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

From: william.mcgrath@bms.com on behalf of William P McGrath [william.mcgrath@bms.com]
Sent: Friday, September 28, 2007 11:10 AM
To: NIOSH Docket Office (CDC); hazardouddrugs@cdc.gov; MacKenzie, Barbara A. (CDC/NIOSH/DART); Reed, Larry (CDC/NIOSH/DSHEFS)
Cc: William P McGrath
Subject: Docket number NIOSH 105

Attachments: Diane Miller Sept2707.pdf

Diane Miller Sept2707.pdf (308...

Diane Miller,

Please see the attached Word document which contains comments prepared in reference to the updating of the NIOSH Alert, Hazardous Drug list.

Regards,

William P. McGrath
Bristol-Myers Squibb Company

Bristol-Myers Squibb Company

P.O. Box 191 New Brunswick, NJ 08903-0191 732-227-5000

September 28, 2007

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

Re: Docket No. NIOSH 105 – Proposed Updated List of Hazardous Drugs (Appendix A) for the NIOSH Alert on Hazardous Drugs

Dear Ms. Miller:

Bristol-Myers Squibb Co. appreciates the opportunity to submit comments concerning the draft "NIOSH Hazardous Drugs List Update," 72 Federal Register 116, June 18, 2007. Set forth below are three general comments concerning DHHS (NIOSH) Publication No. 2004-165 (September 2004), *NIOSH ALERT: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings* (hereafter "*Alert*"). Comments are also provided concerning several specific drugs proposed for inclusion on or exclusion from the proposed updated NIOSH list of hazardous drugs.

General Comments

1. The original purpose of the 2004 *Alert*, in part, was to provide guidance to healthcare workers regarding recommended precautions to be taken when handling certain drugs categorized in the *Alert* as hazardous drugs. As the *Alert* stated, "no attempt has been made to perform drug risk assessments." *Alert* at 31. We believe it is important to perform a thorough hazard *characterization*, rather than a simple hazard *identification*, when determining whether a drug should be included on the hazardous drug list.

Hazard characterizations should include both a review of dose-response data and dosage form (bioavailability) as they relate to the exposure potential to staff who may be handling these materials. It is important to recognize that the bioavailability of a drug is a critical factor in an overall hazard characterization. Without recognition of both dose-response and bioavailability a number of drugs would seem to meet the description of a "hazardous drug" as outlined in the current *Alert*, but many such drugs do not present a true risk to a handler in a healthcare setting. For example, we recommend that, based on the greatly reduced potential for exposure, large

molecular weight protein therapeutics generally not be included in the hazardous drug list unless there is a drug specific compelling reason for inclusion.

2. The section of the *Alert* that includes characteristics to be considered when defining a drug as hazardous (*Alert* at 32) includes the following footnote:

> "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 $\mu g/m^3$ 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."

We recommend that the reference to 10 $\mu g/m^3$ be deleted. Manufacturers use a variety of different models and formulas to develop OELs. Therefore, there often is a variation among OELs set by different manufacturers for similar types of compounds. Since currently there are no standards regulating the method by which OELs are set, NIOSH's referencing of a specific number is problematic. For example, it should be considered as to whether this reference might contribute to a possible unintended effect when OELs are set voluntarily, *e.g.*, some parties might consider setting the OEL above 10 $\mu g/m^3$ in order to avoid a "hazardous drug" designation.

3. 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 (Cancer, Pregnancy Category, Reproductive Toxicity, Organ Toxicity, Genotoxicity). In addition, the "how supplied" information would be helpful for workplaces in developing handling guidance. We suggest that the overall utility can be improved by changing the original Appendix A to the new format. This would be useful especially because reference is made in the *Alert* text preceding the table to variations in the level of hazard depending on dosage and use.

Erbitux® (cetuximab) and Orencia® (abatacept)

Erbitux® (cetuximab) and Orencia® (abatacept) should not be identified as hazardous drugs on the updated list.

