

Waiver to Allow Participation in a Food and Drug Administration Advisory Committee

DATE: May 25, 2017

TO: Janice M. Soreth, M.D.
Associate Commissioner for Special Medical Programs
Office of Medical Products and Tobacco
Office of the Commissioner, FDA

THROUGH: Jeffrey Anderson, M.S., R.A.C.
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

FROM: Jayne E. Peterson, B.S.Pharm., J.D.
Director, Division of Advisory Committee and Consultant Management
Center for Drug Evaluation and Research

Name of Advisory Committee Member: **Brenda Weigel, M.D.**

Committee: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (PedsODAC)

Meeting date: June 22, 2017

Description of the Particular Matter to Which the Waiver Applies:

The Best Pharmaceuticals for Children Act of 2002 (BPCA) expressly charged that the PedsODAC, a subcommittee of the Oncologic Drugs Advisory Committee (ODAC), shall: (A) evaluate and, to the extent practicable, prioritize new and emerging therapeutic alternatives available to treat pediatric cancer; (B) provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies; and (C) advise on ways to improve consistency in the availability of new therapeutic agents. (Pub. Law 107-109, Section 15(a)(1)).

The role of the Pediatric Subcommittee is legislated by BPCA. Notably, the PedsODAC does not provide advice to FDA with respect to approval of any specific product for any specific pediatric cancer indication. The Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research brings issues related to approval of any product for a cancer indication, including any pediatric cancer indication, to the ODAC, not the PedsODAC.

The cancers of adults and children are very different and although the outcome for children with cancer has improved dramatically during the past several decades, cancer remains the leading cause of death from disease in children. Those children who survive often do so at an enormous cost associated with the long term and late effects of existing therapy, which are frequently debilitating. Thus, there is an urgent need for new drugs and biologic products for the treatment of childhood cancer.

Pediatric cancer drug development is complex and very different from drug development in other disease areas and is largely dependent upon cancer drug discovery and development in adults. Early consideration of new promising agents for study in children is critical to timely development of new treatments. On June 22, 2017, the PedsODAC will meet to discuss two chemical entities in various stages of development for adult cancer indications to assess their relevance for possible development for use in one or more pediatric cancers. The subcommittee will consider and discuss issues concerning possible pediatric cancers and stages of disease to be studied, patient populations to be included, and possible designs of clinical trials to expedite early evaluation to facilitate the development of these chemical entities as potential new drugs for use in pediatric cancer. The discussions may also provide information to FDA pertinent to the formulation of Pediatric Written Requests (PWRs), if appropriate.

Because pediatric cancer care is very closely integrated with pediatric cancer clinical research and new drug development, all children with cancer are treated at academic centers, and nearly all of these centers are members of a National Cancer Institute-funded clinical trials network. As a result, the experts are invariably researchers at these institutions. The expertise that FDA seeks cannot be found outside of this context. The insights the Agency seeks can be provided only by learned researchers with extensive experience with studies of investigational agents in the pediatric age group. These investigators generally do not derive substantial personal financial benefit from industry grants and contracts to their institutions, and their institutions receive the industry funds necessary to offset institutional costs for patient care and other institutional clinical research costs.

Dr. Brenda Weigel is serving as a temporary voting member of the PedsODAC; she has been invited to participate in the June 22, 2017 PedsODAC meeting. The products under consideration are: Session 1, Olaratumab, application sponsored by Eli Lilly and Company; and Session 2, Prexasertib, application sponsored by Dista Products/Eli Lilly and Company. The topics of this meeting are particular matters involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Weigel is Professor in the Division of Pediatric Hematology/Oncology at the University of Minnesota Medical School. She has not identified any personal financial interests that are likely to be affected by the particular matters to be discussed at the subcommittee meeting. However, she has identified financial interests of her employer, which are imputed to her under the federal conflict of interest statute 18 U.S.C. § 208. The financial interests to which this waiver applies is the imputed financial interest related to Olaratumab (LY-3012207), sponsored by Eli Lilly and Company and Company; and Prexasertib, application sponsored by Dista Products/Eli Lilly and Company.

