1) The appropriateness and relevancy of the NIOSH definition of Hazardous Drugs;
2) The appropriateness and relevancy of the drugs that fit the NIOSH definition; and
3) The appropriateness and relevancy of the drugs that do not fit the NIOSH definition.

Therefore, we assume that comments relevant to the NIOSH definition are appropriate for comment at this time. These comments are provided below.

In addition, although there is a website titled "Process for Updating the List of Hazardous Drugs (Appendix A) for the NIOSH Alert," we were unable to find a clearly identified process that NIOSH is using for the update. We assume that the process involves the request for comments, review of the lists of drugs "Fitting" and "Not Fitting," and review by an expert panel, but we would appreciate it if we could have more information about the process in the form of details about the methodology used (or perhaps the process is on the website and we were unable to find it).

General Comments

1. **Lists of Drugs "Fitting" and "Not Fitting" NIOSH Criteria** – On the website, there are two lists upon which comment is solicited: "New FDA Drugs and Warnings Not Fitting NIOSH Criteria for Hazardous Drugs 2006" and "New FDA Drugs and Warnings Fitting NIOSH Criteria for Hazardous Drugs 2006." We are unclear about the specific reason for the conclusion that a particular drug is "Fitting" or "Not Fitting" the criteria based on the information provided in the charts. We understand that during the 28 August 2007 Public meeting on this topic, NIOSH officials stated that a "qualitative approach" was used. It would be very helpful for the public in understanding the bases for the conclusions if further details were provided for each drug.

   Recommendation: NIOSH provide the specific basis for each conclusion that a drug is identified as "characteristic of drug does not fit NIOSH definition" or "characteristic of drug fits NIOSH definition."

2. **Harmonization with Other Handling Recommendations** - We are concerned that if the scientific evidence for handling a hazardous drug in a particular manner is not supportable,

and is not harmonized with handling recommendations of the U.S. Food and Drug Administration (FDA) and other expert groups, then risk decisions and hazard control measures by employers and employees in health care settings will not be appropriate and will not reflect the hazards that exist.

Recommendation: NIOSH ensure that the information in the Alert reflects the hazards that exist to employees and is consistent with other recommendations to avoid confusion for both employers and employees.

3. **Hazard Characterization Needed** – The original purpose of the Alert was to identify "hazardous drugs" for workers to handle with caution and not necessarily to provide a risk assessment, it is nevertheless important to perform a hazard characterization, rather than a simple hazard identification, when determining whether a drug should be included on the Alert. Beyond even a quantitative assessment of dose-response data, it is also important for NIOSH to recognize that the bioavailability of a drug is also a critical factor in the overall hazard characterization. Without recognition of both dose-response and bioavailability, many drugs that will not present a true risk to the handler in a healthcare setting would seem to meet the criteria for a "hazardous drug" as outlined in the current Alert. The net effect of ignoring these components of hazard characterization would be to dilute the effectiveness of the list and the recommended handling practices, as well as defeating the commendable goal of identifying those drugs that present real worker risk exposure.

   We encourage NIOSH to consider route of exposure and likelihood of exposure in its assessment of drugs that should be listed in the Alert. If a particular drug is biologically active only after injection, and the workplace exposure routes are inhalation and dermal contact, warning healthcare workers and their employers of a hazard unlikely to be faced may take attention and resources away from other hazards more likely to be present in that workplace.

   Recommendation: (1) NIOSH consider route of exposure and likelihood of exposure in consideration of drugs that should be defined or listed as hazardous so that appropriate training and control measures reflect the hazard posed in the workplace.

   (2) NIOSH consider the route of exposure and likelihood of exposure in its definition of a "hazardous drug."

Specific Comments

1. **Apparent Inconsistent Application of the Criteria Defining "Hazardous Drug"** - We are concerned that there are some cases in which the criteria for defining a "hazardous drug" has not been followed consistently. For example, in comparing Vectibix with Avastin and Erbitux, we reviewed the findings from the chart on the website as follows:

   - Each drug has "NT" under Cancer;
   - Each drug has "C" under Pregnancy;
   - Each drug has "+" under Reproductive Toxicity;

- Each drug has "+" under Organ Toxicity; and
- Vectibix has "NT" under Genotoxicity, while Avastin and Erbitux have "- -," meaning "characteristic of drug does not fit NIOSH definition."

While Vecitbix is listed as "Not Fitting" the criteria, Avastin and Erbitux are listed as "Fitting" the criteria. While the mode for supplying the drugs is tablets for Vectibix and intravenous for Avastin and Erbitux, we had understood that the potential for exposure was greater with tablets than with intravenous administration.

