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: Steven Dubois, M.D.

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

Meeting date: June 28-29, 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.

Description of the Particular Matter to Which the Waiver Applies

As discussed in more detail below, the financial interests to which this waiver applies are the imputed financial interests related to (1) atezolizumab, sponsored by Roche, (2) tazemetostat, sponsored by Epizyme, Inc., and (3) entrectinib, sponsored by Igynta. Steven Dubois, M.D., is Director of Experimental Therapeutics, Dana-Farber Children's Center and Blood Disorders Center, Dana-Farber Cancer Institute (Dana Farber). He 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, he has identified the following financial interests of his employer, which are imputed to him under a federal conflict of interest law, 18 U.S.C. § 208.

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

Atezolizumab

Dr. DuBois's employer has a current study underway funded by Roche of atezolizumab, one of the products being reviewed by the committee. Dr. Dubois serves as the institutional Principal Investigator for this trial.

Study titled "An Early-Phase, Multicenter, Open-Label Study Of The Safety And Pharmacokinetics Of Anti-Pd-L1 Antibody (MPDL3280A) In Pediatric and Young Adult Patients With Previously Treated Solid Tumors." MPDL3280A is also known as atezolizumab.

The total funding from industry to Dana Farber is anticipated to be $50,001-$100,000 per year, based on a per patient enrollment. This site was activated in December 2015; anticipated duration is 2 years. Dr. DuBois's employer intends to dedicate a small percentage of these funds to offset Dr. DuBois's salary; however, his salary remains the same regardless of funds received by Dana Farber for this study.

Tazemetostat

Dr. Dubois's employer has two current studies funded by Epizyme of tazemetostat, one of the products being reviewed by the committee. Dr. Dubois serves as a Sub-Investigator on both of these trials.

Study titled "A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma"

Study titled "A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects (16 years and older) With INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma"

The total possible funding from industry to Dana Farber is $100,001-$300,000 per year, per study, for a cumulative total of $200,002-$600,000 per year. Both studies were activated at this site in December 2015 with anticipated duration of two years. Dr. DuBois will not receive any salary support or personal remuneration for his involvement.

Entrectinib

Dr. Dubois's employer has a current study underway with Ignyta, Inc., of entrectinib, one of the products coming before the committee. Dr. Dubois serves as a Sub-Investigator on this trial.

Study titled "A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX 101) in Children and Adolescents With Recurrent or Refractory Solid Tumors and Primary CNS Tumors"

The total funding from industry to Dana Farber is between $0 - $50,000 per year. This site was activated in May 2016; anticipated duration is 2-3 years. Dr. DuBois will not receive any salary support or personal remuneration for his involvement.

Dr. Dubois also has two interests related to Loxo Oncology's LOXO 101. (b) (6) which will be addressed in the fourth session and has a mechanism of action that partly overlaps with that of entrectinib. Dr. Dubois will not speak on behalf of Loxo Oncology at this meeting and will not participate in the fourth session. This waiver does not authorize participation in the session related to LOXO 101.

Dr. Dubois's (b) (6)

Study titled "A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients With Advanced Solid or Primary Central Nervous System Tumors."

Dr. Dubois's employer also has a current study related to Loxo Oncology's Loxo 101. Dr. Dubois serves as a Principal Investigator on this trial. The total funding from industry to Dana Farber is between $0 - $50,000 per year. This site was activated in May 2016; anticipated duration is 2-3 years. Dr. DuBois's employer intends to dedicate a small percentage of these funds to Dr. DuBois's salary; however, his salary remains the same regardless of funds received by Dana Farber for this study.

Basis for Granting the Waiver

As discussed below, the waiver is supportable because the financial interests at issue are relatively small and the focus of the studies in which Dr. DuBois is participating is not closely related to the advisory committee discussion, which will focus on the potential for demonstrating efficacy of products in pediatric cancer patients.

Because 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, it has proved very difficult to identify candidates who have that expertise. Dr. DuBois has significant experience in this subject matter.

The financial interests are relatively small and the focus of the studies is not closely related to the advisory committee discussion: a scientific discussion that will not culminate in a vote.

It is expected that the total industry funding to Dana Farber under the financial interests at issue will be between $250,003 and $750,000 per year. This represents a relatively small amount of money for a research institution such as Dr. DuBois's employer. According to the consolidated financial statement for Dana Farber Cancer Institute Inc. and subsidiaries, Dana-Farber had assets of approximately $2 billion dollars as of September 30, 2014.[1]

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."[2] 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

[1] *See* Dana-Farber Cancer Institute Inc. and Subsidiaries Consolidated Financial Statements and Supplementary Information Years ended 9/30/2014 and 2013. Available at https://www.dana-farber.org/uploadedFiles/Library/modules/IRS_990_Form/audited-consolidated-financial-statements.pdf (Accessed: June 13, 2016)

[2] *See* Page 9 of the OGE Memo on Waiver Under 18 U.S.C. §208. Available at https://www.oge.gov/Web/OGE nsf/All+Advisories/328CE4B5A300EAEB85257E96005FBDE5/$FILE/do-07-006.pdf?open. (Accessed: June 9, 2016)

that these chemical entities might address. The PedsODAC meeting will focus on preliminary discussions and general considerations in pediatrics, including discussions around molecular abnormalities, potential indications that might be feasible for the drug substances, and 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.

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. Steven DuBois is Director of Experimental Therapeutics for the Dana-Farber Children's Cancer and Blood Disorders Center, and on the faculty of pediatrics at the Harvard Medical School. Dr. DuBois earned his medical degree at the University of California, San Francisco, where he also completed his residency in pediatrics prior to completing a fellowship in pediatric hematology/oncology at Dana-Farber/Boston Children's. Dr. Dubois is a recognized expert in early phase clinical trials in children. He has particular expertise in the evaluation of new agents in neuroblastoma, a relatively common tumor in childhood for which there is serious need for less toxic and more effective drug therapies. Although there is overlap with Dr. DuBois' subspecialties, we need the broadest experience from the group of investigators with the most extensive experience with and expertise in early phase studies of new agents in children. He will be the only expert with specific interest in neuroblastoma. In the interest of public health, it is critical that FDA have available the unique expertise that Dr. DuBois will provide for the discussion of the particular matter before the committee.

Relevant expertise is concentrated in the institutions comprising the Children's Oncology Group, but other candidates with the necessary expertise have not been found

Given the relative rarity of childhood cancer, collaboration and concentration of expertise are essential. 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. Almost 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 U.S. 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 U.S. 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 Dana-Farber) 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 already noted, finding experts for this meeting has been challenging. Approximately 95% of the experts with the expertise and experience needed are affiliated with COG institutions. These experts are likely to be at least or more conflicted than the SGEs for which we seek waivers. 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 are unable to attend due to scheduling conflicts.

Accordingly, I recommend that you grant a waiver for Dr. Steven DuBois, 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):

_____ Denied – The individual may not participate.

/S/ 6/24/16

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