Session 1: Olaratumab

The University of Minnesota Medical School is participating in a clinical study funded by Eli Lilly: A Phase 1, Open-Label, Dose-Escalation Study of Olaratumab (LY-3012207) as a Single Agent and in Combination With Doxorubicin, Vincristine/Irinotecan, or High-Dose Ifosfamide in Pediatric Patients With Relapsed or Refractory Solid Tumors (NCT02677116). The University of Minnesota Medical School is one of twenty-three sites participating in the study and a total of seventy patients are anticipated to enroll nationally. The clinical study began on December 22, 2015 and the industry funding support is dependent on enrollment.

Total funding for this study is anticipated between \$0 - \$50,000 from Eli Lilly. Dr. Weigel does not receive any salary support or personal remuneration for her role as the Site Principal Investigator.

Session 2: Prexasertib:

The University of Minnesota Medical School is participating in a clinical study: A Phase 1 Study of LY2606368 (Prexasertib), a CHK1/2 Inhibitor, in Pediatric Patients With Recurrent or Refractory Solid Tumors, Including CNS Tumors (NCT02808650). This study is open through the Children's Oncology Group (COG) Phase I Consortium and the University of Minnesota Masonic Cancer Center is one of sixteen sites participating in the study. A total of sixty-five patients are anticipated nationally and The University of Minnesota Medical School anticipates enrolling 2 to 6 patients. The financial support is provided by COG, a National Cancer Institute supported clinical trials group, and the study drugs are provided by Eli Lilly.

Total funding for the study is anticipated between \$0 - \$50,000. Dr. Weigel does not receive any salary support or personal remuneration for her role as the Site Co-Investigator.

In addition, a (b) (4) is under review by the University of Minnesota. Eli Lilly has a contract with (b) (4) and the University of Minnesota is in negotiation of a (b) (4). This (b) (4) is in addition to the funding received from (b) (4). The University of Minnesota Medical School anticipates enrolling (b) (4) patients in the study.

Total funding for this study is anticipated between \$0 - \$50,000. Dr. Weigel does not receive any salary support or personal remuneration for her role as the Site Co-Investigator.

Basis for Granting the Waiver:

As discussed in more detail below, the waiver is supportable for a number of reasons. The financial interests at issue are small, particularly for a research institution the size of University of Minnesota Medical School. Dr. Weigel's research at University of Minnesota is not closely related to the advisory committee discussions, which will focus on the potential for demonstrating efficacy of products in pediatric cancer patients. Finally, the subject of this meeting requires the participation of individuals with a wide ranging knowledge of pediatric oncology and requires a rare level of expertise. Dr. Weigel has significant experience with this subject matter.

The dollar value of the potential gain or loss that may result from participation in the particular matter is small relative to the University of Minnesota Medical School's revenue.

As noted above, it is expected that the total funding to University of Minnesota will be between \$0 - \$50,000 total, per study. This represents a very small amount of money for a research institution such as University of Minnesota. The University of Minnesota receives approximately \$788 million in externally sponsored research funding.

In its February 23, 2007, Memorandum to Designated Agency Ethics Officials regarding Waivers Under 18 U.S.C. § 208, the Office of Government Ethics has provided guidance in determining whether the need for an individual's services on an advisory committee outweighs the potential for a conflict of interest created by the disqualifying financial interest. This guidance provides that the responsible official should consider the dollar value of the potential gain or loss that may result from participation in a particular matter – "Although an important factor to consider, the value of the potential gain or loss often may be only an estimate. Furthermore, depending on the type of interest affected, it may be difficult to estimate. For example, it would be simpler to estimate the value of the potential gain that a decision to award a \$1 million contract would have on a relatively small company, compared to the impact of the same award on a Fortune 500 company. Of course, the greater the potential gain or loss, the more unlikely it is that a waiver can be justified."¹ A consideration of the financial interests at issue here leads us to conclude that the interests are not so great that a waiver could not be justified.