In trying to understand why Vectibix was listed as "Not Fitting" the criteria, we wonder whether there is a second level set of criteria that is being used. It is not clear how the criteria are being applied to the drugs being evaluated. Again, we believe that scientific accuracy is very important, and that if criteria are being used to define a "hazardous drug," that criteria must be consistently applied to all drugs being assessed for possible listing in the revised Alert.

Recommendation: NIOSH provide information on the process or approach used in evaluating the drugs to determine whether or not they fit the criteria.

2. **Understanding the Process** – In some cases, drugs have not been tested for a particular category, for example, Vectibix results indicate it has not been tested for Genotoxicity. We are confused about why a drug that has not been tested would be on a list of drugs "Not Fitting" and why a drug that has as its conclusion "characteristic of drug does not fit NIOSH definition" would be on the list of drugs "Fitting" the NIOSH criteria. It would be helpful for an explanation of the process and approach used in evaluating the drugs.

   Recommendation: NIOSH provide information on the process or approach used in evaluating the drugs to determine whether or not they fit the criteria.

3. **Monoclonal Antibodies** – Although opinions differ, credible individuals in the area seem to agree that monoclonal antibodies (MAbs), due to their size and potential for exposure, should not be included in the Hazardous Drugs Alert. Luci Power, senior pharmacist and manager of parenteral support services at the University of California San Francisco Medical Center, was largely responsible for the hazardous drug guidelines published by the American Society of Health-System Pharmacists (ASHP). According to "Drug Topics, she questions "whether monoclonal antibodies and other large-molecule products belong on the list. Large proteins are very unlikely to enter the body unless injected or otherwise inserted directly." She is quoted as follows:

   > "You could probably sit in the stuff and not get anything in you, absent a cut... Monoclonal antibodies are hazardous, but they are not a workplace hazard. Too many people do not recognize the difference."

   Attached as an Appendix is a brief paper entitled "Concepts of Occupational Exposure to Monoclonal Antibody" written by Robert C. Blink, M.D., M.P.H. This paper presents the suggestion that MAbs "deserve a fresh approach regarding their ability to cause harm in the

occupational setting." Finally, we believe that the fact that six MAbs are including in the "Not Fitting" list, while the rest are listed as "Fitting" the criteria. A consistent approach would be useful and reasonable.

Recommendation: NIOSH carefully re-evaluate the inclusion of monoclonal antibodies as appropriate additions to the roster of hazardous drugs. Certainly some of these materials might present appreciable health risks upon intravenous or subcutaneous dosing; however, there is little or no evidence to suggest MAbs as relevant occupational hazards given the low likelihood of substantial systemic exposure in healthcare settings where dermal and possibly respiratory exposure predominate. Articles in the recent scientific literature attest to the variable, but generally very limited respiratory bioavailability of high molecular weight proteins unless special means (creation of specifically-sized aerosols, use of penetration enhancers, deliberate intratracheal instillation) are employed to enhance uptake. It seems prudent and scientifically justifiable that NIOSH incorporate elements of the pharmacokinetics that contribute to a detailed hazard assessment and characterization into consideration in order to allow a true assessment of the risk of occupational adverse effects of MAbs. Without this, there is a likelihood that many MAbs, especially those used in oncology practice, will eventually end up on the NIOSH list of hazardous drugs, raising unnecessary and inappropriate concerns.

Conclusion

Again, we believe that it is critically important for NIOSH's credibility and for the uses that will be made of the revised Alert that the information presented be scientifically accurate. Since employers and employees are expected to make decisions based on the Alert, it would be inappropriate for them to develop training programs and take measures not reflecting the hazards that exist. To do otherwise would be to dilute the effectiveness of the Alert.

Thank you for your consideration of these comments. We would be pleased to discuss them further with you or members of the NIOSH staff.

Sincerely,

Elizabeth A. Treanor

Elizabeth A. Treanor
Chair
BioPharma EHS Forum

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Appendix
Concepts of Occupational Exposure to Monoclonal Antibody

Robert C. Blink, M.D., M.P.H.

1. Overview

Historically, NIOSH has listed various industrial chemicals as to the risk they may pose to a worker exposed to these agents. This has generally been done based on the intrinsic risk of the chemicals, since any contact with traditional chemical agents may cause harm. This practice has been applied to pharmaceuticals as well. However, a new class of materials is now under consideration for such listing, the monoclonal antibodies (MAb's) produced by genetic engineering in the biotechnology pharmaceutical industry. These agents throw into question the practice of rating by "intrinsic" risk, due to very low bioavailability unless deliberately introduced into a person's body by a parenteral route. An alternate method of rating these materials is proposed.

