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

From: Thomas White-Consultant [TWhite@phrma.org]
Sent: Thursday, September 20, 2007 4:27 PM
To: NIOSH Docket Office (CDC)
Cc: Reed, Larry (CDC/NIOSH/DSHEFS); MacKenzie, Barbara A. (CDC/NIOSH/DART); Connor, Thomas H. (CDC/NIOSH/DART)
Subject: PhRMA Comments to Docket NIOSH 105 Re Hazardous Drug List Update 092007
Attachments: Final PhRMA Comments NIOSH Docket 105 092007.pdf

Ms. Miller, PhRMA comments in response to the June 18, 2007 FR Notice and the August 28, 2007 Public Workshop are attached for submission to the NIOSH Docket 105.

Please advise that the comments have been received and are in the appropriate format for your use.

Thank you for your consideration of the enclosed comments, reflecting the scientific knowledge and experience of a group of our company experts.

Let me know if there are any questions that may need follow-up.

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September 20, 2007

Diane Miller
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Via Email to: niocindocket@cdc.gov

Re: Docket Number NIOSH 105; Request for Public Comments on Draft NIOSH Hazardous Drugs List Update; (72 FR 33507, June 18, 2007.

Dear Ms. Miller,

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated $43 billion in 2006 in discovering and developing new medicines. Industry wide research and investment reached a record $ 55.2 billion in 2006

PhRMA appreciates the opportunities provided by NIOSH for the review of the above-noted public documents that are under review by NIOSH and its expert panel of peer reviewers. PhRMA member companies have reviewed the call for comments that appeared in the June 18, 2007, Federal Register Notice and considered comments made during the course of the NIOSH public meeting on "Updating the NIOSH List of Hazardous Drugs" held on August 28, 2007 in Washington, DC. As a result, PhRMA is forwarding for your attention several important comments on the NIOSH Hazardous Drug Alert (DHHS (NIOSH) Publication No. 2004-165) and the process of updating the Hazardous Drug list contained in Appendix A of that publication. Individual member companies will submit compound-specific comments concerning the updated drug list separately through the process NIOSH has established on the relevant website.

Updating Process for Hazardous Drug Definition and List

General Comments:

First and foremost, PhRMA believes that the list of Hazardous Drugs contained in the Alert needs to remain focused on those drugs that present the highest health hazard. Therefore, taking into account dose and potency are imperative for comprehensive hazard characterization with respect to the Alert. It is PhRMA's view that the definition of "hazardous drugs" used in the Alert does not appear to have been taken into account when assembling the list of candidate drug active ingredients included in the current listing as "Fitting" the NIOSH Criteria for Hazardous Drugs. Indeed, this was acknowledged at the 28 August public meeting, where it was indicated in comments from the podium that the candidate list was derived based on a qualitative, but not quantitative, reading of the source materials used. In the PhRMA comments leading up to the original publication of the Alert, we proposed a low-dose definition to read,

> "Low doses are defined as clinical drug doses of 10 milligrams per day or less for a major indication, or doses less than 1 milligram/kilogram/day for studies in laboratory animals."

In the final version of the Alert, this concept was reflected in the footnote to the definition of Hazardous Drugs. PhRMA applauds NIOSH for including this statement and trying to relate these doses to safe levels of potential workplace exposure to hazardous drugs. Thus, PhRMA emphasizes the importance of making reference to low-dose exposures associated with the hazard categories identified in the definition of hazardous drugs so that only the subset of drugs that require special handling are included on the NIOSH list.

The original purpose of the Alert was to identify to workers in healthcare settings "hazardous drugs" that they ought to handle with caution. It was recognized, though, that without workplace-specific exposure information, it would be impossible to provide a full and complete occupational risk assessment. In order to properly identify hazardous drugs, is important to perform a complete hazard characterization, rather than a simple, qualitative hazard identification, when determining whether a drug should be included on the list. Beyond even a quantitative assessment of dose-response data, it is also important for NIOSH to recognize that the bioavailability of a drug and other pharmacokinetic parameters are also critical factors in the overall hazard characterization. Without recognition of both dose-response and pharmacokinetics as part of the characterization, many drugs will not present a true risk to the handler in a healthcare setting although the drug would seem to meet the criteria for a "hazardous drug" as outlined in the current Alert. The net effect of ignoring dose-response and pharmacokinetics as components of an overall, complete hazard characterization would be to dilute the effectiveness of the list and the recommended handling practices as they appear in the Alert, by failing to identify those drugs that present real worker risk potential.

