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

DATE: March 11, 2022

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 Temporary Voting Member: **Jessie Lai-Sim Au, PharmD, Ph.D.**

Committee: Oncologic Drugs Advisory Committee

Meeting date: April 22, 2022

Description of the Particular Matter to Which the Waiver Applies:

Dr. Jessie Lai-Sim Au, PharmD, Ph.D., is a temporary voting member of the Oncologic Drugs Advisory Committee (ODAC). The committee's function is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for the use in the treatment of cancer and make appropriate recommendations to the Commissioner of Food and Drugs.

On April 22, 2022, the committee will discuss supplemental new drug application (sNDA) 213176/S-002, for Ukoniq (umbralisib) tablets, and biologics license application (BLA) 761207, for ublituximab injection, both submitted by TG Therapeutics, Inc. The proposed indication (use) for these two products is in combination for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). In addition, the committee will also discuss the existing umbralisib indications in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma under 21 CFR 314.500 (subpart H, accelerated approval regulations).

Type, Nature, and Magnitude of the Financial Interests:

Dr. Au reported that she and her spouse have a financial interest in four healthcare sector funds: (b)(6) In

addition, Dr. Au is the Founding Director and Chair of IQSP (Institute of Quantitative Systems Pharmacology). Her institution has a financial interest in (b) (6). The aggregate market value of her and her spouse's personal financial interests in these sector funds is between (b) (6), and the aggregate market value of the IQSP's financial interests is between (b) (4), (b) (6).

At the writing of this waiver, based on publicly available fund information, (b) (6) contains assets in competing entities, including (b) (6) For (b) (6), no competing or affected entity has been identified in this sector mutual fund. Due to the changing nature of sector fund's holdings where underlying assets could include competing or affected entities before the advisory meeting[1], in the utmost of caution (b) (6) is included to ensure there is no recusal requirement on the day of the advisory committee meeting.

Under a regulatory exemption (5 CFR § 2640.201(b)) issued by the Office of Government Ethics, an employee may participate in any particular matter affecting one or more holdings in a sector mutual fund where the disqualifying financial interest in the matter arises because of ownership of an interest in the fund and the aggregate market value of interest in all funds in which there is a disqualifying financial interest, and which concentrates in the same sector does not exceed $50,000. Because Dr. Au's financial interests exceeds that amount, she has a disqualifying financial interest based on (b) (6) underlying investment holdings.

Basis for Granting the Waiver:

Dr. Jessie Lai-Sim Au has unique qualifications and specialized expertise needed for this particular matter.

Dr. Jessie Lai-Sim Au is Research Professor and Mosier Endowed Chair for the Department of Pharmaceutical Sciences at the University of Oklahoma. She also is Co-Founder and Chief Scientific Officer for Optimum Therapeutics LLC and Founding Director and Chair of the Institute of Quantitative Systems Pharmacology (IQSP). Optimum Therapeutics focuses on linking academic discoveries with commercial applications with the goal of providing the maximum benefit to cancer research and patients. They research experimental approaches to improve nanomedicine delivery and transport in solid tumors. IQSP, a nonprofit organization, works to stimulate and facilitate inter-institutional collaborations. They use Quantitative Systems Pharmacology, which is an emerging discipline with the primary focus on using

[1] (b) (6) prospectus has a stated investment strategy of (b) (6)

computation and modeling to interpret, interrogate, and integrate drug effects on multiple scales (molecule, cellular, organ, whole organism, time, space). The goal is to forecast treatment outcomes and improve the success rate of clinical drug development (which is currently believed to be at less than 7%).

Dr. Au received her Pharm.D. and subsequently her Ph.D. in Pharmaceutics from the University of California, San Francisco and completed a post-doctoral fellowship in Biochemical Pharmacology at the Roswell Park Memorial Institute in Buffalo, New York. She is the author of over 170 peer-reviewed, 10 book chapters, over 260 abstracts and holds 28 patents and copyrights. Her work is typically at the interface between diverse disciplines, with the goal of translating laboratory findings to survival-extending cancer treatments.

The committee will discuss umbralisib (Ukoniq) and ublituximab in combination for the treatment of adult patients with CLL or SLL. In addition, the committee will discuss the existing umbralisib indications for relapsed or refractory follicular lymphoma and marginal zone lymphoma. According to the review division responsible for review of the application at issue for this meeting, clinical pharmacologists are needed for this meeting because exposure-response analyses for safety and efficacy in relation to pharmacokinetic measures such as Cmax, Cavg, AUC etc. are used to better understand the benefit:risk profile of the drug. Dr. Au possesses the expertise to conduct, review and understand these analyses and will provide valuable insight/understanding to this aspect of the data.

