



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

DATE: June 22, 2016

TO: Jill Hartzler Warner, J.D.
Associate Commissioner for Special Medical Programs, FDA

THROUGH: Michael F. Ortwerth, Ph.D.
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

FROM: Jayne E. Peterson, BSP Pharm., J.D.
Director, Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

Name of Advisory Committee Member: Ira Dunkel, M.D.

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

Meeting date: June 28, 2016

Description of the Facts on Which the Waiver is Based

The Best Pharmaceuticals for Children Act of 2002 (BPCA) expressly charged that the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (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 28-29, 2016, the PedsODAC will meet to discuss five 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.

Description of the Particular Matter to Which the Waiver Applies

On June 28-29, 2016, information will be presented to the subcommittee to elicit discussion on potential pediatric development plans for five chemical entities, including atezolizumab, sponsored by Roche. The committee will be discussing scientific issues related to the mechanism of action of a given drug, its non-clinical development, its toxicity profile in adults, any ongoing studies in children, and whether the drug appears to be a potential candidate for pediatric development by industry sponsors in collaboration with academic investigators and publicly funded clinical research networks.

Dr. Ira Dunkel is Professor, Weill Cornell Medical College; Attending Pediatrician, Memorial Sloan Kettering Cancer Center; and Attending Physician, New York Presbyterian Hospital. He has identified a financial interest related to atezolizumab. Dr. Dunkel has a consulting agreement with (b) (4), which, to date, has total funding between \$0 – 5,000.

Type, Nature, and Magnitude of the Financial Interest(s)

Atezolizumab will be discussed at the June 28-29, 2016 PedsODAC meeting, and its mechanism of action/drug class are similar to another chemical entity, (b) (4) will not be discussed at the June 28-29, 2016 PedsODAC meeting. Dr. Dunkel has a consulting agreement with (b) (4) related to (b) (4). However, no specific disease indications were decided. Dr. Dunkel is not aware whether he will have any further role in the

development of (b) (4). FDA is also not aware of any planned or ongoing pediatric studies for (b) (4). Dr. Dunkel has no consulting agreement related to atezolizumab.

The total funding to Dr. Dunkel is between \$0 – 5,000 to date.

Basis for Granting the Waiver:

As discussed in more detail below, the waiver is supportable because the financial interest at issue is small and Dr. Dunkel's research is not closely related to the advisory committee discussions, which will focus on the potential for demonstrating efficacy of products in pediatric cancer patients. Moreover, 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. Dunkel has significant experience with this subject matter.

The financial interest is small and not closely related to the advisory committee discussion.

Dr. Dunkel's financial interest at issue is a small amount of money for a consulting agreement. In its February 23, 2007 Memorandum to Designated Agency Ethics Officials regarding Waivers Under 18 U.S.C. § 208, the Office of Government Ethics provided guidance on 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." A consideration of the financial interest at issue here leads us to conclude that the interest is 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 other known 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 FDA 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 to the Pediatric Subcommittee.

The meeting requires a wide knowledge of pediatric oncology and subspecialties, and expertise in designing clinical trials.

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 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. This is particularly true for experts in rare pediatric cancers; patients frequently must travel to be treated by a physician with experience in a particular rare cancer.

Dr. Dunkel's participation in the discussion of atezolizumab is critical given his background and training in pediatric oncology. He received his medical degree from Duke University in 1985, where he also completed his fellowship training, and he has been in practice for over 30 years. Dr. Dunkel is also Chair of the Pediatric Brain Tumor Consortium (PBTC), a multidisciplinary cooperative research organization devoted to the study of correlative tumor biology and new therapies for primary CNS tumors of childhood. He is one of only two neuro-oncologists on the advisory committee; issues related to the brain tumors in children will be important in providing advice related to the appropriateness of pediatric studies. In addition to his expertise as a neuro-oncologist and his experience in pediatric oncology, Dr. Dunkel is board certified in pediatric hematology-oncology. He has a special interest and recognized expertise in melanoma and retinoblastoma. His expertise in pediatric brain tumors and neuro-oncology in the consideration of the products to be discussed for possible pediatric evaluation is absolutely critical. In the interest of public health, it is critical that the agency have the unique expertise that Dr. Dunkel will be able to provide for the discussion of the particular matter before the committee.

Relevant expertise is concentrated in the institutions comprising the children's oncology group, and other candidates with the necessary expertise have not been found.

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.

Pediatric cancer care is very closely integrated with pediatric cancer clinical research and new drug development. 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 at institutions, which employ the most expert researchers, such as Dr. Dunkel. 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. Due to their expertise, qualified candidates face many demands on their time. Dr. Dunkel is one of only two neuro-oncologists attending this meeting; three others were unable to participate. Brain tumors represent a major unmet clinical need in children. Therefore, his participation is critical. He has a special interest and recognized expertise in pediatric patients with brain tumors, melanoma, and retinoblastoma.

Accordingly, I recommend that you grant a waiver for Dr. Ira Dunkel, a temporary member of the Pediatric 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 Special Government Employee’s Ability to Act:

 Non-voting

 Other (specify):

 Denied – The individual may not participate.

 /S/
Jill Hartzler Warner, J.D.
Associate Commissioner for Special
Medical Programs

 6/24/16
Date