For example, PhRMA suggests a careful re-evaluation of the inclusion of high molecular weight (HMW) protein therapeutics, such as monoclonal antibodies (MAbs), as candidate additions to the list of hazardous drugs. Certainly some of these materials might present appreciable health risks to patients after intravenous or subcutaneous dosing. However, there is little or no evidence to suggest that MAbs are relevant occupational hazards given the low likelihood of substantial systemic exposure in healthcare settings where dermal and, possibly respiratory, exposures predominate. 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. Therefore, 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 high molecular weight substances. Without consideration of pharmacokinetics, there is a likelihood that many HMW substances, such as MAbs used especially in oncology and rheumatology practice, eventually will be included on the NIOSH list of hazardous drugs and raise inappropriate concerns.

Many of the drug products on the current iteration of the NIOSH list (2004) probably have sufficient information from non-clinical and clinical characterization to merit inclusion on the NIOSH hazardous drugs list. However, many of the drugs currently proposed for addition to the NIOSH list have limited history of clinical use; therefore, their hazard profile is drawn largely or exclusively from pre-clinical characterization. NIOSH should appreciate that much of the pre-clinical hazard profiling is done according to International Conference on Harmonization (ICH) and/or Organization for Economic and Community Development (OECD) Test Guidelines with the idea to "test to failure" in order to provide an appropriate margin of safety regarding doses selected for medicinal use and to explore possible toxicities that may later have been observed in special populations (such as pregnant women). This situation makes it near-imperative that NIOSH give further thought to the criteria used to consider and select drugs for inclusion on the list of hazardous drugs in healthcare settings.

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Mechanistic Considerations:

Another important consideration is the relevance of certain mechanistic endpoints to human health that reflects the unique pharmacologic properties of drugs in certain therapeutic classes. Some have mechanisms of action and thresholds of response that, while of concern at therapeutic levels that may be relatively high (e.g., hundreds of milligrams per day), represent little concern at the low (nanogram or microgram) levels that may be encountered in the healthcare environment.

For example, certain classes of new antineoplastic agents have mechanisms of action that do not involve damage to DNA. These agents act by inhibiting specific enzymes involved in cell division that, like other more traditional pharmacologic endpoints, have clear no-effect levels below which no effects on cell division would be expected. Some of these compounds have very high therapeutic doses and some (e.g., monoclonal antibodies) may not be absorbed into the body in significant amounts following inhalation or dermal contact (as discussed above). Likewise, there are fewer concerns regarding compounds that have positive *in vitro* chromosomal aberration assay results but negative *in vivo* mouse micronucleus test results at limiting doses. The latter represents a very low risk of genotoxicity, especially at low levels of exposure.

Other mechanistic considerations that should be included in any hazard assessment and characterization include the relevance of certain findings such as:

- rodent liver/thyroid tumors that occur at high doses as a result of enzyme induction,
- mouse liver tumors in general,
- tumors associated with peroxisome proliferation or specific receptor-mediated reactions,
- chemicals that are carcinogenic only at toxic doses and which do not demonstrate mutagenicity,
- tumors found in animals of only one sex/one species,
- developmental effects that are clearly the result of maternal toxicity, or
- high dosages administered to specifically elicit a response per protocol.

All should be examined, but put into proper perspective when assessing hazard. Professional judgment from experienced toxicologists is required to make these distinctions.