Erbitux® (cetuximab) and Orencia® (abatacept) are large molecular weight proteins that do not have the same potential for systemic exposure as is assumed for small molecules. Systemic exposure from these proteins via dermal and oral routes is assumed to be negligible, and is very limited from the inhalation route. The physicochemical parameters of these proteins (*i.e*,

molecular weight, particle size) severely limit the potential for systemic exposure via inhalation. It would be appropriate to use a modifier of 1% for bioavailability via inhalation for large molecular weight proteins. If a 1% bioavailability factor is applied to the dose that resulted in the effect of concern, the resulting exposure of concern level would be much greater than the 10 mg/day (therapeutic dose) or 1 mg/kg/day (preclinical studies) cut off in the NIOSH Hazardous Drug Alert 2004.

Erbitux® (cetuximab), supplied as a solution for intravenous injection, is used for the treatment of cancer. This large molecular weight protein is a human/mouse chimeric monoclonal antibody that binds to human epidermal growth factor receptor. The Erbitux® (cetuximab) label indicates that reproductive effects occurred in monkeys at 0.4 to 4 times the human dose. Organ toxicity was reported in humans and animal studies after exposure to Erbitux® (cetuximab). The lowest therapeutic dosage and administration is 250 mg/m^2 per week, and if adjusted for limited bioavailability, the exposure of concern level is orders of magnitude greater than the NIOSH Hazardous Drug Alert cut off of 10 mg/day (therapeutic dose). Reference: Erbitux® Label, Bristol-Myers Squibb Co., 2006

Conclusion: Erbitux® Cetuximab does *not* meet the definition of a hazardous drug as per the NIOSH Hazardous Drug Alert criteria.

Orencia® (abatacept), a lyophilized powder for intravenous infusion, is used for the treatment of rheumatoid arthritis (RA). This large molecular weight protein is a human IgG1/CTLA-4 fusion protein that functions by inhibiting T-cell activation. Compounds for the treatment of RA are similar in that they target the immune system and are immunosuppressive. Immunosupressive activity in mammals can result in increased incidence of infections and possible increased incidence of secondary cancers. In addition, tumors potentially due to abatacept would not be from a direct action on DNA since Orencia® (abatacept) was negative in a battery of genotoxicity studies. Therefore, cancer is not considered an endpoint of concern with regard to the hazardous drug alert. The dosage and administration by intravenous infusion, is 500 mg every 4 weeks in a <60 kg individual, and if adjusted for limited bioavailability, the exposure of concern level is orders of magnitude greater than the NIOSH Hazardous Drug Alert cut off of 10 mg/day (therapeutic dose). Reference: Orencia® Label, Bristol-Myers Squibb Co., 2007

Conclusion: Orencia® (abatacept) does *not* meet the definition of a hazardous drug as per the NIOSH Hazardous Drug Alert criteria.

Sustiva® (efavirenz)

Sustiva® (efavirenz) should not be identified as a hazardous drug on the updated list.

Sustiva® (efavirenz) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) being used for the treatment of HIV-1. Sustiva® (efavirenz) is supplied as capsules, tablets and an oral solution. There was equivocal evidence of tumors in rodent carcinogenicity studies. The mechanism of the carcinogenic potential is unknown. However, given the lack of genotoxic activity of Sustiva® (efavirenz) and the high doses used in the carcinogenicity studies, cancer is

