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From: Debora Van der Sluis [vandersluis.debora@gene.com]

Sent: Tuesday, June 30, 2009 2:35 PM

To: NIOSH Docket Office (CDC)

Subject: Genentech Comments on NIOSH Hazardous Drugs List Update; Federal Register 74 19570; 29 April 2009

Attachments: NIOSH.pdf; ATT430734.htm

Attached are Genentech's comments on the NIOSH notice entitled "Updating the List of Hazardous Drugs for the NIOSH Alert: Additions and Deletions to the NIOSH Hazardous Drug List." These additions and deletions revise NIOSH's list of Hazardous Drugs that is Appendix A to the 2004 "NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings," DHHS Publication No. 2004-165 (2004).

We appreciate your consideration of these comments. Feel free to contact me if you have any questions.

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June 26, 2009

NIOSH Docket Office
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Docket 105
Cincinnati, OH 45226

Re: Genentech, Inc. comments on NIOSH Hazardous Drugs List Update; Federal Register 74 19570; 29 April 2009

Dear Docket Officer:

Genentech, Inc. (Genentech) is pleased to submit comments on the NIOSH notice entitled "Updating the List of Hazardous Drugs for the NIOSH Alert: Additions and Deletions to the NIOSH Hazardous Drug List." We support the additions and deletions to NIOSH's list of Hazardous Drugs that is Appendix A to the 2004 "NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings," DHHS Publication No. 2004-165 (2004). Our comments are divided into General Comments on the proposed additions and deletions and Specific Comments addressing the scientific issues regarding high molecular weight protein (HMWP) drugs manufactured by Genentech and other biotechnology companies. The handling of hazardous drugs is an important issue for healthcare workers and Genentech supports the efforts NIOSH has taken to update the Hazardous Drugs List. We applaud 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.

Background

Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes biotechnology therapeutics (biotherapeutics), antibody drug conjugates, and small molecule drug products to meet significant unmet medical needs. Over sixteen of the currently approved biotechnology products originated from or are based on Genentech science. Our leading products have been recombinant proteins and monoclonal antibodies that are unique (as compared to previously employed synthetic) chemical therapies for the treatment of human diseases. Genentech was the first company to produce a human protein and the first to clone human insulin using recombinant DNA technology. Protropin® was the first recombinant biotechnology drug manufactured and marketed by a biotechnology company. Rituxan® (rituximab) was the first therapeutic antibody approved for cancer in the U.S. Genentech is uniquely positioned to provide information to NIOSH on the potential hazards of occupational exposure to HMWP therapeutic agents.

Genentech is committed to the highest standards of integrity in contributing to the best interests of patients, the medical profession, our employees, and our communities, with one of our core values being the continual pursuit of scientific and operational excellence. We truly appreciate the opportunities you have given us to collaborate on the Hazardous Drug Alert process, and your consideration of data we have provided in written communications, conference calls, and in-person meetings.

General Comments

The scientific accuracy of the NIOSH Alert is essential to achieving its goals, and contributing to best practices for worker occupational health and safety programs and hazard communication. 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, as outlined below, then risk decisions and hazard control measures by employers and employees in healthcare settings will not be appropriate and will not reflect the hazards that exist. We therefore support NIOSH's additions and deletions to Appendix A as proposed in the April 29, 2009 notice. We further support NIOSH's continued transparency in seeking public comment on the proposed additions and deletions to the list of Hazardous Drugs.

1. We support NIOSH's use of well-accepted scientific principles in the decision-making process, 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, including 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. Otherwise, biotherapeutics that are administered intravenously or subcutaneously, by default, will meet the NIOSH criteria for a hazardous drug as currently defined, but will not present a true risk to healthcare workers. In healthcare settings, the primary routes of exposure to hazardous drugs are respiratory and dermal. HMWP drugs can only have a significant pharmacologic effect when deliberately introduced into a person's body by a parenteral route and absorbed into the systemic circulation, or possibly if specifically engineered to be absorbed by the lungs. With molecular weights ranging from 100-150 kD and particle sizes of $\geq$ 10 microns, there is general agreement in the scientific community that there is an *extremely* low likelihood of absorption following dermal or inhalation exposure in the workplace.

