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

DATE: May 19, 2020

TO: Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

FROM: Byron Marshall
Director, Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

Name of Advisory Committee Meeting Member's Name: **Leo Mascarenhas, M.D.**

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

Meeting date: June 17-18, 2020

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 Oncologic Diseases 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 17-18, 2020, during the PedsODAC meeting, information will be presented regarding pediatric development plans for two products that are in development for an adult oncology indication. The subcommittee will consider and discuss issues relating to the development of each product for pediatric use and provide guidance to facilitate the formulation of Written Requests for pediatric studies, 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. Mascarenhas is serving as a temporary voting member of the PedsODAC and has been invited to participate in the June 17-18, 2020, PedsODAC meeting. The products under consideration, relevant to this waiver are: on June 17th, SP 2577 application presentation by Salarius Pharmaceuticals, Inc. and marizomib, application presentation by Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb; on June 18th, CD30.CAR-T, application presentation by Tessa Therapeutics. SP 2577 has one study in pediatrics in refractory or recurrent Ewing sarcoma. Marizomib has no ongoing pediatric clinical trials, but one is planned in diffuse intrinsic pontine glioma (DIPG). CD30.CART has no ongoing pediatric clinical trials, but one is planned in relapsed/refractory classical Hodgkin lymphoma. These topics are particular matters involving specific parties.

Type, Nature, and Magnitude of the Financial Interest:

Dr. Mascarenhas is the Deputy Director of the Children's Center for Cancer and Blood Diseases and Section Head of Oncology, Children's Center for Cancer and Blood Diseases at Children's Hospital Los Angeles (CHLA). He is also the Director of the Solid Tumor Program and the Bone and Soft Tissue Tumor program, and the Principal Investigator of the National Cancer Institute (NCI) funded Children's Oncology Group (COG) at CHLA. 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, that may be affected by the particular matter that is the subject of the subcommittee meeting.

CHLA is participating in a clinical study titled: Phase I Trial of the LSD1 Inhibitor SP-2577 in Patients with Relapsed or Refractory Ewing Sarcoma [NCT03600649], sponsored by Salarius Pharmaceuticals. This study began in June 2018, is still recruiting patients, and is expected to run through December 2021. The population being studied includes patients aged 12 years and older. CHLA is one of eight sites participating in the study nationally. Financial support comes from the National Pediatric Cancer Foundation (NPCF), a 501(c)(3) organization, as part of the NPCF's "Sunshine Project Clinical Trials Initiative." The study drug is provided by Salarius and there is no established dollar value for the drug.

The total funding for this study, to CHLA, is anticipated to be between $(b) (4) per year. Dr. Mascarenhas does not receive any salary support or personal remuneration for his role as Site Investigator.

In addition, CHLA is participating in a clinical study titled: A Phase I, Open-Label, Single Institution Study to Assess the Safety, Tolerability, and Pharmacokinetics of Durvalumab in Pediatric Patients With Relapsed or Refractory Solid Tumors, Lymphoma, and Central Nervous System Tumors [NCT02793466]. The study began in 2016, is still recruiting patients and is targeted to end in December 2020. Due to the broad inclusion of multiple tumor types, patients with central nervous system tumors, including DIPG, Ewing sarcoma, and lymphoma are eligible if they meet the study criteria. This study is funded by AstraZeneca. The drug being studied potentially competes with the drugs under review by the committee.

The total funding for this study, to CHLA, is anticipated to be between $(b) (4) to $(b) (4) per year. Dr. Mascarenhas does not receive any salary support or personal remuneration for his role as Principal Investigator.

Basis for Granting the Waiver:

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

Unlike advisory committee meetings focused on a product and indication, this meeting will be a scientific collaboration on the currently available data to gain information that could inform the formulation of a Written Request, if appropriate. 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.

Dr. Mascarenhas earned his medical degree from St. John's Medical College in Bangalore in India.

He completed his residency in pediatrics at New York Medical College and finished his hematology-oncology fellowship at Children's Hospital Los Angeles where he also completed a research fellowship in Immunology/Bone Marrow Transplantation. He is board certified in Pediatrics and Pediatric Hematology/Oncology. His research interests include acute lymphoblastic leukemia, bone and soft tissue tumors, hepatoblastoma, Ewing sarcoma, and osteosarcoma.

