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

DATE: February 7, 2018

TO: Rachel Sherman, M.D., M.P.H.
Principal Deputy Commissioner
Office of the Commissioner, Food and Drug Administration

THROUGH: Russell Fortney
Director (Acting), 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 Meeting Member: **Jean-Pierre Raufman, M.D.**

Committee: Gastrointestinal Drugs Advisory Committee

Meeting date: March 8, 2018

Description of the Particular Matter to Which the Waiver Applies:

Dr. Raufman is the Chair and standing, voting member of the Gastrointestinal Drugs Advisory Committee (GIDAC). The Committee's function is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of gastrointestinal diseases, and make appropriate recommendations to the Commissioner of Food and Drugs.

The committee will meet on March 8, 2018, to discuss supplemental new drug application (sNDA) 203214, supplement 18, Xeljanz (tofacitinib) 5 mg and 10 mg tablets, submitted by Pfizer Inc., proposed for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine or tumor necrosis factor (TNF) inhibitor therapy. The topic of this meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Raufman is the Division Director of Gastroenterology and Hepatology at the University of Maryland School of Medicine. 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 are likely to be affected by the particular matter under review by the advisory committee.

Dr. Raufman's employer, University of Maryland School of Medicine (UMD), was awarded three research contracts funded by AbbVie, one funded by Celgene, and one funded by Takeda that is administered through (b) (4) a contract research organization. These contracts are for studies of drugs that would compete with the drug under review by the GIDAC. As the Division Director of Gastroenterology and Hepatology, Dr. Raufman has managerial oversight of the faculty within the division, including the principal investigators of these studies. However, he is not involved with these studies and does not receive salary support or personal remuneration from any of the studies.

1. AbbVie: A Phase 3 Multicenter, Open-Label Extension (OLE) Study to Evaluate the Long-Term Safety and Efficacy of ABT-494 in Subjects with UC; NCT 03006068. The study began on May 9, 2017, and will last until (b) (4). The total funding to UMD for the study is between $0 - $50,000 per year.

2. AbbVie: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABT-494 for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active UC; NCT02819635. The study began on April 29, 2017, and will last until (b) (4) The total funding to UMD is between $0-$50,000 per year.

3. AbbVie: A Long-Term Non-Interventional Post Marketing Study to Assess Safety and Effectiveness of Humira® (adalimumab) in Patients with Moderately to Severely Active UC, NCT 01848561. The study began on October 1, 2014, and will last until (b) (4) The total funding to UMD is between $0 - $50,000 per year.

4. Celgene: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe UC, NCT02435992. The study began on February 1, 2016, and will last until (b) (4). The total funding to UMD is between $0 - $50,000 per year.

5. Takeda: A Phase 3, Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab (MLN0002) in Subjects with UC and Crohn's Disease NCT0790933. The study began on June 26, 2009 and will last until (b) (4). The total funding to UMD is between $ 0 - $50,000 per year.

Basis for Granting the Waiver:

The primary issue for discussion at this GIDAC meeting will be the benefit/risk assessment of the use of tofacitinib 10 mg twice a day dosing, beyond the 8 weeks of initial induction

treatment. The proposed dose is above the maximum recommended dosage for the current approved uses, therefore the key discussion point will be whether safety and efficacy data supports the long-term use of the 10 mg twice daily dosage in refractory (prior tumor-necrosis factor inhibitor failure) UC patients.

Inflammatory bowel disease (IBD) involves chronic inflammation of the digestive tract, which includes UC. UC is a disease affecting the colon and the primary endpoint for trials for drugs intended to treat UC includes measurement of findings on colonoscopy. A fruitful discussion of these matters depends upon having strong expertise in this area and hearing many perspectives. It is particularly important to include Dr. Raufman, given his experience in adult gastroenterology, gastrointestinal regulatory molecules and signal transduction, as well as his in-depth knowledge in the correlation of bile acids functionality relative to IBD and colon cancer. Further, as an experienced member and Chair of previous GIDAC meetings, his participation would be beneficial, particularly because there are new members who will be participating in a GIDAC meeting for the first time.

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

Jean-Pierre Raufman, M.D. received his medical degree from Albert Einstein College of Medicine and did his Internal Medicine Residency at Montefiore Medical Center. He then pursued a Gastrointestinal Fellowship at the University of Michigan. He went on to obtain three more years of research training at the Digestive Diseases Branch of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH). Dr. Raufman is board certified in Internal Medicine and Gastroenterology.

