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

DATE: May 22, 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 Temporary Voting Member: **Theodore Laetsch, M.D.**

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

Meeting date: June 17-18, 2020

Description of the Particular Matters 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.

On June 17-18, 2020, during the PedsODAC meeting, information will be presented regarding pediatric development plans for four 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. Laetsch is serving as a temporary voting member of the PedsODAC. He has been invited to participate in the June 17-18, 2020, PedsODAC meeting. The products under consideration for 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; and on June 18th, SNDX-5613, application presentation by Syndax Pharmaceuticals, Inc., and CD30.CART, application presentation by Tessa Therapeutics. The topics are particular matters involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Laetsch is Co-Director, Tumor Microenvironment and Immune Therapy Theme in the Experimental Therapeutics Program (ETP), University of Texas Southwestern (UTSW). 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 can be affected by the particular matters that are the subject of the subcommittee meeting. The studies described below involve drug products and medical indications that are related to those that will be addressed during the upcoming PedsODAC meeting and the funding to Dr. Laetsch's employer can be affected by the particular matters under review by the committee.

A Phase 1 Study to Evaluate Safety and Pharmacokinetics of Palbociclib (Ibrance) in Combination with Irinotecan and Temozolomide In Pediatric Patients with Recurrent or Refractory Solid Tumors [NCT03709680] is opened through the Children's Oncology Group (COG), under a contract between COG and Pfizer, and will enroll children with any relapsed solid tumor, including CNS tumors. The study began in May 2019, will end in April 2024, and the total funding from the COG to UTSW for this study is anticipated to be between $ (b) (4) per year. Dr. Laetsch serves as study chair and receives salary support anticipated to be between $10,000 - $25,000 per year; however, his salary remains the same regardless of funds received by UTSW for this study.

A Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination with Trametinib in Children and Adolescent Patients with BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG) [NCT02684058] began in January 2018 and will end in January 2023. The amount of funding from Novartis to UTSW is anticipated to be between (b) (4) per year. Dr. Laetsch is the Site Principal Investigator (PI); he does not receive salary support or personal remuneration.

A Phase 1, Open-Label, Multicenter, Dose Escalation Study of TB-403 in Pediatric Subjects with Relapsed or Refractory Medulloblastoma, Neuroblastoma, Ewing Sarcoma or Alveolar Rhabdomyosarcoma [NCT02748135] began in August 2016 and will end in August 2021. The amount of funding from Neuroblastoma and Medulloblastoma Translational Research Consortium to UTSW is anticipated to be between (b) (4) per year. Dr. Laetsch is the Site Principal Investigator (PI); he does not receive salary support or personal remuneration.

A Phase 2, Multicenter, Open-label Study to Assess Safety and Preliminary Activity of Eribulin Mesylate in Pediatric Subjects with Relapsed/Refractory Rhabdomyosarcoma (RMS), Non-rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS) and Ewing Sarcoma (EWS) [NCT03441360] began in January 2018 and will end in January 2023. The amount of funding from Eisai Co., Ltd. to UTSW is anticipated to be between (b) (4) per year. Dr. Laetsch is the Site Principal Investigator (PI); he does not receive salary support or personal remuneration.

Phase 1b Study of Carfilzomib in Combination with Induction Chemotherapy in Children with Relapsed or Refractory Acute Lymphoblastic Leukemia [NCT02303821] began in April 2015 and will end in April 2021. Funding from Onyx Pharmaceuticals to UTSW is anticipated to be (b) (4) per year. Dr. Laetsch is a PI; he does not receive salary support or personal remuneration.

A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Pediatric Patients with Relapsed and Refractory B-cell Acute Lymphoblastic Leukemia [NCT02435849] began in March 2015 and will end in August 2020. Funding from Novartis to UTSW is (b) (4) Dr. Laetsch is a PI and receives salary support of $0-$10,000 per year.

A Pilot Study of Vincristine Sulfate Liposome Injection (Marqibo®) in Combination with UK ALL R3 Induction Chemotherapy for Children, Adolescents, and Young Adults with Relapse of Acute Lymphoblastic Leukemia [NCT02879643] Sponsored by Therapeutic Advances in Childhood Leukemia Consortium in collaboration with Spectrum Pharmaceuticals began in October 2016 and will end in October 2021. Funding from Children's Hospital of Los Angeles to UTSW is anticipated to be (b) (4) for the patients enrolled in the study. Dr. Laetsch is a PI and does not receive salary support or personal remuneration.