Dr. Mascarenhas is an internationally 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 being reviewed by the committee and will be a significant part of the discussion. He 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. Dr. Mascarenhas plays key roles nationally and internationally in the clinical trial networks engaged in the evaluation of new drugs for bone sarcomas. His expertise in experimental therapeutics is essential to the success of this meeting.

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. Dr. Mascarenhas has been a long-standing participant of the PedsODAC and his contributions have been very impactful in Agency decision-making.

The particular matter is not sensitive.

The meeting topics for these sessions are not considered sensitive and the FDA Division with responsibility for these products does not expect that the meeting is likely to receive significant public interest, (non-trade) press 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' expertise in this particular matter is necessary in the interest of public health.

On June 17-18, 2020, the subcommittee will meet to discuss SP-2577, marizomib, and CD30.CART. These products are all in early stages of development in pediatric patients. The pediatric cancers that will be discussed for these products will include, but are not limited to, DIPG, refractory or recurrent Ewing sarcoma, and relapsed/refractory classical Hodgkin lymphoma. The treatment of DIPG is a critical unmet clinical need in pediatric and adolescent cancer. DIPG tumors account for 10 percent of all childhood central nervous system tumors. Approximately 300 children in the United States are diagnosed with DIPG each year. No effective drugs have been developed for this disease. The current treatment is limited to radiotherapy and even with radiotherapy, median survival for children with DIPG is only 9 to 11 months. Even drugs in early development have failed to yield robust efficacy signals. Ewing sarcoma is a rare bone

tumor that occurs most often in adolescents; it is a very rare cancer in adults. The National Institutes of Health reports that Ewing sarcoma accounts for about 1.5 percent of all childhood cancers, and it is the second most common type of bone tumor in children. The potential use of marizomib in Ewing sarcoma is in the context of recurrent/relapsed disease, for which no curative therapies currently exist, therefore, the need for new therapies represents a particularly dire, unmet clinical need. Relapsed/refractory classical Hodgkin lymphoma is a malignant lymphoma that accounts for approximately 7 percent of childhood cancers and 1 percent of childhood cancer deaths in the United States. The American Cancer Society reports that classical Hodgkin lymphoma (cHL) accounts for more than 9 in 10 cases of Hodgkin lymphoma in developed countries and comprises 6% of childhood cancers. Approximately 90% to 95% of children with Hodgkin lymphoma can be cured, prompting increased attention to devising therapy that lessens long-term morbidity for these patients. Therefore, in the interest of public health, it is critical that FDA have available the unique expertise that Dr. Mascarenhas will provide the committee with regards to these products.

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Mascarenhas' expertise in this matter.

The PedsODAC meeting is meant to elicit discussion of the data currently available. Significantly, the advisory committee members will not recommend approval or disapproval of this product. Such recommendations would be grossly premature and simply could not be made at this early stage in product development.

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. Mascarenhas has particular expertise in treating patients with pediatric bone sarcomas (including Ewing sarcoma).

Multiple pediatric oncologists, each with specific sub-specialty expertise and with internationally recognized expertise in pediatric cancer drug development are needed for this meeting given the multiplicity of clinical indications to be considered. The complexity of clinical study design and conduct in rare pediatric cancer populations requires multiple clinical and scientific perspectives.

Dr. Mascarenhas plays key roles nationally and internationally in the clinical trial networks engaged in the evaluation of new drugs for bone sarcomas and is a key opinion leader in the diagnosis and management of sarcomas. His expertise in experimental therapeutics and longstanding efforts in early phase studies in children is essential to the success of this meeting. Further, he has been a consistent contributing participant at past PedsODAC

meetings. Given his extensive background in the specific areas needed for this meeting, and experiences with past PedsODAC meetings, any potential for a conflict of interest is significantly outweighed by the need for Dr. Mascarenhas' expertise on this panel.

Accordingly, I recommend that you grant Dr. Leo Mascarenhas, a temporary voting member of the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee, a waiver from the conflict of interest prohibitions of 18 U.S.C. § 208(a) to participate in the June 17-18, 2020, PedsODAC meeting.

Certification:

✓ 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.

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Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

June 1, 2020
Date