Since 1983, Dr. Raufman has maintained an independent research program focused on the study of gastrointestinal regulatory molecules and signal transduction. He has been awarded a wide variety of research grants by NIH, VA Merit Program, American Gastroenterological Association and Industries. Dr. Raufman's work has been presented at many prominent national meetings and he has published over 180 peer-reviewed research papers, reviews and book chapters, including 19 first or senior author scientific publications. In addition, Dr. Raufman is a member of the Molecular and Structural Biology Program within the University of Maryland Marlene and Stewart Greenebaum Cancer Center Program in Oncology. As such, he collaborates with both basic and clinical research investigators to identify candidate proteins and genes that are relevant to muscarinic receptor signaling in colon cancer and may serve as markers for malignancy and/or targets for new drugs. The program's long term goal is to apply resulting advances in knowledge towards preventing and treating colon cancer.

Dr. Raufman's experience in adult gastroenterology, gastrointestinal regulatory molecules and signal transduction, and his in-depth knowledge in the correlation of bile acids functionality relative to inflammatory bowel disease and colon cancer, would be a significant addition to the panel for the GIDAC meeting. Dr. Raufman is well versed in the issues involved in conducting IBD trials, in understanding safety data from clinical trials in IBD, and is familiar with the limitations of safety data that are often present in IBD development programs, which may result in the need for longer term post-marketing safety studies. His experience with ongoing and past clinical trials of other systemic immunosuppressant agents (including both small molecules and

biologic agents) for the treatment of patients with IBD is essential to the meeting. Specifically, his familiarity with the uncertainties related to the safety assessment of products that represent a new therapeutic option, similar to the matter before the committee, would be a valuable addition to the discussion. Dr. Raufman's comprehensive background in gastroenterology and gastrointestinal signals, as well as extensive experience with advisory meetings, will be valuable as the committee considers the potential risks and benefits of the proposed new treatment for the UC population.

Multiple experts are needed.

There are several gastroenteroogists scheduled to attend this meeting. It is necessary for the committee to include multiple gastroenterologists, ideally both those who treat adults as well as pediatric patients, to help provide a balanced assessment of the acceptability of the known and anticipated risks associated with the proposed treatment, tofactinib, for UC. Having a diverse collection of professional experiences represented on the panel would allow for a robust and productive discussion of the meeting topic.

The particular matter is not sensitive.

The meeting topic is not considered to be sensitive. The Division does not expect that the meeting is likely to receive significant public interest, (non-trade) press interest, or Congressional interest.

Dr. Raufman's expertise in this particular matter is necessary in the interest of public health.

UC is a chronic, idiopathic inflammatory disease that affects the colon, most commonly afflicting adults aged 30–40 years and resulting in disability. It is characterized by relapsing and remitting mucosal inflammation, starting in the rectum and extending to proximal segments of the colon. The annual direct and indirect costs related to UC are estimated to be as high as $8 – $15 billion in the USA.

Although several treatment options are available, none of them are curative. This leads to most patients experiencing periods of illness after intervals of remission. Goals of treatment are induction and maintenance of remission of symptoms to provide an improved quality of life, reduction in need for long-term corticosteroids, and minimization of cancer risk. Currently, agents approved for moderate-severe active UC that have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, are azathioprine, 6-mercaptopurine (6-MP) or TNF inhibitor therapy, including infliximab, vedolizumab, golimumab, and adalimumab. These agents require intravenous or subcutaneous administration. However, tofacitinib, the product at issue, is an oral medication proposed to be administered twice daily. This product, if approved, represents the first systemic immunosuppressant in a new drug class, and the first oral treatment option available to patients with severe disease.

Dr. Raufman's extensive experience in conducting and assessing data from clinical trials in IBD is essential given the uncertainties that surround the potential risk and benefit assessment of products that represent a new therapeutic option, such as the drug under review by the

committee. His experiences will ensure a fruitful discussion and a broader public health benefit.

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

The conflicting financial interests described in this waiver are those of Dr. Raufman's employer and are imputed to him under the federal conflict of interest law. Although, Dr. Raufman has managerial oversight of the faculty within the division where the studies are being conducted, he does not manage or have any other personal involvement in the studies, nor does he receive salary support or personal remuneration from any of the studies. As indicated above, his participation at this advisory committee meeting is essential; it would add to the diversity of experiences on the panel, allow for a comprehensive discussion of the meeting topic, and would ensure the presence of an experienced advisory committee expert to help guide discussion of the meeting topic.

Accordingly, I recommend that you grant Dr. Jean-Pierre Raufman, the Chair and voting member of the Gastrointestinal Drugs Advisory Committee, a waiver 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.

Kathleen Davies -S

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for Rachel Sherman

February 15, 2018

Rachel Sherman, M.D., M.P.H.
Principal Deputy Commissioner
Office of the Commissioner, Food and Drug Administration

Date