These agents deserve a fresh approach regarding their ability to cause harm in the occupational setting, since it is believed that they can only have significant pharmaceutical effect when absorbed into the systemic circulation, a result that is difficult to achieve even when this is the goal of a pharmaceutical delivery system; no such agent is currently available as anything but a parenterally administered material.

Rather than the blanket approach previously used for chemicals that either have physiologic effects on external exposure or that can be significantly absorbed via accidental exposure, a new method may be more appropriate for monoclonal antibodies. This is because under conditions of accidental, nonparenteral exposure, these agents are believed to be very poorly absorbed, and therefore not bioavailable in sufficient quantity to cause harm. Furthermore, they require multiple dosing even under clinical treatment, to show a significant effect.

Finally, the two proposed lists of pharmaceutical agents under consideration are split into those "fitting" and "not fitting" criteria as "hazardous drugs". Confusion is risked by including at least six MAb's in the "non-hazardous" list, while the rest are listed as "hazardous" under the proposal. A consistent approach would be useful and reasonable.

2. Estimating risk from accidental MAb exposure

In order to approach the issue of potential harm from accidental workplace exposure to MAb's, two primary issues must be considered beyond the risk of the agents when used parenterally. These are the questions of whether a given MAb is capable of causing harm from external exposure, and if it is capable of being absorbed in effective quantities from accidental exposure.

A complete summation of the possibility of harm to an accidentally exposed worker includes adding the likelihood of harm from external effects to the likelihood of harm from absorption into the body. Each risk itself is a risk derived from a chain of risks that must be multiplied by one another to obtain the true risk. That is,

Total risk of harm from accidental exposure
= REt (total risk of harm from external effects)
+ RAt (risk of harm from absorption).

In turn,
REt (risk of harm from external effects)
= REc (risk of harm to skin or mucous membranes from chemical properties)
+ REa (risk of harm to skin or mucous membranes from allergic response to direct exposure);

and
RAt (risk of harm from absorption) must be evaluated at each possible route of absorption. For each route,

RAt = RAq (quantity available to be absorbed by that route)
* RAp (percentage of material available that actually reaches the systemic circulation).

Regarding external effects, there are no known ill effects from the physical or chemical properties of MAb's on skin or mucous membranes. As far as the possibility of allergic reactions, these agents are proteins and thus an allergic response is possible; however, no such reaction has ever been reported to our knowledge. Some of these agents may have toxic effects on skin, mucus membranes and lung when administered parenterally in therapeutic does; it is not known whether similar effects could occur on direct application to these tissues by accidental exposure in small amounts, very briefly, and from a single occurrence rather than repeated dosing. Since these materials are of human genetic origin rather than xenogeneic, allergenicity is expected to be very low, and no greater than for other human antibodies such as are found in human blood fractions. Precautions due to allergenicity for handling these materials should thus be similar to those required for handling human immune globulins, such as gamma globulin, hepatitis B immune globulin, etc.

3. Routes of Absorption
There are five routes of possible absorption to consider:
Skin; mucous membranes of eyes, nasal mucosa, and oropharynx; the tracheobronchial tree; the alveoli; and the GI tract.

In the setting of an accidental workplace exposure, the MAb would either be in powdered, lyophilized form, or in a liquid vehicle. For external effects, these forms would likely be similar. For alveolar exposure, only the powder form would deserve further consideration since no liquid aerosol capable of reaching the alveoli would be created under accidental conditions of the workplace (which would require mechanical agitation not found in normal use). For the other routes, either liquid or powder would have similar properties since the powdered material would quickly become hydrated on exposure to mucous membranes.

Liquid exposures could either be by splash or droplet spray. Splashed material could conceivably land on skin, mucous membrane, be swallowed, or be inhaled to reach the tracheobronchial tree; it would not be expected to reach the alveoli.

Powder exposures could conceivably reach any of the exposure routes. If inhaled, the location of deposition would be dependent on particle size. Particles larger than about 5 microns of aerodynamic diameter would settle in the oropharynx; particles between about 2.5 and 5 microns would settle in the tracheobronchial region; and particles smaller than about 2. 5 microns would deposit in the alveoli.

Absorption of MAb from these regions depends on various factors. Principal among these is the fact that these agents are extremely large molecules, about 120-200 kDa. Dr. Kim's report outlines the difficulties passing through various layers.