2. In Genentech's comments to NIOSH dated September 20, 2007, we recommended that NIOSH consider and, to the extent possible, be consistent with guidance put forth by other expert groups. We were concerned that if the scientific evidence for handling a hazardous drug in a particular manner was not supportable, and was not harmonized with other expert groups, then risk decisions and hazard control measures by employers and employees in health care settings would not be appropriate and would not reflect the actual, potential hazard(s) that exist. Specifically, the British Centralized Intravenous Additives Group (CIVAS) and the British Oncology Pharmacy Association (BOPA) have made the following joint statement regarding the handling of monoclonal antibody therapeutics the class of compounds, (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...
>
> They do not interact directly with the transcription of DNA or RNA and would not be expected to be mutagenic or teratogenic...
>
> As a class, these do not require specific facilities for their safe handling since they pose no special risk to the operator or the environment. Therefore, they can be handled in the same facilities as those for other aseptic products. Those presently used routinely do not appear to be carcinogenic or teratogenic and so they can be handled in the same facilities used for non-cytotoxic aseptic products."

We agree with NIOSH's position that, based in sound science, it is optimal for the Alert to be consistent with existing government regulations and recommendations, even those established outside of the U.S.

In the 2007 comments, we also recommended that NIOSH consider the more scientifically-based approach to risk assessment of the U.S. Environmental Protection Agency (EPA). EPA has a long history of using the basic principles and practices of risk assessment to ensure appropriate risk management and this approach could be easily adopted by NIOSH. Risk assessment has been defined as "the characterization of the potential adverse health effects of human exposures to environmental hazards" (NRC, 1983). According to EPA, risk assessment is "the extent to which a group of people has been or may be exposed to the kind and degree of hazard posed by a chemical, thereby permitting an estimate to be made of the present or potential health risk to the group of people involved" (EPA, 2007). Risk assessment information (from the process of hazard identification -> dose-response assessment -> exposure assessment -> risk characterization) is then used in the risk management process to implement administrative and engineering controls to protect people. We fully support NIOSH's decision to include the principles of risk assessment in making decisions about which drugs fit or did not fit the definition of a hazardous drug.

3. The lowest molecular (MW) protein reported in the literature to become systemic and bioavailable, following subcutaneous or intramuscular injection, is Leuprorelin/Luprin Injection (leuprolide acetate), with a MW of 1,209. Inhalation bioavailability in humans was found to be 17%, with an absorption time (Tmax) of 1.2 hours.

Specific Comments

In addition to our general comments described above, we agree with NIOSH's decision that Genentech's HMWP drugs, rituximab and bevacizumab, do not meet the criteria for a hazardous drugs. This position is supported by data previously submitted in our letters dated April 11, 2004 and September 20, 2007.

Rituximab (Rituxan®)

Genentech strongly recommended in our 2004 and 2007 letters, in conference calls, and in-person meetings that NIOSH delete rituximab from the list of "New FDA Drugs and Warnings Fitting NIOSH Criteria for Hazardous Drugs 2006". Our concern was that Rituxan® (rituximab) was on the proposed Hazardous Drugs List but did not meet the NIOSH criteria for a "hazardous drug" stated in the Hazardous Drug Alert. The scientific

evidence for deleting rituximab from the list of hazardous drugs was strongly supported by the available toxicological and clinical data summarized below:

Drugs that are considered hazardous include those that exhibit one, or more, of the following six characteristics in humans or animals:

1. Carcinogenicity- Rituximab has not been tested for its carcinogenic potential. Its pharmacological mechanism of action (it binds to the antigen CD20, which regulates the activation process for cell cycle initiation and differentiation, and causes lysis of the B-lymphocytes by activating the complement cascade and immune effector cells, inducing apoptosis) suggests that it would not be carcinogenic. No human cancers directly attributable to rituximab were reported in clinical studies.