not considered an endpoint of concern with regard to the hazardous drug alert. Teratogenic effects were noted in 3 of 20 cynomolgus monkey fetuses after maternal dosages of 60 mg/kg given daily throughout gestation. Plasma drug concentrations were similar to those in humans given 600 mg/day of Sustiva® (efavirenz). There have been four retrospective reports of findings consistent with neural tube defects in pregnancy in HIV-infected women orally exposed to 600 mg of efavirenz, however no prospectively identified cases of neural tube defects have been identified. The high therapeutic dose of 600 mg/day is well above the NIOSH Hazardous Drug Alert cut off of 10 mg/day (therapeutic dose) and relatively high doses were required for organ toxicity and teratology (60 mg/kg/day) in animals. The evidence indicates that Sustiva® (efavirenz) has a low potential to result in any of these effects as a consequence of routine occupational contact. Given the high therapeutic dose of 600 mg/day, reproductive toxicity, genotoxicity and organ toxicity are not considered endpoints of concern with regard to the hazardous drug alert. Reference: Sustiva® (efavirenz) Label, Bristol-Myers Squibb Co., 2007.

Conclusion: Sustiva® (efavirenz) does *not* meet the definition of a hazardous drug as per the definition in the NIOSH Hazardous Drug Alert.

Videx® (didanosine)

We agree that Videx® (didanosine) does *not* fit the criteria for a hazardous drug.

Videx® (didanosine) is a synthetic purine nucleoside analogue active against the Human Immunodeficiency Virus-1. Videx® (didanosine) is supplied as delayed release capsules or a powder for oral administration, 125 mg twice a day. In mutagenicity studies, Videx® (didanosine) was both negative and positive in *in vitro* studies and negative in animal studies. The weight of evidence indicates that Videx® (didanosine) has a low potential to cause genotoxicity in animals. Carcinogenicity, developmental toxicity and reproductive toxicity studies indicate that these endpoints are not of concern with regard to the hazardous drug alert. Organ toxicity was observed in humans at the therapeutic dose. The exposure of concern level, 250 mg/day is well above the NIOSH Hazardous Drug Alert cut off of 10 mg/day (therapeutic dose). Videx® (didanosine) Label, Bristol-Myers Squibb Co., 2006

Conclusion: Videx® (didanosine) does *not* meet the definition of a hazardous drug as per the NIOSH Hazardous Drug Alert criteria.

Abilify® (aripiprazole).

Finally, in at least one instance, there appears to be some inconsistency in assigning compounds to the "fitting" and "not fitting" proposed lists. For example, five drugs, aripiprazole, ziprasidone, risperidone, quetiapine fumerate and olanzapine, all have the same therapeutic indication and, for the most part, similar class-related adverse effects (prolactin-mediated tumors and reproductive effects in rodents; central nervous system effects in patients). A review of the two proposed lists finds that aripiprazole, ziprasidone, risperidone, and quetiapine fumerate are all listed as "fitting" the criteria while olanzapine is listed as "not fitting". The primary difference between the five compounds is the therapeutic dose. However, the 10 mg/day cut off

does not appear to be applied consistently across the class of compounds. Quetiapine, which has a very high therapeutic dose (50 - 300 mg/day), and aripiprazole, with a therapeutic dose of 10-15 mg/day, which have hazard profiles similar to olanzapine (therapeutic dose 3 -12 mg/day), were listed, while olanzapine was not. It does not appear that NIOSH has consistently applied the criteria. Abilify® (aripiprazole) should be listed in a matter consistent with olanzapine.

The issue of consistent evaluation of similar compounds is particularly important as the make-up of the hazardous drug list appears to be growing to include additional classes of substances beyond the original list which was predominantly anti-neoplastic and steroidal preparations.

It also is important to point out that the "fitting" list incorrectly identifies aripiprazole as having *in vivo* genotoxic potential. The Abilify® (aripiprazole) label indicates the genotoxicity occurs via a mechanism not relevant to humans and thus this endpoint is not a concern with regard to the Hazardous Drug Alert. Supporting documentation on the mechanism was supplied to the FDA.

Bristol-Myers Squibb Co. appreciates the opportunity to provide these comments on the *Alert* and the proposed updated list. Please contact the undersigned if any clarification of these comments or other further information is needed.

Sincerely,

William McGrath
Associate Director, Environmental Health & Safety

Cc: L. Reed
B. MacKenzie