Weight-of-Evidence Considerations:

Likewise, across the genetic toxicity field, it is common practice to conduct a battery of various mutagenicity and clastogenicity studies in order to assess the potential for genotoxic damage. These batteries usually start with simple *in vitro* models that assess potential to cause bacterial mutations or chromosomal damage in animal or human cell culture systems, progressing to more complex *in vivo* models for relevant endpoints. Experts in the field of genotoxicity have fewer concerns regarding compounds that have positive findings in *in vitro* assays (e.g. chromosomal aberration) but negative *in vivo* test results (e.g. mouse micronucleus) at limiting doses. Generally, the latter would be thought to represent a very low risk of genotoxicity, especially at low levels of exposure. Thus, NIOSH should consider adoption of a weight-of-evidence consideration into its hazard assessment process. Generally, this assessment is also made the using professional judgment of toxicologists.

Unintended Consequences of an Overly Conservative Listing Process:

If the dose-response, mechanistic characteristics, and weight-of-evidence considerations are not adequately addressed in the definitional criteria, the inclusion of many more compounds than intended will unnecessarily be included on the List, resulting in an unintended ineffectiveness of the NIOSH Alert. Utility as

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well as credibility will soon be lost if the list expands to cover drugs for which hazard and/or exposure potential is increasingly hypothetical. There is a risk that healthcare facilities may chose to ignore the Alert and its Hazardous Drug List if it is perceived as being overly conservative.

As an addendum to the list, PhRMA recommends that the following wording be included:

The intent of this list is to include those drugs that have a potential to cause significant adverse health effects in healthcare workers at the exposure levels that may be encountered during normal handling. There should be a sufficiently large 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. Generally, drugs that can produce these effects at clinical drug doses of 10 milligrams per day or 1 mg/kg/day for animal studies should receive special attention. Additionally, drugs with published Occupational Exposure Limits (OELs) ≤10 mcg/m^3 should be carefully examined in consultation with a professional occupational hygienist to determine whether special handling would be warranted. Dose information is readily available in the Physicians Desk Reference (PDR), Product Labels, Package Inserts, Material Safety Data Sheets (MSDS), various medical and toxicology web sites, or directly from the manufacturer.

Hazardous drug classification should be made on the basis of well-conducted, sufficiently validated tests such as those performed according to ICH and/or OECD Test Guidelines. Evaluation of the test results should be done using expert judgment and all the available evidence should be weighed for appropriate inclusion on the list.

Additionally, PhRMA recommends updating references to include published criteria from the *Globally Harmonized System of Classification and Labeling of Chemicals (GHS) Guidance (Second revised edition, 2007)* in the following sections of the Alert:

- Page 31, last paragraph under "ASHP Definition of Hazardous Drugs" starting with "Additional guidance for defining hazardous drugs…"
- Page 32 footnotes under the "NIOSH Revision of ASHP Definition"

Consideration of Dosage Form:

In addition to consideration of mechanism of action, dose-response, and which pre-clinical toxicological endpoints are of use in placing drugs on the list of hazardous drugs, further thought needs to be given to final dose formulation and how this impacts exposure potential. Some drugs defined as hazardous may not pose a significant direct occupational exposure risk due to dosage form, such as being delivered as coated tablets or capsules. However, NIOSH has recognized that handling such dosage forms may pose an indirect risk if handled improperly, such as crushing tablets to prepare alternative dosing media outside a biological safety cabinet, containment isolator, or ventilated enclosure, or from the handling of patient excreta or associated clothing or bedding.

It seems of little relevance to include drugs that are only available in the healthcare community as film-coated tablets where it is likely that even crushing the tablet would result in large particles with very little in the way of fines susceptible to air-borne entrainment and inhalation. The same argument regarding potential for exposure could be raised for products designed for inhalation or parenteral administration that are delivered into the healthcare setting in a sturdy, sealed, dose delivery system. PhRMA's recommendation to address these concerns is that of a tiered approach to exposure potential and risk, thereby placing certain drugs on the list that might otherwise meet the hazard characterization criteria above others and into different handling categories. This would help to keep the list useful and focus the limited healthcare resources on occupationally-relevant exposures (i.e., on those exposures that might truly be expected while someone is preparing or administering the drug). For example, the risk of inadvertent injection of a drug preparation by a

healthcare worker is low, and the potential risk for injecting a clinically significant amount of drug is even lower.

