DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring MD 20993

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, BSPharm., 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: Kathleen A. Neville, 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, which are required solely for research purposes and not necessarily as part of standard medical care. Such patient care costs attributed to research cannot be charged to private or public third party payors. Other institutional clinical research costs include research pharmacy support, data management and clinical record abstraction, data submission, laboratory tests, and diagnostic imaging procedures.

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

Dr. Kathleen Neville is Professor, Department of Pediatrics, University of Arkansas for Medical Sciences, and Pediatrician, Clinical Pharmacology and Toxicology, Arkansas Children's Hospital. She has not identified any personal financial interests that will be affected by the particular matters to be discussed at the subcommittee meeting. However, she has identified the following financial interest of her employer, which is imputed to her under a federal conflict of interest statute, 18 U.S.C. § 208.

Dr. Neville's employer, University of Arkansas for Medical Sciences, is participating in a clinical study funded by Roche and titled "An Early-Phase, Multicenter, Open-Label Study of the Safety and Pharmacokinetics of Anti-PD-L1 Antibody (atezolizumab) in Pediatric and Young Adult Patients with Previously Treated Solid Tumors." This is a Phase 1 study to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of atezolizumab in pediatric and young adult patients. The study began February 9, 2016 and is anticipated to end September 1, 2016. Dr. Neville is serving as a sub-investigator. Atezolizumab is a chemical entity that will be discussed in one session of this meeting.

The total industry funding to the University of Arkansas for Medical Sciences under the financial interest at issue is expected to be between $0 and $50,000 per year.

Basis for Granting the Waiver

It is critical that the Agency have access to the unique expertise that Dr. Neville can provide during the discussion of the particular matter before the committee.

Dr. Neville's participation in the discussion of atezolizumab is critical given her background and training (and Board certification) in clinical pharmacology. She received her medical degree from State University of New York Downstate Medical Center College of Medicine and has been in practice for over 20 years. She is the ***only*** trained and Board-certified pharmacologist on the advisory committee, and her input on issues related to the absorption, distribution, and metabolism of drugs in children will be important in providing advice related to the appropriateness of pediatric studies. In addition to her expertise as a clinical trialist and her experience in experimental therapeutics, Dr. Neville is a board certified pharmacologist and a board-certified oncologist. She has a special interest and recognized expertise in the pharmacology of new agents in very young children. Her expertise in pharmacology 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 access to the unique perspectives that Dr. Neville can provide during the discussion of the particular matter before the committee.

The financial interest is small.

The total funding to the University of Arkansas for Medical Sciences under the financial interest at issue is expected to be between $0 and $50,000 per year. This is a relatively small amount of money for a research institution such as Dr. Neville's employer, which is part of a large state university system. According to the consolidated financial statement for the University of Arkansas University System, the University System had assets of approximately $3.8 billion dollars as of June 30, 2014.[1] Dr. Neville does not receive any salary support or personal remuneration for her involvement in the study. Dr. Neville's institution receives these industry funds merely to offset institutional costs for patient care, which is required solely for research purposes and not necessary as part of standard medical care. Such patient care costs attributed to research cannot be charged to private or public third party payors as clearly communicated to research subjects in the Informed Consent Documents. These institutional clinical research costs include, but are not limited to, research pharmacy support, special nursing procedures, data management and clinical record abstraction, data submission, laboratory tests, surgical biopsies, and diagnostic imaging procedures.

A consideration of the financial interest at issue here leads to the conclusion that the interest is not so great that a waiver could not be justified. 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 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

[1] *See* University of Arkansas System Consolidated Financial Statement FY 2013-2014. Available at http://www.uasys.edu/wp-content/uploads/2015/01/UofA-Finance-Report-FINAL-2014.pdf. (Accessed June 13, 2016).

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."

It is also important to note that the PedsODAC does not provide advice to FDA with respect to approval of any specific product for any specific pediatric cancer indication, and the committee will not vote on any matter nor will they make regulatory recommendations to FDA.

Relevant expertise is concentrated in the institutions comprising the children's oncology group; 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. 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 U.S., Canada, and other foreign sites.

Although efforts were taken to seek out individuals with the least potential for a conflict of interest, for the reasons noted, finding alternative experts for this meeting has been difficult. 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 for their time. In fact, eight other individuals with expertise in Pediatric Oncology and Pediatric Hematology were contacted but were unable to attend due to scheduling conflicts. Dr. Neville, the only pharmacologist, has a special interest and recognized expertise in the pharmacology of new agents in very young children.

Accordingly, I recommend that you grant a waiver for Dr. Kathleen A. Neville, a temporary voting 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):

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_____ Denied – The individual may not participate.

/S/ 6/24/16

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