2. Teratogenicity or other developmental toxicity- In studies in non-human primates, rituximab was not found to be a teratogen or developmental toxicant. In a reproductive toxicity study, rituximab at doses of 20, 50, or 100 mg/kg were given weekly to pregnant female cynomolgus monkeys during the period of organogenesis. There were no findings of toxicity to the dams or developing fetuses, and the only effect noted was the dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the fetuses.

3. Reproductive toxicity- Repeated dose studies in laboratory animals have not indicated the reproductive system to be a target organ of toxicity, and pharmacological studies do not indicate that the reproductive system organs would bind rituximab (a monoclonal antibody specific for to CD20 antigen).

4. Organ toxicity at low doses- Rituximab has some toxic properties including hematological effects but, at a clinical dose of 375 mg/m^2, or approximately 700 mg/dose, it does not meet the low dose criteria in the NIOSH Alert.

5. Genotoxicity- Although not studied, there are no data to suggest rituximab is genotoxic as per the International Conference on Harmonization (ICH) guideline for testing of pharmaceuticals, genotoxicity/mutagenicity studies are not generally performed. For rituximab, the mechanism of action of the drug would preclude it from entering the cells used to assess mutagenic endpoints.

6. Structure and toxicity profile of new drugs that mimic existing drugs that are hazardous by the above criteria- rituximab is a monoclonal antibody. As a class of targeted and specific therapies to prevent cancer, they do not mimic the traditional cytotoxic, antineoplastic cancer chemotherapy treatments, which would be considered hazardous.

We also strongly believed that rituximab should not be included on any list of hazardous drugs as supported by the U.S. Food and Drug Administration (FDA)-required labeling of this commercial biotherapeutic. After a thorough review of Genentech's clinical and toxicology data, no requirement to apply precautionary special handling labeling, as would occur for traditional cytotoxic, antineopleastic cancer chemotherapy treatments, has been mandated by FDA (Rituximab, 2007). The Center for Drug Evaluation and Research (CDER) of FDA has a policy, as cited in several letters to manufacturers (www.fda.gov search term - cytotoxic labeling policy), that requires references for safe handling of antineoplastic and cytotoxic drugs be included in the labeling. These are not required for rituximab as it does not meet the criteria for requiring this labeling by FDA.

Bevacizumab (Avastin®)

Genentech has not previously submitted written comments to NIOSH regarding bevacizumab (Avastin®) and we would do so at your request; however, this monoclonal antibody therapeutic has a molecular weight of 149,000 daltons and, like rituximab, does not meet the criteria for a "hazardous drug" stated in the Hazardous Drug Alert. I communicated this information and other data at our meeting with other expert reviewers in Washington, D.C. on December 7, 2007. The scientific evidence for deleting bevacizumab from the list of drugs not fitting the criteria is strongly supported by the available toxicological and clinical data, and we agree that NIOSH should not include it on the List of Hazardous Drugs.

Conclusion

NIOSH is known for its scientific rigor, and we fully support its decision-making process in determining the final proposed list of hazardous drugs. It is essential the information developed for the Hazardous Drug Alert be scientifically supported and consistent with the listing criteria. We are pleased that NIOSH considered our recommendations and supporting data, and continue to believe that the inappropriate listing of monoclonal biotherapeutics as drugs hazardous for workers in healthcare settings dilutes the important information provided on drugs that truly meet the criteria for "hazardous".

The new scientific approach, considering hazard characterization and risk assessment, is consistent with the warnings, precautions, controls and recommendations of expert groups for the handling of HMWP therapeutics for worker protection. Consistent and scientifically-supported information will be provided to patients, employees, and healthcare workers who handle and administer biotherapeutics to millions of people worldwide. We take our mission- to discover and bring to market new, innovative products that address previously unmet medical needs- seriously and our company culture fully supports this goal. Genentech supports NIOSH in appropriately applying scientific rigor to the updating of the Hazardous Drug List and is pleased to provide any additional data or assistance needed by the Agency.

Respectfully submitted,

Gene Murano, Ph.D.

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Vice President of Regulatory Policy & Strategy