A Study of Venetoclax in Combination with Navitoclax and Chemotherapy in Subjects with Relapsed/Refractory Acute Lymphoblastic Leukemia or Relapsed/Refractory Lymphoblastic Lymphoma [NCT03181126] began in March 2018 and will end in March 2023. Funding from Abbvie to UTSW is anticipated to be $ (b) (4) per year. Dr. Laetsch is a PI and does not receive salary support or personal remuneration.

A Phase 1, Open Label, Non-comparative Study to Evaluate the Safety and the Ability of UCART19 to Induce Molecular Remission in Pediatric Patients with Relapsed/Refractory B-cell Acute Lymphoblastic Leukemia [NCT02808442] began in February 2019 and will end in February 2024. Funding from (b) (4) to UTSW is anticipated to be (b) (4) per year. Dr. Laetsch is a PI and does not receive salary support or personal remuneration.

An Open-label, Multicenter, Phase 2 Study Evaluating the Efficacy and Safety of Daratumumab in Pediatric and Young Adult Subjects >=1 and <=30 Years of Age with Relapsed/Refractory Precursor B-cell or T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma." [NCT03384654] began in April 2019 and will end in March 2022. Funding from Janssen Research and Development to UTSW is anticipated to be (b) (4) per year. Dr. Laetsch is a PI and does not receive salary support or personal remuneration.

A Phase II Trial of Tisagenlecleucel in First-line High-risk (HR) Pediatric and Young Adult Patients with B-cell Acute Lymphoblastic Leukemia (B-ALL) Who Are Minimal Residual Disease (MRD) Positive at the End of Consolidation (EOC) Therapy [NCT03876769] began in January 2019 and will end in January 2040. Funding from Novartis to UTSW is anticipated to be (b) (4) per year. Dr. Laetsch is a PI and does not receive salary support or personal remuneration.

A TACL Phase 1/2 Study of PO Ixazomib in Combination with Chemotherapy for Childhood Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma IND# 140730 (NCT03817320). Sponsored by Therapeutic Advances in Childhood Leukemia Consortium in collaboration with Takeda and CHLA began in May 2019 and will end in December 2040. Funding from Children's Hospital of Los Angeles to UTSW is anticipated to be (b) (4) per year. Dr. Laetsch is a PI and does not receive salary support or personal remuneration.

A Phase I/II Study of Nivolumab in Combination With 5-azacytidine in Pediatric Patients with Relapsed/Refractory Acute Myeloid Leukemia (BMS Reference CA209-9JY) [NCT03825367]. Sponsored by Therapeutic Advances in Childhood Leukemia Consortium in collaboration with Bristol-Myers Squibb began in August 2019 and will end in December 2040. Funding from Children's Hospital of Los Angeles to UTSW is anticipated to be (b) (4) per year. Dr. Laetsch is a PI and does not receive salary support or personal remuneration.

(b) (4) The study is under negotiation and has not begun; (b) (4) Dr. Laetsch is a PI and will not receive salary support or personal remuneration.

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Basis for Granting the Waiver:

Dr. Laetsch has unique qualifications and specialized expertise needed for the particular matters.

This meeting will be a scientific collaboration on the currently available data to gain information that could inform the formulation of a Written Request and whether there are any other pediatric cancers in which there is an unmet clinical need that these products might fulfill. In addition to his role as Co-Director of the Tumor Microenvironment and Immune Therapy Theme in the ETP at UTSW, he is also Director of the ETP in the Pauline Allen Gill Center for Cancer and Blood Disorders at Children's Medical Center of Dallas. Dr. Laetsch received his undergraduate degree in Agricultural and Biosystems Engineering from the University of Arizona and his medical degree in 2005 from the University of California, San Francisco. Dr. Laetsch completed his residency at the University of Colorado/Children's Hospital Colorado, where he also served as chief resident. He completed his fellowship training and an instructorship at the Children's Hospital of Philadelphia (CHOP), where he conducted translational laboratory research focused on mechanisms to restore apoptotic signaling in neuroblastoma. In 2013, he joined the faculty at UTSW.