The PedsODAC meeting is meant to elicit discussion of the data currently available from adult studies and whether there is any pediatric cancer type for which there is an unmet clinical need that these chemical entities might address. The PedsODAC meeting will focus on preliminary discussions and general considerations in pediatrics, including discussions around molecular abnormalities, about potential indications that might be feasible for the drug substances, and about international collaborative efforts. Significantly, the advisory committee members will not recommend approval or disapproval of any particular product. Such recommendations would be grossly premature and simply could not be made at this early stage in product development. The majority of oncology products studied in the Phase 1 setting in children do not proceed through development to submission and approval of a new drug application. Very few chemical entities in these early stages of evaluation and development ever proceed to a marketing application.

Moreover, the role of the PedsODAC is not to provide any advice to the Agency with respect to approval of any specific product for any specific pediatric cancer indication. Any recommendations to FDA with respect to approval of any product for a cancer indication are provided by the ODAC, and not the Pediatric Subcommittee.

Dr. Weigel has unique qualifications and specialized expertise needed for this particular matter.

To meet statutory responsibilities to evaluate and prioritize new and emerging therapeutic alternatives to treat pediatric cancer and to provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies, this

¹ See Page 9 of the OGE Memo on Waiver Under 18 U.S.C. §208. Available at [https://www.oge.gov/Web/OGEnsf/All+Advisories/328CE4B5A300EAEB85257E96005FBDE5/\\$FILE/do-07-006.pdf?open](https://www.oge.gov/Web/OGEnsf/All+Advisories/328CE4B5A300EAEB85257E96005FBDE5/$FILE/do-07-006.pdf?open). (Accessed: May 25, 2017)

meeting of the PedsODAC requires the participation of experts with a wide and deep knowledge of pediatric oncology and product development. Such experts typically develop their knowledge through their work at centers of excellence for the treatment of pediatric cancers, the very sites where investigational drugs are studied.

Dr. Weigel is the Director of the Division of Pediatric Hematology/Oncology and Director of the Clinical Trials Office. She received her medical degree from McMaster University, Hamilton, Ontario; she completed her residency at the University of Western Ontario, London, Ontario, and a fellowship in Pediatric Hematology/Oncology & Blood and Marrow Transplantation at the University of Minnesota, Minneapolis, Minnesota. She is a professor cross-appointed at the University of Minnesota's Cancer Center and the Department of Pediatrics, and the recipient of the Lehman/Children's Cancer Research Fund Endowed Chair in Pediatric Cancer. She is also the Co-Director of the Sarcoma Program for the Masonic Cancer Center, and an Associate Director of the Cancer Experimental Therapeutics Initiative for the Masonic Cancer Center. She is a recognized leader in the treatment of sarcomas, such as rhabdomyosarcoma, Ewings sarcoma, and osteosarcoma. Dr. Weigel's research areas focus on new immunotherapy strategies for pediatric cancers, especially on rhabdomyosarcoma and acute myeloid leukemia. She is working on identification of new agents that may improve the treatment of childhood cancers using laboratory models, which can be translated into clinical trials for patients.

Dr. Weigel's unique roles as Chair of the COG's Phase 1 Consortium and Chair of the COG Developmental Therapeutics Committee provides an extraordinary opportunity for the agency to benefit from the vast experience and knowledge base she has related to the evaluation of investigational drugs in children, especially in the setting of relapsed and refractory solid tumors, notably sarcomas, for which there is a high unmet clinical need. Her experience in the Phase 1 studies of the drugs being discussed makes her contribution to the committee's discussion essential as the committee examines the potential for the products under discussion to have a potential impact on one or more pediatric cancers refractory to standard therapy.

Dr. Weigel's personal experience in the design and conduct of investigational drug trials in children with cancer, and her knowledge of the possible benefit-risk ratios for individual children enrolled in investigational drug studies are critical to the quality of the discussion. The outcome of this meeting presents the potential for significant impact on improving the chances of cure for children diagnosed with pediatric cancer. In the interest of public health, it is critical that the agency have the unique expertise that Dr. Weigel will provide for the discussion of this particular matter before the committee.