4. Estimates of exposure and absorption:

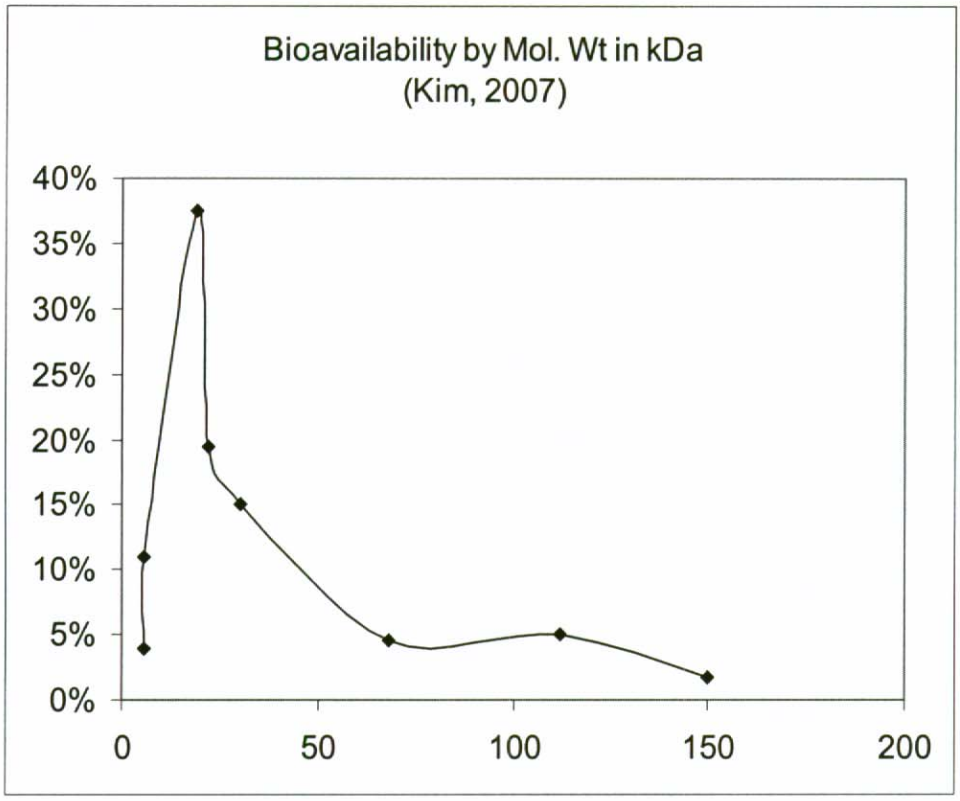
In general, the bioavailability of a compound via a given route is equal to:
(Total quantity delivered to that route entry point) * (fraction absorbed via that route) * (fraction remaining active after local factors such as digestion).
In addition, the toxicity would then need to be calculated by multiplying (bioavailable dose) * (fraction of physiologic effect from single exposure compared with pharmaceutical dosing schedule).

Via the skin, there is no known mechanism for absorption of antibody.

Via the mucosae of eye, nose, and oropharynx, comparison with the size of the absorptive surface of the alveoli suggests that the vastly larger alveolar surface area and much thinner epithelium of the alveoli would dominate over absorption from the upper airways.

Via the tracheobronchial tree and via the alveoli: see Dr. Kim's report.

The data on bioavailability assembled by Dr. Kim shows a definite trend when plotted against molecular weight (the range of 4-11% bioavailability at 5.7 kDa is shown as separate points):



Although the data are a mix of inhalation and tracheal instillation, in more than one species, and with more than one mAb, the curve appears to be strongly suggestive that for higher molecular weight biotherapeutics such as monoclonal antibodies (with weights between about 120-200 kDa), the likely absorption is expected to be less than 5 %. This is consistent with theoretical considerations and suggests that there is a built-in protection factor of 20 or more for bioavailability by this route.

Via the GI tract, antibody is exposed to acid-peptic digestion in the stomach and duodenum, and will be destroyed before reaching the absorptive epithelium of the intestines.

Finally, once absorbed into the circulation, the question remains whether a single exposure could cause a harmful effect. Each MAb evaluated would need to be reviewed to determine the likely harm of such a single accidental event, as repeated and regular dosing is required for pharmaceutical effect in clinical settings.

Ref:

1. Corkery, K Inhalable Drugs for Systemic Therapy, Resp Care, July 2000, 45:7, 831-835
2. Kim, ST , Low Inhalation Bioavailability of mABs, 2007