Dr. Laetsch conducts both clinical and laboratory-based research testing of potential novel therapeutics in high-risk pediatric solid tumors with a goal of "bridging the gap" between laboratory research and early phase clinical trials. In the laboratory, he has focused on signaling pathway inhibitors and novel drug delivery mechanisms in sarcomas, and the use of beta-lapachone in atypical teratoid rhabdoid tumors. Brain tumors represent a major unmet clinical need in children.

The particular matters are not sensitive.

The meeting topics are not considered sensitive and the FDA Division with responsibility for the products under review 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. Laetsch's expertise in the particular matters is necessary in the interest of public health.

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, the subcommittee will meet to discuss SP 2577, marizomib, SNDX-5613, and CD30.CART. These products are in the early stages of development. The pediatric cancers that will be discussed for these products will include, but are not limited to, refractory or recurrent Ewing sarcoma, DIPG, and Mixed Lineage Leukemia (MLL) gene rearranged acute leukemia.

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[1]. The median age of patients with Ewing sarcoma is 15 years, and more than 50% of patients are adolescents. Approximately 200-250 children and adolescents in the United States are diagnosed with a tumor in the Ewing family of tumors each year.[2] Treatment options for Ewing sarcoma include chemotherapy, surgery, radiation therapy and high-dose chemotherapy and stem cell transplant. Patients experience side effects of treatment for Ewing sarcoma including severe delayed late effects from radiation therapy, such as bone growth retardation and secondary cancers. The 5-year survival rate is 76% for children younger than 15 and 60% for adolescents aged 15 to 19.[3] About 30% of patients have a recurrence within the first five years. The same chemotherapy drugs that were used during initial treatment cannot be used again due to toxicity concerns.[4] As a result, physicians must seek alternatives to treatment. The actual context in which the use of SP 2577 in Ewing sarcoma is being discussed is in the setting of relapse or recurrent/refractory disease for which there is no curative therapy, highlighting the importance of new drug discovery and development.

The treatment of DIPG is a critical unmet clinical need in pediatric and adolescent cancer. Diffuse intrinsic pontine gliomas 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.

Aggressive leukemias arise in both children and adults as a result of rearrangements to MLL genes and are associated with both acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL). The MLL gene is frequently rearranged through chromosomal translocations, most notably in >70% of cases of infant leukemia with 5.2% of all the AML cases and in 22% of all the ALL cases. Whereas treatment of non-mixed lineage leukemia in children has become the textbook success story of modern medicine, with 5-year survival rates approaching 90%, mixed lineage leukemia treatment seems to have hit a roadblock with hardly 40% of all infants surviving five years after diagnosis. Patients with MLL rearrangements not only have poorer prognosis, but they also have shorter event free and overall survival rates. They do not respond at all well to the standard therapies for ALL (acute lymphoblastic or lymphocytic leukemia) and

[1] https://ghr nlm nih.gov/condition/ewing-sarcoma#statistics
[2] https://rarediseases.org/rare-diseases/ewing-sarcoma/
[3] https://www.cancer.net/cancer-types/ewing-sarcoma-childhood-and-adolescence/statistics
[4] https://www hopkinsmedicine.org/health/conditions-and-diseases/sarcoma/ewing-sarcoma-in-adults

often suffer from early relapse after chemotherapy. Therefore, new treatment modalities are urgently needed. Recent advances have begun to reveal the molecular mechanisms driving MLL associated leukemias, which provide opportunities for therapeutic development. Dr. Laetsch's expertise in early phase evaluation of new drugs in children with solid tumors is essential to this meeting.

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

The PedsODAC meeting is meant to elicit discussion of the data currently available. The advisory committee members will not recommend approval or disapproval of the products under discussion.

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. 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.

As the leader of the Experimental Therapeutics Program, Dr. Laetsch serves as the Principal Investigator (PI) of several phase 1 and phase 2 studies of new agents for children with relapsed or refractory cancer and serves as the institutional Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) PI. Dr. Laetsch has a strong interest in the use of tumor molecular profiling to guide therapy. In addition to these research activities, Dr. Laetsch continues to see children with cancer in the clinic at Children's Medical Center. Therefore, his participation in the PedsODAC meeting is critical as he has significant experience in this subject matter.

Accordingly, I recommend that you grant Dr. Theodore Laetsch, 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).

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