Multiple clinical pharmacologists were invited but declined invitations due to schedule conflicts. Dr. Au is a nationally recognized clinical pharmacologist and translational researcher. Her knowledge in quality systems pharmacology using modeling to interpret, interrogate and integrate drug effects and to forecast outcomes of treatments make Dr. Au uniquely qualified to provide insight and feedback on the matters coming before the committee.

The particular matter is sensitive.

The FDA Division responsible for review of umbralisib and ublituximab does expect the matter coming before the committee to garner public interest as it relates to the regulatory pathway of accelerated approval which was promulgated in 1992. This pathway has been used extensively in oncology approvals to bring new therapies to patients in an expedited fashion. The Division seeks ODAC input on the risk-benefit of the combination in the proposed indication and how the current information impacts the existing indications under accelerated approval.

Dr. Jessie Lai-Sim Au's expertise in this particular matter is necessary in the interest of public health.

Non-Hodgkin lymphoma (NHL) is one of the most common cancers in the United States, accounting for about 4% of all cancers. The American Cancer Society's estimates for Non-Hodgkin Lymphoma in 2022 are about 80,470 people (both adults and children) will be diagnosed with NHL and about 20,250 people will die from this cancer. There are an estimated 672,980 people living with or in remission from non-Hodgkin lymphoma. Indolent lymphomas are slow-moving and tend to grow more slowly and have fewer signs and symptoms when first

diagnosed. Slow-growing or indolent subtypes represent about 40 percent of all NHL cases. Indolent NHL subtypes include but are not limited to Follicular lymphoma (FL), which is the most common subtype of indolent NHL, followed by Marginal Zone Lymphoma (MZL) and Chronic Lymphocytic Leukemia or Small-Cell Lymphocytic Lymphoma (CLL/SLL).

Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) is an indolent malignancy characterized by increased production of mature but dysfunctional B lymphocytes. CLL comprises 25 to 30% of total leukemias in the United States. According to the American Cancer Society, in 2021 there were an estimated 21,250 new CLL cases and about 4,320 deaths from CLL. Patients with CLL or SLL are not cured with conventional therapy, and most will relapse eventually.

There are many current first-line treatment options for CLL or SLL. Active treatment is started if the patient begins to develop disease-related symptoms or there are signs that the disease is progressing based on testing during follow-up visits. The choice of treatment depends on the stage of the disease, the patient's symptoms, the age and overall health of the patient, and the benefits versus side effects of treatment. The treatment landscape has also expanded with the development of targeted agents, in addition to the traditional chemotherapy agents. For relapsed or refractory disease, treatment may incorporate one or more of the following targeted agents, often administered as combinations: Bruton tyrosine kinase inhibitors, phosphoinositide 3'-kinase (PI3K) inhibitors, BCL2 inhibitors and anti-CD-20 monoclonal antibodies.

For lymphoma, about 1 out of 5 lymphomas in the United States is a follicular lymphoma. FL is the second common form of NHL in the U.S with an estimated incidence of six new cases/ 100 000 persons/year. The vast majority of patients treated for FL will have an initial response to therapy with 40 to 80 percent demonstrating a complete response, depending on the initial regimen used. However, conventional therapy for FL is not curative and most of these patients will ultimately develop progressive disease. In addition, less than 10 percent of patients treated with initial chemoimmunotherapy will not respond to treatment (i.e., refractory disease). Marginal zone lymphomas account for about 5% to 10% of lymphomas. MZL is the second most common indolent non-Hodgkin's lymphoma which accounts for approximately eight percent of all NHL cases. Although conventional first-line treatment options are proved beneficial, many the patients become resistant to or experience a relapse following treatment. In the interest of public health, it is important that the Agency has available the unique expertise that Dr. Au will provide for the discussion of the particular matter coming before the committee.

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Jessie Lai-Sim Au's expertise in this matter.

Dr. Au's expertise will be helpful in understanding the issues around safety and efficacy of the products at issue, as well as the dose selection and exposure-response studies and analyses that were conducted to assess the overall safety and efficacy of the products. Multiple clinical pharmacologists are needed for this meeting because some of the other experts who were requested have extensive hands-on experience with respect to conduct/participation in clinical studies and would provide valuable insight into trial design issues from a clinical pharmacology perspective. Although the other clinical pharmacology experts understand exposure-response

relationships for drugs, Dr. Au has practical experience in conducting these analyses and intimately understands the details involved in the technical aspects of exposure-response modeling, simulation and analysis.

Accordingly, I recommend that you grant Dr. Jessie Lai-Sim Au, a temporary voting member of the Oncologic 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):

_____

_____

_____ Denied – The individual may not participate.

Russell Fortney -S Digitally signed by Russell Fortney -S Date: 2022.04.01 19:31:16 -04'00'

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

April 1, 2022
Date