There is limited expertise available and it is difficult to locate similarly qualified individuals without a disqualifying financial interest.

Given the relative rarity of childhood cancer, collaboration and concentration of expertise are essential. This is particularly true for rare pediatric cancers, which most pediatric oncologists would never see, or may see only once in a lifetime of practice. Although the majority of adult patients with cancer are cared for in the community and enroll in clinical trials at a rate of only 3%, nearly all children with cancer are treated at academic centers, and the vast majority are enrolled in clinical trials. Nearly all of these academic centers are members of the Children's Oncology Group (COG), a National Cancer Institute-funded clinical trials network of more than 230 pediatric institutions throughout the United States, Canada, and other foreign sites.

Pediatric cancer care is very closely integrated with pediatric cancer clinical research and new drug development. The COG and its predecessor cooperative groups have a more than 50-year history. Cooperation and collaboration in the design and conduct of clinical trials over this period of time has changed childhood cancer from a nearly uniformly fatal disease to one where more than 85% are cured. But, despite the dramatic increase in cure rates, cancer remains the major cause of children's death from disease in the United States and other developed countries. Cure often comes at a substantial cost in the form of severe and often debilitating late effects due to toxicity of therapy. Development of new cancer therapies remains a pressing need.

Industry sponsors work closely with investigators and institutional members of the COG, which employ the most expert researchers. In fact, definitive licensing studies, incorporating randomized controlled trial design, are generally only conducted within the COG and its clinical trial infrastructure, which is federally funded for NIH/NCI approved research. Reimbursement for this federally funded infrastructure is provided by industry sponsors in the form of per case reimbursement.

More than 90% of pediatric cancer patients in the United States are treated at COG institutions and most are enrolled in clinical trials. Of the approximately 230 COG institutions, a much smaller number of institutions (up to about 50, including University of Minnesota) are involved in early clinical trials of drugs to treat rare pediatric cancers. These institutions employ researchers with the highest levels of expertise in pediatric cancers and drug development, the very experts FDA needs to hear from on the issues before the PedsODAC.

Although efforts were taken to seek out individuals with the least potential for a conflict of interest, for the reasons noted above, finding experts for this meeting has been challenging. Approximately 95% of the experts with the expertise and experience needed are affiliated with COG institutions. Due to their expertise, qualified candidates face many demands on their time

A productive discussion of the application depends on having a broad contribution of pediatric hematology/oncology experts at the meeting. Multiple experts with diverse pediatric cancer backgrounds are needed in order to have a collaborative scientific discussion of the current available data from the adult studies and whether there are any pediatric cancers in which there is an unmet clinical need that these products might fulfill. In fact, ten other individuals with expertise in Pediatric Oncology and Pediatric Hematology were contacted but were unable to attend due to conflicts of interest, scheduling conflicts and incomplete paperwork.

The particular matter is not sensitive.

Sessions 1 and 2 of the June 22, 2017, PedsODAC meeting, are not considered to be sensitive and the Division does not expect that the meeting is likely to receive significant public interest, (non-trade) press interest, or congressional interest nor is it considered highly controversial. Moreover, the discussion at the meeting will be only one source of information for the Agency's plans related to the submission of a Written Request for evaluating this drug in children.

Dr. Weigel has served effectively on past PedsODAC meetings.

Dr. Weigel has been a consistent and productive participant in and contributor to the success of past PedsODAC meetings. Her contributions to the development of novel research approaches to therapeutic strategies for children with cancer is internationally recognized; her knowledge in the area of pediatric oncology and Phase 1 clinical trials development will provide necessary expertise for this important discussion.

Accordingly, I recommend that you grant a waiver for Dr. Brenda Weigel, a temporary voting member of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

X The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual’s services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Regular Government Employee’s or Special Government Employee’s Ability to Act:

Non-voting

Other (specify):

Denied – The individual may not participate.

/S/
Janice M. Soreth, M.D.
Associate Commissioner for Special Medical Programs
Office of Medical Products and Tobacco
Office of the Commissioner, FDA

06/02/2017
Date