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

DATE: May 31, 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: **Leo Mascarenhas, 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. Leo Mascarenhas is serving as a temporary voting member of the PedsODAC. He has been invited to participate in the June 22, 2017 PedsODAC meeting. The products under consideration for this waiver 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. Mascarenhas is the Deputy Director, Children's Center for Cancer and Blood Diseases, and Section Head, Oncology, Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles (CHLA). He has not identified any personal financial interests that are likely to be affected by the particular matters to be discussed by the subcommittee. However, he has identified financial interests of his employer, which are imputed to him under the federal conflict of interest statute, 18 U.S.C. § 208.

Session 1: Olaratumab

CHLA is participating in a clinical study funded by Eli Lilly. The study is titled 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 CHLA is one of twenty-three sites participating in the study and a total of seventy patients are anticipated to enroll nationally; CHLA is anticipated to enroll a total of eight patients. The clinical study began on August 3, 2016 and is estimated to end on August 2, 2021.

The total funding from Eli Lilly is anticipated between $100,001 – $300,000. Dr. Mascarenhas does not receive any personal remuneration or salary support for his role as the Site Investigator.

Session 2: Prexasertib:

CHLA is participating in a clinical study titled 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 began on April 11, 2017; CHLA is anticipated to enroll between 1 to 2 subjects. CHLA is one of sixteen sites participating in the study and a total of sixty-five patients are anticipated nationally. This study was opened through the Children's Oncology Group (COG) Phase I Consortium at Children's Hospital of Philadelphia (CHOP). COG is a National Cancer Institute supported clinical trials group. The study drugs are provided by Eli Lilly and the financial support to CHLA comes from a subcontract with CHOP.

The total funding from CHOP is anticipated between $0 - $50,000. Dr. Mascarenhas does not receive any salary support or personal remuneration for his role as the Director of Clinical Trials Office, and COG Phase 1 Consortium Sub- Investigator.

Basis for Granting the Waiver:

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. Mascarenhas 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 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. Mascarenhas is currently the Deputy Director of the Children's Center for Cancer and Blood Diseases and the Section Head of Oncology within the Division of Hematology, Oncology and Blood and Marrow Transplantation at Children's Hospital Los Angeles (CHLA). He is also the Director of the Solid Tumor Program and the Director of the Clinical Trials Program within the Center, and the Sub- Investigator of the National Cancer Institute (NCI) funded Children's Oncology Group (COG) at CHLA. Dr. Mascarenhas received his medical degree from St. John's Medical College, Bangalore, India, and served his residency at New York Medical College, Department of Pediatrics, Valhalla, NY. He also completed fellowships in Hematology/Oncology and Research Immunology/Bone Marrow Transplantation at Children's Hospital Los Angeles, CA. He is an internationally recognized expert in pediatric bone and soft tissue tumors. His research areas of interest include Bone Sarcomas, Soft Tissue Sarcomas, and Rare Pediatric Cancers, and Vascular Anomalies including Lymphangiomatosis, Gorham's Disease, and Hemangioendothelioma.

In addition, Dr. Mascarenhas is a recognized expert in pediatric and adolescent sarcomas of both bone and soft tissue. These types of tumors are relevant to the development of the products coming before the committee and will be a significant part of the discussion. Dr. Mascarenhas is also known internationally as a key opinion leader in the diagnosis and management of sarcomas. His longstanding efforts in early phase studies in children will enrich the discussions and assure ethical and efficient study designs. This will be especially important in delineating appropriate response criteria and study endpoints for metastatic bone tumors. In the interest of public health, it is critical that FDA have available the unique expertise that Dr. Mascarenhas will provide 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 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.

The June 22, 2017, PedsODAC meeting sessions 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 these drugs in children.

Dr. Mascarenhas has served effectively on past PedsODAC meetings.

Dr. Mascarenhas has been a consistent contributing participant at past PedsODAC meetings. The clinical research leadership roles he holds at one of the largest pediatric cancer programs in the country will be critical to the discussion of potential clinical trials of these products in the pediatric age group.

Accordingly, I recommend that you grant a waiver for Dr. Leo Mascarenhas, 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):

_____

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_____ Denied – The individual may not participate.

_____/S/_____ 06/05/2017

Janice M. Soreth, M.D. Date

Associate Commissioner for Special Medical Programs

Office of Medical Products and Tobacco

Office of the Commissioner, FDA