Specifically, on page 34 of the Alert, and in the footnote to the list on page 40, there are two brief sentences related to reduced risk of exposure based on the formulation. Specific examples include coated tablets or capsules. PhRMA asserts that there is a need to expand on the concept of exposure and its effect on the subsequent risk assessment done in the workplace in the Alert as revisions are made in the spirit of continuous improvement. PhRMA suggests that the example below would be an appropriate addition:

> *The risk of an adverse health effect from a hazardous drug depends on a variety of factors that should be considered when determining appropriate handling. For example, the product's dosage formulation may be a factor in the handlers' potential for exposure.*

Perhaps a ranking of common formulation types, shown in terms of relative risk of occupational inhalation exposure during the dispensing and administration of hazardous drugs would be of help:

Low - Oral suspension, coated / uncoated tablets (intact), capsules (intact), transdermal systems

Moderate - Crushed / broken tablets / capsules

High - IV solutions

Another option would be listing the formulation types in column 1 and then the potential for inhalation and dermal exposure as columns 2 and 3. For example:

Formulation	Inhalation Exposure Risk	Dermal Exposure Risk
Oral Suspension	Low	Moderate
Coated tablets (intact)	Low	Low
Capsules (intact)	Low	Low
Transdermal Systems	Low	High
IV Solutions (inadvertent injection)	Low	Low
Uncoated Tablets (intact)	Low	Moderate
Crushed Tablets	Moderate	Moderate
Broken Tablets / Capsules	Moderate	Moderate
IV Solutions (aerosolization)	High	Moderate

A second alternative approach would be to use a 2X2 matrix for High and Low categories for both Hazard and Exposure potential. Only those compounds/dosage forms that are assigned to the High/High cell (Drugs A, B, and C in the following example Table) would require the special precautions outlined in the Alert:

		HAZARD POTENTIAL	
		HIGH	LOW
EXPOSURE POTENTIAL	HIGH	Drug A Drug B Drug C ...	Drug D Drug E Drug F ...
	LOW	Drug G Drug H Drug I ...	Drug J Drug K Drug L ...

Additional Comments:

PhRMA compliments NIOSH on the format which it has used to present the lists of drugs "Fitting" and "Not Fitting" the NIOSH Criteria for Hazardous Drugs. The table used provides additional information beyond that included in the original 'Appendix A' list with respect to understanding the rationale for listing by providing the Hazard Criteria columns. In addition, the "How Supplied" information would be helpful for workplaces in developing handling guidance. PhRMA suggests that the overall utility of the list would be improved by adopting these conventions and changing the original Appendix A to this as a new format.

PhRMA believes that:

- For the NIOSH Hazardous Drug Alert to be most effective, there needs to be an agreed peer-review system for addition/deletion of drugs on a periodic basis as they are approved by FDA. A periodic (quarterly) review would lessen the burden on the reviewers and would expedite getting the drugs of most concern on the list.
- A readily-available publication or repository for the ongoing compilation of drugs should be decided upon, and, if feasible, a NIOSH or other web-based link should be provided for easy access by the healthcare community. An out-of-date or otherwise incomplete list could constitute a risk to healthcare professionals and other employees by providing incorrect or inadequate information.
- There should be a mechanism for removing drugs as appropriate, based on the updated definition or for scientifically valid reasons.
- PhRMA strongly suggests that NIOSH should be more transparent in how and what criteria were used to select the NIOSH Alert Committee/Panel of Experts, and the process by which they determine what drugs should be on the list.

Finally, PhRMA believes that NIOSH should recommend that health professionals attend training classes in safety awareness about the use of and exposure to hazardous drugs (referring to OSHA's Hazard Communication Standard, CFR 29, Part 1910.1200).

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PhRMA appreciates the opportunities provided by you and your colleagues to comment on the above-noted process and the public documents that are under review by NIOSH and its peer-review panel of experts.

Sincerely,

Alice E. Till

Alice E. Till, PhD

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